A mis padres (Javier y Aurea) e Iker,
por hacerme quien soy.

A Jon Ander,
te volvería a decir que SÍ un millón de veces más.

A la cúpula,
la familia que volvería a elegir.

A Estefi,
la hermana que nunca tuve

A la cuadrilla, familiares, amigos y amigas,
los que siempre están ahí

PROGRAMA DE DOCTORADO

Ciencias de la Actividad Física y del Deporte

THESIS PROGRAM

Science of Physical Activity and Sports

TESIS DOCTORAL

"Efectos de diferentes programas de ejercicio físico aeróbico con intervención nutricional en personas con hipertensión primaria y sobrepeso: estudio EXERDIET-HTA"

DOCTORAL THESIS

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"Effects of different aerobic exercise programs with nutritional intervention in overweight and obese adults with primary hypertension: the EXERDIET-HTA study"

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“Ese instante de felicidad..., cuando has acabado una tarea pendiente y quizá te ha costado un gran esfuerzo y no estabas seguro de lograrlo. Pero sí, lo has conseguido. Y te sientes una campeona, pero una de esas que ganan en secreto, corriendo de noche en una pista desierta, sin público.”

Federico Moccia

“No busques cuentos con final feliz, busca ser feliz sin tanto cuento”

Anónimo

“¿Te ha pasado alguna vez que estás buscando un lápiz y lo tienes en la mano? Pues algo similar ocurre con la felicidad.”

Anónimo

“El humor y la curiosidad son la más pura forma de inteligencia”

Roberto Bolaño

Esta tesis doctoral se ha realizado con la ayuda del Gobierno Vasco, del área educación, Política Lingüística y Cultura para el Programa Predoctoral, de Formación de Personal Investigador No Doctor. (2015-2018) [PRE_2014_1_276].

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The future belongs to those who believe in the beauty of their dreams. So proud of you all.

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DECLARACIÓN

La autora de esta tesis doctoral ha participado en todo el proceso de investigación, desde el diseño hasta el producto final en forma de publicaciones y congresos. Para ello, ha revisado la bibliografía existente, participado en el diseño de las intervenciones y en su puesta en práctica, así como en las distintas valoraciones y en la obtención y análisis de datos, y ha tratado de hacer una buena discusión tras haber interpretado los resultados en profundidad. Por otro lado, ha sido responsable, junto con la directora de la tesis, del proceso de divulgación en forma de publicación de artículos en revistas científicas.

Este trabajo no podría haberse llevado a cabo sin la supervisión de la tutora y directora del mismo, quien ha sido parte activa durante todo el proceso, y ha contado con la participación de alumnado de grado en prácticas obligatorias y de alumnado de posgrado, así como de colaboradores externos que han participado en la valoración de las personas participantes para su inclusión en el estudio.

La investigación se ha llevado a cabo en instalaciones y con recursos de la Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU), Facultad de Educación y Deporte (Sección Ciencias de la Actividad Física y del Deporte) y del Departamento de Educación Física y Deportiva de la UPV/EHU. Además, las becas de la UPV/EHU (GIU14/21 y EHU14/08) así como la beca SAIOTEK del Gobierno Vasco (SAI12/217) han ayudado en la financiación de la investigación. El Igualatorio Médico Quirúrgico (IMQ) de Vitoria-Gasteiz ha participado de forma altruista con la colaboración de sus especialistas médicos Javier Pérez Asenjo y Rodrigo Aispuru. Exercycle S.L. (BH Fitness Company) ha donado material deportivo que ha facilitado la intervención de ejercicio físico. Otros dos integrantes del grupo de investigación que han participado de forma activa en este proyecto disfrutan de una beca predoctoral del Gobierno Vasco (Pablo Corres y Aitor Mtz. de Aguirre).

No ha existido conflicto de interés alguno a la hora de realizar esta investigación, y las becas y ayudas no han repercutido en los resultados obtenidos y presentados.

RECOMENDACIONES PARA LA LECTURA

La tesis doctoral que tiene entre manos se ha realizado en forma de compendio de artículos. Para seguir el hilo de los contenidos que forman este trabajo, se debe partir de la introducción en el primer capítulo, que sirve como justificación de la necesidad de este estudio, da cohesión a los apartados siguientes, y establece el estado de la cuestión referente a un tratamiento no farmacologico dual de dieta y ejercicio fisico en personas con hipertensión arterial primaria y sobrepeso u obesidad.

En el segundo capítulo se marcan los objetivos y se plantean las hipótesis de investigación que se han resuelto siguiendo la metodología descrita en el tercer capítulo.

Los capítulos 4-7 ahondan en el estado de la cuestión de los distintos objetivos de investigación de forma más específica, concretan la metodología que se tiene en cuenta para cada apartado, y presentan los resultados de investigación con cuatro artículos científicos publicados en revistas internacionales. El capítulo cuarto corresponde al artículo "*Clinical, physical, physiological, and dietary patterns of obese and sedentary adults with primary hypertension characterized by sex and cardiorespiratory fitness: EXERDIET-HTA study"*, que presenta el estado de salud mediante algunos marcadores físicos, fisiológicos, clínicos y nutricionales clave en personas adultas con sobrepeso u obesidad e hipertensión arterial primaria caracterizada por sexo y capacidad cardiorespiratoria, antes de comenzar una estrategia terapéutica no farmacológica. En el siguiente capítulo, el artículo *"Assessment of cardiovascular risk and vascular age in overweight/obese adults with primary hypertension: EXERDIET-HTA study"* se estima el perfil de riesgo cardiovascular y edad vascular en personas con hipertensión primaria a través del método Framingham antes de comenzar una estrategia terapéutica no farmacológica. En el capítulo sexto, el artículo *"Effects of different aerobic exercise programs with nutritional intervention in sedentary adults with overweight/obesity and hypertension: EXERDIET-HTA study"* evalua el efecto de distintos programas de ejercicio aeróbico (distintos tipos, intensidades y duraciones) con intervención nutricional en la tensión arterial, composición corporal y capacidad cardiorespiratoria en personas adultas con sobrepeso u obesidad con hipertensión primaria tratados con dieta hipocalóra. Por ultimo, en el capítulo séptimo "*Effects on cardiovascular risk scores and vascular age after aerobic exercise and nutritional intervention in sedentary and overweight/obese adults with primary hypertension: the EXERDIET-HTA randomized trial study*" evalua el efecto de distintos programas de ejercicio físico aeróbico con intervención nutricional en los factores de riesgo cardiovascular, en el riesgo cardiovascular y edad vascular, estimados a través del método Framingham

y New Pooled Cohort Equation en personas adultas con sobrepeso u obesidad con hipertensión primaria tratados con dieta hipocalóra.

En la parte final de esta tesis se presentan las conclusiones (cap.8), las limitaciones del trabajo y las propuestas para futuras investigaciones (cap.8).

Se trata de una tesis internacional, por lo tanto, a lo largo de este documento se van a encontrar dos lenguas (castellano e inglés). En las primeras páginas del documento podrá leer dos listas de abreviaturas, en castellano e inglés, respectivamente. El formato de los artículos ha sido cambiado para crear un trabajo más homogéneo y hacer más fácil su lectura, aunque existe copia de los originales en los anexos al final del documento.

ABREVIACIONES

ACC: *Colegio Americano de Cardiología*

ACSM: *Colegio Americano de Medicina del Deporte*

AF: *actividad física*

AHA: *Sociedad Americana del Corazón*

CCR: *capacidad cardiorrespiratoria*

CPET: *prueba de esfuerzo cardiopulmonar*

CV: *cardiovascular*

CO_2 *dióxido de carbono*

CT: *colesterol Total*

DM: *diabetes mellitus*

DLP: *dislipemia*

ECG: *electrocardiograma.*

ECV: *enfermedad cardiovascular*

EF: *ejercicio físico*

ESC: *Sociedad Europea de Cardiología*

ESH: *Sociedad Europea de Hipertensión*

FC: *frecuencia cardiaca*

FCR: *frecuencia cardiaca de reserva*

FITT: *principio FITT; frecuencia, intensidad, tiempo y tipo*

FR: *factores de riesgo*

FRCV: *factor de riesgo cardiovascular*

HDL: *lipoproteínas de alta densidad*

HIIT: *entrenamiento interválico de alta intensidad*

HTA: *hipertensión arterial.*

ICC: *índice cintura-cadera*

IMC: *índice de masa corporal.*

LDL: *lipoproteínas de baja densidad*

MET: *equivalente metabólico*

O_2: *oxígeno*

OMS: *Organización Mundial de la Salud.*

PA: *presión arterial*

PAD: *presión arterial diastólica*

PAS: *presión arterial sistólica*

RCV: *riesgo cardiovascular*

UV1: *umbral ventilatorio 1*

UV2: *umbral ventilatorio 2*

$\dot{V}CO_2$: producción de dióxido de carbono

$\dot{V}O_2$: consumo de oxígeno

$\dot{V}O_{2max}$: consumo de oxígeno maximo

$\dot{V}O_{2pico}$: consumo de oxígeno pico

ABBREVIATIONS

ABPM: ambulatory blood pressure monitoring

AC: attention control group

ACEI: angiotensin-converting-enzyme inhibitors

ACSM: American College of Sports Medicine

ALT: alanine Transaminase.

ANOVA: analysis of variance

ANCOVA: analysis of covariance

ESC: European Society of Cardiology

ESH: European Society of Hypertension

FFM: fat free mass

FITT: FITT principle; frecuency, intensity, time, type

FM: fat mass

FRS: Framingham risk score

GGT: gamma-glutamyl transferase

HDI: healthy diet indicator

HDL-C: high-density lipoprotein *cholesterol*

HIIT: high-intensity interval training

HOMA-IR: homeostasis model assessment of insulin resistance

HTN: arterial hypertension

HR: heart rate

HV-HIIT: high-volume and high-intensity interval training

LDL-C: low-density lipoprotein *cholesterol*

LITT: low-intensity interval training

LV-HIIT: low-volume and high-intensity interval training

MBP: mean blood pressure

MET: metabolic equivalent of task

MICT: moderate-intensity continuous training

MSWT: modified shuttle walk test

n: sample size

P: P-value, significant differences

PP: pulse pressure

RER: respiratory exchange ratio

SBP: systolic blood pressure

SD: standard deviation

T0: pre-intervention

T1: post-intervention

TBW: total body water

TC: total cholesterol

TG: triglycerides

UPV/EHU: University of the Basque Country

VA: vascular age

$\dot{V}O_2$*: oxygen uptake*

$\dot{V}O_{2max:}$ *maximum oxygen uptake*

$\dot{V}O_{2peak}$*: peak oxygen uptake*

ω^2*: omega squared*

WHO: World Health Organization

WHR: waist-to-hip circumference ratio

Índice

ÍNDICE

Abstract

Aim: The main objectives of the present doctoral thesis based on four of the EXERDIET-HTA project's sub-studies were: **(a)** to determine some key physical, physiological, clinical, and nutritional markers of health status in obese and sedentary adults with primary hypertension (HTN) characterized by sex and cardiorespiratory fitness (CRF) level, **(b)** to estimate cardiovascular risk (CVR) and vascular age (VA) profiles analyzing potential sex differences, in order to determine whether VA is higher than chronological age, and whether CVR is associated with a low level of CRF, **(c)** to determine the effectiveness of different 16-week aerobic exercise programmes with hypocaloric diet on blood pressure (BP), body composition, CRF and pharmacological treatment, and **(d)** to evaluate the influence of diet and aerobic exercise program intervention on CVR factors and predicted CVR and VA profiles in overweight/obese people with HTN, and to analyze the potential sex differences in the ability to predict VA and CVR via different methods.

Methods: Sedentary overweight/obese non-Hispanic white adults (n=175) with HTN participated in the EXERDIET-HTA study. All participants received a hypocaloric diet. Following baseline data collection, participants were randomly allocated to one of the four intervention groups: the attention control (AC) group (only physical activity recommendations), or the three supervised exercise groups (high-volume and moderate-intensity continuous training [MICT], high-volume and high-intensity interval training [HITT], or low-volume HIIT) exercising 2 days a week during 16 weeks. Body composition, BP (by wearing an ambulatory BP monitor), CRF (by Modified Shuttle Walking Test and a peak, symptom-limited cardiopulmonary exercise test), biochemical profile and nutritional condition were measured before and after the intervention. Cardiovascular risk and VA were determined using the Framingham method (FRS) and the new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk.

Results: (a) The studied population showed a high CVR profile including metabolically abnormal obese, with poor CRF level (22.5 ± 5.6 $mL \cdot kg^{-1} \cdot min^{-1}$), and with non-healthy adherence to dietary pattern (Dietary Approaches to Stop Hypertension, 46.3%; Mediterranean Diet, 41.1%; and Healthy Diet Indicator, 37.1%). Women showed a better biochemical and dietary pattern profile than men ($P<0.05$), but physical and peak exercise physiological characteristics were poorer ($P<0.001$). **(b)** The CVR, but not VA ($P=0.339$), was higher ($P<0.001$) in men compared with women irrespective of age. Irrespective of sex, VA was higher than chronological age ($P<0.001$). **(c)** Following the intervention, there was a significant reduction in BP and body mass in all groups with no between-group differences for BP. However, there was a significantly lower reduction in

body mass in the AC group compared with all exercise groups (AC: 6.6%; high-volume MICT: 8.3%; high-volume HIIT: 9.7%; low-volume HIIT: 6.9%). HIIT groups had significantly higher CRF than high-volume MICT, but there were no significant differences between HIIT groups (AC: 16.4%; high-volume MICT: 23.6%; high-volume HIIT: 36.7%; low-volume HIIT: 30.5%). Medication was removed in 7.6% and reduced in 37.7% of the participants. **(d)** Participants had a significantly lower ($P \leq 0.001$) FRS-CVR score and VA post-intervention. For ASCVD risk changed neither in men nor in women. After the intervention, women had a lower CVR score than men ($p \leq 0.001$), irrespective of the calculation method.

Conclusions: (a) The results strongly suggest that targeting key behaviours such as improving nutritional quality and CRF via regular physical activity might contribute to improve health with independent beneficial effects on CVR factors. **(b)** ASCVD could underestimate the risk of suffering a cardiovascular event in the following 10 years in overweight/obese non-Hispanic white women with HTN compared with men. The VA appears to be a useful tool in communicating CVR in this population irrespective of sex. **(c)** The combination of a hypocaloric diet with supervised aerobic exercise 2 days/week offers an optimal nonpharmacological tool in the management of BP, CRF and body composition in overweight/obese and sedentary individuals with HTN. High-volume HIIT seems to be better for reducing body mass compared with low-volume HIIT. The exercise-induced improvement in CRF is intensity dependent with low-volume HIIT as a time-efficient method in this population **(d)** The improvement in CVR factors after 16-week lifestyle changes reduced the risk of suffering a cardiovascular event in overweight/obese adults with HTN through the FRS estimation tool, but not with the ASCVD score. The risk score algorithms could underestimate CVR in women. In contrast, VA could be a useful and easier tool in the management of individuals with CVR factors.

Capítulo 1 / Chapter 1

Introducción

1. INTRODUCCIÓN / Introduction

Las enfermedades cardiovasculares (ECV) son la causa principal de mortalidad y morbilidad en el mundo provocando un enorme impacto en la calidad de vida y costos relacionados con el cuidado de la salud.[1]

En 2012 murieron 17,5 millones de personas por esta causa, lo cual representa un 31% de las muertes registradas en el mundo. De estas muertes, 7,4 millones se debieron a la cardiopatía coronaria y 6,7 millones a los accidentes cardiovasculares (CV).[2] Dentro de los denominados países desarrollados, las ECV, suponen la mayor causa de mortalidad. La sociedad actual acusa un alto índice de desarrollo de ECV con un alto índice, en consecuencia, de morbi-mortalidad asociado.[3]

Las ECV son un grupo de desórdenes del corazón y de los vasos sanguíneos. Se clasifican en: cardiopatía coronaria, enfermedad cerebrovascular, enfermedad vascular periférica, insuficiencia cardíaca, cardiopatía reumática, cardiopatía congénita, miocardiopatías y la ateroesclerosis.[4]

Los factores de riesgo cardiovascular (FRCV) están relacionados con el desarrollo de ECV, teniendo relación causal con la muerte prematura y los eventos CV.[5] El conocimiento de los FRCV en las ECV, especialmente los factores de riesgo modificables, tales como el fumar, colesterol, hipertensión (HTA), sobrepeso/obesidad e inactividad física es algo esencial y podría contribuir a una reducción en la incidencia de las ECV.[6]

Entre los factores que tienen relación directa con las ECV está la HTA, que afecta aproximadamente al 35% de las personas mayores de 18 años en España.[7]

1.1. Hipertensión arterial primaria

La presión arterial (PA) o sanguínea, también denominada tensión arterial, es la presión o fuerza que ejerce la sangre a su paso por las paredes de las arterias. La presión sanguínea se cuantifica con dos valores: presiones sistólica y diastólica, medidas en milímetros de mercurio (mmHg). La PA sistólica (PAS) representa el pico de presión que corresponde con la contracción ventricular durante la sístole, mientras que la PA diastólica (PAD) representa la presión durante la relajación ventricular, la diástole.[8]

El incremento de los valores de PAS y/o PAD mantenido en el tiempo puede causar lesiones y enfermedad en distintos órganos, lo que se consideraría una elevación crónica de la PA. Este tipo de tensión arterial alta es lo que se conoce como HTA.[8]

La relación continua entre la PA y eventos CV y renales hace que la distinción entre la normo tensión e HTA sea difícil a la hora de poner un punto de corte natural sobre el cual se pueda considerar la existencia de HTA. Los valores de PA tienen una distribución normal en la población. Sin embargo, se ha demostrado en diversos estudios epidemiológicos que el riesgo de padecer enfermedad asociada a la PA tiene una relación continua por encima de mediciones de 115/70 mmHg, donde 115 representa la PAS, y 70 la PAD, y que el riesgo de padecer eventos CV se dobla por cada 20/10 mmHg que se eleva la PA.[9] Teniendo en cuenta estas estimaciones del riesgo para la salud que supone la PA alta, se establece un umbral de PA como criterio que determina la presencia de HTA. El umbral de HTA lo concretan los valores de PA sobre los que el tratamiento puede reducir la evolución de la enfermedad, dando así unos límites a la PAS y PAD para definir la HTA (Tabla 1).[9] La HTA se define con valores >140 mmHg en la PAS y/o >90 mmHg en la PAD, y basándose en evidencia científica se indica que estos valores se pueden reducir a través de tratamientos diversos, farmacológicos y no farmacológicos.[9]

Tabla 1. Definiciones y clasificación de los valores de presión arterial (mmHg).[9]

CATEGORIA	PAS	PAD
Óptima	<120	<80
Normal	120-129	80-84
Normal alta	130-139	85-89
Hipertensión grado 1	140-159	90-99
Hipertensión grado 2	160-179	100-109
Hipertensión grado 3	≥180	≥110
Hipertensión sistólica aislada	≥140	≤90

PAD: presión arterial diastólica; PAS: presión arterial sistólica. El grado de la hipertensión sistólica aislada debe ser calificado (1, 2,3) en función de los valores de presión arterial sistólica de los limites indicados, siempre que los valores diastólicos sean<90 mmHg. Los grados 1, 2 y 3 corresponden a la clasificación de hipertensión leve, moderada y grave, respectivamente. Estos términos se han omitido ahora para evitar confusiones con la cuantificación del riesgo cardiovascular total.

Sin embargo, en 2017, el Colegio Americano de Cardiología (ACC) y Sociedad Americana del Corazón (AHA)[10] también presentaron la clasificación de la HTA, dividiendo los grados de PA

en cuatro grados para la toma de decisiones clínicas en la salud pública en un entorno de atención primaria: normal, elevada, e HTA grado 1 e HTA grado 2, ilustrando esquemáticamente las categorías de PAS y PAD que definen la PA normal, la PA elevada y la HTA en grado 1 y 2 (Tabla 2).[10] Esta clasificación difiere de la previamente recomendada y validada en Europa con HTA definida ahora con valores >130 mmHg en la PAS y/o >80 mmHg en la PAD.[9] La razón para este cambio en la clasificación se basó en datos observacionales relacionados con la asociación entre PAS/PAD y riesgo de ECV. Se llevó a cabo un estudio controlado aleatorizado para la modificación del estilo de vida para descender la PA con y sin medicación antihipertensiva, y así prevenir la ECV.[10] Aquellos adultos en un grado 2 de HTA tienen el mayor riesgo de ECV. Sin embargo, estas guías aún no han sido aceptadas en Europa y solo están validados en Estados Unidos. Cada vez más estudios y meta-análisis de datos observacionales han demostrado un aumento progresivo de ECV que va desde una PA normal a una HTA grado 2.[11-14]

Tabla 2. Categorías de la PA en adultos* (mmHg)[10]

Categoría PA	**PAS**		**PAD**
Normal	<120	y	<80
Elevada	120-129	y	<80
Hipertensión			
Grado 1	130-139	o	80-89
Grado 2	≥140	o	≥90

*Individuos con PAS y PAD en dos categorías deben ser designados a la categoría de PA más alta. PA indica presión arterial (basada en ≥2 cuidadosas medidas en ≥2 ocasiones; PAD, presión arterial diastólica; y PAS, presión arterial sistólica)

Se pueden distinguir dos tipos de HTA, dependiendo de la o las causas que la hayan originado: HTA primaria y secundaria. La HTA primaria o idiopática se refiere a la no existencia de una causa obvia o identificable que haya promovido el desarrollo de la HTA. El 90% de las personas con HTA padece este tipo desconocido, mientras que el 10% restante, responde a la denominada HTA secundaria. La HTA secundaria puede ocurrir por distintas causas específicas: adenoma de Conn, enfermedad reno- vascular, feocromocitoma, hipotiroidismo o hipertiroidismo, apnea obstructiva del sueño, acromegalia, o consumo de drogas. Los casos de HTA secundaria, donde hay una causa identificable, suelen ser más abundantes en personas menores de 40 años.[8]

La HTA primaria es sorprendentemente común en el contexto internacional. En cuanto a población mundial, al menos un cuarto de las personas adultas padece HTA, lo cual correspondió en el año 2000 a 972 millones de personas. Si se tiene en cuenta el nivel de desarrollo, 1/3 de los afectados corresponde a países económicamente desarrollados, y 2/3 a países en vías de desarrollo.[7,8,15,16] La prevalencia de HTA en la población adulta de España es elevada. Aproximadamente el 42,6% de los individuos mayores de 18 años son hipertensos (PA ≥140/90 mmHg o en tratamiento farmacológico antihipertensivo) y es más común en hombres (49.9%) que en mujeres (31.5%).[17] Estas cifras se elevan exponencialmente cuanto mayor es la edad de la población, subiendo al 50% en edades medias, y al 68% en mayores de 60 años.[7] Se prevé que la prevalencia de HTA y la necesidad de tratamiento farmacológico continúen creciendo, ya que la población es cada vez de mayor edad, más sedentaria y más obesa.[7,8,15] De hecho, según un análisis sobre la tendencia de la carga que supone la HTA a nivel mundial, se estima que la población adulta que tendrá HTA pasará del 26,4% en el año 2000, al 29,2% en 2025.[16] Así, se puede afirmar que la HTA es uno de los mayores problemas de salud pública.[9]

La gran prevalencia de HTA en la población y el riesgo que supone una PA elevada, en un informe de la Organización Mundial de la Salud (OMS) se ha citado la HTA como primera causa de muerte en todo el mundo,[9] que en 2010 provocó 2.1 millones de muertes más que en 1990;[18] la pérdida del 7 % del total de años de vida y 9.4 millones de muertes. La HTA junto con estilos de vida cada vez más sedentarios y unos hábitos nutricionales incorrectos es la causa de ECV modificable más potente.[19]

1.2. Sobrepeso/obesidad

El sobrepeso y la obesidad se definen como una acumulación anormal o excesiva de grasa y que puede ser perjudicial para la salud.[20] La obesidad es el resultado del desequilibrio entre el consumo y el aporte de energía.[21] La proporción y cantidad de macronutrientes ingeridos como energía, (*i.e.* carbohidratos, proteínas y grasas), está destinada a convertirse en energía y en elementos celulares, o cuando el consumo excede los requerimientos, a almacenarse en forma de grasa y por lo tanto, es la grasa la principal fuente de almacén y origen de la obesidad. Los ácidos grasos son almacenados en la célula en forma de triglicéridos. Los triglicéridos son hidrolizados por la enzima lipoproteína lipasa localizada en los capilares sanguíneos, para ser introducidos en el adipocito y re-esterificados como triglicéridos tisulares. Sin embargo, las personas con obesidad tienen disminuida la actividad de la lipoproteína lipasa; por lo cual, se

origina un aumento de triglicéridos y un descenso de lipoproteínas de alta densidad (HDL-C) en sangre, acompañándose ello de una mayor incidencia de coronopatias.[21,22] Además, en la medida en que se acumulan lípidos en el adipocito, este se hipertrofia y en el momento en que la célula ha alcanzado su tamaño máximo, se forman nuevos adipocitos a partir de los preadipocitos o células adiposas precursoras, y se establece la hiperplasia.[23] Se ha demostrado que estos incrementos se asocian con un aumento de enfermedades cardiovasculares, diabetes tipo 2, HTA, colesterol de baja densidad (LDL-C) e incluso algunos tipos de cáncer.[21,24] Por todo ello, el exceso de grasa se ha convertido en una de las amenazas de salud pública más importantes a las que se enfrentan las sociedades actuales en los países desarrollados. Por su parte, la inactividad física y una inadecuada alimentación, son los principales factores que provocan el desequilibrio energético y que conducen a la acumulación de tejido adiposo en el organismo.[25]

El índice de masa corporal (IMC) es un indicador simple de la relación entre la masa corporal y la talla que se utiliza frecuentemente para identificar el sobrepeso y la obesidad en los adultos. Se calcula dividiendo la masa corporal de una persona en kilogramos por el cuadrado de su talla en metros (kg/m^2). La OMS[20] clasifica como sobrepeso los valores de IMC iguales o superiores a 25 kg/m^2 y como obesidad el IMC igual o mayor que 30 kg/m^2 (Tabla 3). El IMC proporciona la medida más útil del sobrepeso y la obesidad en la población, puesto que es la misma para ambos sexos y para los adultos de todas las edades. Los autores del Framingham Heart Study sugieren que el riesgo relativo de desarrollar insuficiencia cardíaca en un periodo de 14 años aumenta un 5% en hombres y un 7% en mujeres por cada incremento de 1 kg/m^2 en el IMC.[22] Sin embargo, hay que considerarla a título indicativo porque es posible que no se corresponda con el mismo nivel de adiposidad en diferentes personas.[20]

Tabla 3. Clasificación de la Organización Mundial de la Salud del estado nutricional de acuerdo con el IMC.[20]

	IMC (kg/m^2)
Masa corporal insuficiente	**<18,50**
Normopeso	18,50 - 24,99
Sobrepeso	**≥25,00**
Grado I	25,00 - 27,49
Grado II	27,50 - 29,99
Obesidad	**≥30,00**
Grado I	30,00 – 34,99
Grado II	35,00 – 39,99
Grado III/Mórbida	≥40,00

IMC, índice de masa corporal

También tiene interés conocer el patrón de distribución de la grasa corporal por su relación con el RCV. Con esta finalidad se utiliza el índice cintura-cadera (ICC), que pone en relación el perímetro de cintura con el perímetro de la cadera dividiendo uno con el otro, para determinar si existe riesgo de contraer determinadas enfermedades asociadas a la obesidad. El ICC es aceptado como un buen indicador de la obesidad central y, aunque no están claramente definidos los valores a partir de los cuales se observa un aumento del RCV, se han propuesto como valores delimitadores del riesgo > 1 en los hombres y > 0,85 en las mujeres (Tabla 4).[25,26] Por otra parte, se ha sugerido que valores superiores al percentil 90 suponen un riesgo muy elevado para la salud. De acuerdo con este criterio, estudios epidemiológicos transversales de diferentes comunidades autónomas españolas sitúan este valor de riesgo para el ICC en > 1 para los hombres y > 0,90 para las mujeres. Si bien este índice no permite diferenciar si se trata de una acumulación perivisceral o subcutánea.[25] Además, se recomienda medir el perímetro de cintura como indicador de grasa visceral, para obtener información adicional sobre la composición corporal y poder detectar cambios en la misma.[27] De hecho, se estima que usando solo el IMC no se detecta la mitad de la población con exceso de grasa.[28,29] Aunque los umbrales de perímetro de cintura para valorar la obesidad varían según grupos étnicos y, por tanto, es difícil de estandarizar[26], en algunos trabajos se ha observado que el riesgo de obesidad central, complicaciones metabólicas y RCV asociadas a la obesidad aumenta en los hombres a partir de una circunferencia de la cintura ≥ 94 cm y en las mujeres ≥ 80 cm y este riesgo está muy aumentado para los hombres a partir de valores ≥ 102 cm y en las mujeres ≥ 88 cm (Tabla 4).[25] Además, el perímetro de cintura junto con el IMC sirven para estimar el RCV relacionado con la adiposidad (Tabla 5).[27]

Tabla 4. Datos antropométricos para la evaluación de la distribución de la grasa corporal.[25]

Indicador	Punto de corte	Complicación de RCV
Perímetro de cintura	>94cm(H); 80cm (M)	Aumentado
Perímetro de cintura	>102 cm(H); 88 cm (M)	Aumentado substancialmente
Índice cintura-cadera	≥0,90cm(H); 0,85 cm (M)	Aumentado substancialmente

H, hombres; M, mujeres; RCV, riesgo cardiovascular

Tabla 5. Riesgo cardiovascular que confiere el grado de índice de masa corporal y distribución adiposa.[27]

		Riesgo relativo a partir del perímetro de cintura	
	IMC (kg/m^2)	**Hombres ≤ 102 cm** **Mujeres ≤ 88 cm**	**Hombres > 102 cm** **Mujeres > 88 cm**
Normopeso	18,50 - 24,99	Ninguno	Aumentado
Sobrepeso	25,00 - 29,99	Aumentado	Alto
Obesidad	30,00 – 34,99	Alto	Muy alto
Grado II	35,00 – 39,99	Muy alto	Muy alto
Obesidad mórbida	≥40,00	Extremadamente alto	Extremadamente alto

IMC, índice de masa corporal. Adaptado de Nacional Institutes of Health[30], The National Heart, Lung, and Blood Institute Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults[31] y Álvarez et al.[32]

En la actualidad, el empleo de la impedanciometría multifrecuencia, tiene un interés complementario a la valoración de la composición corporal para la estimación de la composición corporal y el grado de adiposidad. Existen técnicas más precisas, como la absorciometría dual de rayos X (DEXA), o la impedancia bioeléctrica, que determina la proporción de masa corporal correspondiente a masa grasa midiendo el agua corporal correspondiente a masa muscular.[33] Su coste y complejidad limitan su utilización generalizada.[33] En función del porcentaje graso corporal, se definen como personas con obesidad aquellas que presentan porcentajes por encima del 25% en los hombres y del 35% en las mujeres. Los valores comprendidos entre el 20,1% y 24,9% en los hombres y entre el 30,1 y el 34,9% en las mujeres se consideran límites. Los valores normales son del orden del 12 al 20% en hombres y del 20 al 30% en las mujeres (Tabla 6).[28]

Tabla 6. Clasificación de masa grasa en adultos.[28]

% grasa	**Hombres**	**Mujeres**
Normalidad	12,0 - 20,0	20,0 – 30,0
Sobrepeso	20,1 – 24,9	30,1 – 34,9
Obesidad	> 25,0	> 35,0

La obesidad es una enfermedad crónica, multifactorial, de prevalencia creciente, que junto con el sobrepeso, afecta a más de la mitad de la población en los países desarrollados, por

lo que ha sido considerada por la International Obesity Task Force y la OMS, como la epidemia del siglo XXI.[20] En España la prevalencia de obesidad ha aumentado de forma constante en los últimos 20 años, y que este aumento ha sido más acentuado para los grados más graves de obesidad (IMC>40 kg/m2).[29] Aproximadamente el 69% de población adulta de España tienen sobrepeso u obesidad, siendo un 35% obesos.[34] El incremento que se viene produciendo se debe fundamentalmente a dos factores, por un lado, el consumo excesivo de alimentos de gran contenido calórico[34] y, por otro, la disminución de la AF,[26] imponiéndose un estilo de vida cada vez más sedentario.[26] Las enfermedades asociadas al sobrepeso y la obesidad suponen un amplio espectro de complicaciones, desde la HTA, hiperinsulinemia, dislipidemia (DLP), y la diabetes mellitus (DM) tipo 2, hasta el agravamiento de enfermedades relacionadas con el asma bronquial.[25]

Asimismo, la obesidad está vinculada al 60% de las defunciones debidas a enfermedades no contagiosas. Así, las consecuencias trascienden lo puramente estético para adquirir su auténtica dimensión en relación con las complicaciones metabólicas y CV, de gran repercusión económica y socio-sanitaria, lo que justifica sobradamente la necesidad de convergencia de esfuerzos hacia la prevención primaria y secundaria.[26,34] Así, la obesidad, tiene para la sociedad importantes costes directos e indirectos que exigen múltiples recursos sanitarios y económicos, es responsable del 10-13% de las defunciones y del 2- 8% de los costes económicos en los países de la Unión Europea.[35]

1.3. Riesgo cardiovascular

Se denomina RCV a la probabilidad de desarrollar un episodio CV, y suele expresarse en forma de riesgo de sufrir en un plazo de 10 años. El RCV lo determinan los valores de PA, la presencia de lesiones en los órganos diana, ECV establecida (isquemia, insuficiencia cardiaca, enfermedad cerebro vascular…), y otros factores de riesgo para la ECV, como estilos de vida no saludables en cuyo cambio habrá que insistir (dieta, tabaquismo, obesidad, inactividad, sedentarismo), DM y dislipidemia.[8,9]

Cuando se habla de RCV hay tres conceptos para tener en cuenta: 1) la población a la que pertenecen esas personas, 2) el evento CV, siendo en la mayoría de los sistemas de clasificación derivados del estudio de Framingham como mortales o no mortales, y 3) el tiempo, durante el cual puede aparecer el evento o no, generalmente en un plazo de 10 años, aunque también hay sistemas que calculan a 5 años, 30 años o durante el resto de vida. El riesgo absoluto se aplica a

nivel individual, de manera que, si obtenemos un 10%, significa que tiene una probabilidad del 10% de presentar un evento CV en los próximos 10 años. Epidemiológicamente significa que de cada 100 individuos iguales al paciente (en cuanto a la edad, el sexo y los diversos factores de riesgo (FR) que intervengan en el cálculo del riesgo), 10 individuos tendrán un evento en los próximos 10 años.[36]

1.3.1. Factores de riesgo cardiovascular

Los FRCV son los que se asocian a una mayor probabilidad de sufrir una ECV: edad, sexo, herencia genética, DM, tabaquismo, colesterol e HTA. Su modificación puede reducir los eventos CV y la muerte prematura tanto en las personas con ECV establecida como en aquellas con alto RCV debido a uno o más FRCV teniendo en cuenta que algunos FR pueden cambiarse, tratarse o modificarse y otros no.[37]

Entre los FRCV no modificables, estarían la edad, el sexo y la historia familiar. Se incluye como riesgo la edad superior a 55 años en hombres y la superior a 65 años en las mujeres. Por lo que respecta a los antecedentes familiares de ECV prematura, se considera como FR el antecedente de la misma en un familiar de primer grado en hombres antes de los 55 años y en mujeres antes de los 65 años. Los FRCV modificables son la DM, el tabaquismo, la DLP y la HTA.[38]

Diabetes mellitus (DM)

La DM es una enfermedad crónica que se caracteriza por la concentración alta de glucosa en la sangre. La DM puede estar causada por factores genéticos, autoinmunes, ambientales como la obesidad especialmente la abdominal o grasa central y/o la falta de AF.[39] Existen cuatro tipos de diabetes: la DM tipo 1 es considerada una enfermedad autoinmune debida a la destrucción de las células que producen insulina en el páncreas. Requiere inyecciones diarias de insulina, ya que el cuerpo no produce suficiente insulina, el 10% de los casos de DM es de este tipo y puede aparecer a cualquier edad, pero se suele diagnosticar con mayor frecuencia en niños, adolescentes o adultos jóvenes. La DM tipo 2 se debe a la incapacidad del organismo para utilizar la insulina, el 90% de los diabéticos son de este tipo. Es más frecuente en la edad adulta y su prevalencia ha aumentado entre adolescentes y adultos jóvenes debido a la obesidad. La DM gestacional es la que se inicia o reconoce por primera vez durante el embarazo y se presentan cantidades de glucosa altas en la sangre. Finalmente, la DM 1,5 también denominada LADA (Latent Autoimmune Diabetes in Adults) es una DM autoinmune que parece quedar justo en

medio de los dos tipos principales, es muy parecida a la DM tipo 2 ya que afecta a personas adultas, pero muestra muchos de los rasgos genéticos, inmunes y metabólicos de la DM tipo 1, afecta a personas entre 25 y 35 años de edad que no tienen sobrepeso ni antecedentes familiares de DM. En un principio puede ser tratada como la DM tipo 2, es decir, con antidiabéticos orales, pero al cabo del tiempo es necesario el uso de insulina debido a que el cuerpo inicia un ataque contra las células beta y especialmente del tipo GAD 65 ubicadas en el páncreas, tal como ocurre en la DM tipo 1.[40] Siguiendo las directrices de las sociedades científicas internacionales, se considera como DM la presencia de una glucemia en ayunas > 7,0 mmol/l (126 mg/dl) o una glucemia postprandial > 11,0 mmol/l (198 mg/dl). Tanto si la producción de insulina es insuficiente como si existe una resistencia a su acción, la glucosa se acumula en la sangre dañando progresivamente los vasos sanguíneos (arterias y venas) acelerando el proceso de aterosclerosis aumentando el riesgo de padecer una ECV: angina, infarto agudo de miocardio (así como sus complicaciones y la mortalidad posterior al infarto) y la muerte cardiaca súbita.[39] También incrementa la posibilidad de padecer enfermedad cerebrovascular o afectación de las arterias periféricas.[39] Estudios previos han sugerido que el riesgo de ECV en las personas con DM es similar al de individuos con infarto de miocardio previo. El riesgo de enfermedad coronaria de las personas diabéticas es superior a las no diabéticas, aunque sin llegar al riesgo de las personas no diabéticos con enfermedad coronaria previa.[40]

Tabaquismo

El tabaquismo es la adicción al tabaco provocada principalmente, por uno de sus componentes activos, la nicotina. Según el Comité Nacional para la Prevención del Tabaquismo, el tabaco provoca cerca de 50.000 muertes anuales en España por dolencias como la bronquitis crónica, el enfisema pulmonar y el cáncer de pulmón y faringe. Por si esto fuera poco, es también el FRCV más importante, ya que la incidencia de la patología coronaria en los fumadores es tres veces mayor que en el resto de la población. La posibilidad de padecer una ECV es proporcional a la cantidad de cigarrillos fumados al día y al número de años en los que se mantiene este hábito nocivo. Existen dos factores por los que el tabaco puede producir una isquemia coronaria: 1) la nicotina, que desencadena la liberación de las catecolaminas (adrenalina y noradrenalina) que producen daño en la pared interna de las arterias (endotelio), aumenta el tono coronario con espasmo, produce alteraciones de la coagulación, incrementa los niveles de LDL-C y reduce los de HDL-C y 2) el monóxido de carbono que disminuye el aporte de oxígeno al miocardio y aumenta el colesterol total (CT) y la agregación plaquetaria (su capacidad de unirse y formar coágulos).[41]

Dislipemia (DLP)

Se entiende por DLP cualquier alteración en los niveles de los lípidos en el plasma, por exceso o por defecto. En la práctica clínica interesan las hiperlipidemias, puesto que son uno de los principales FRCV para el desarrollo de la arteriosclerosis y de la ECV. Entendemos por hiperlipemia la presencia de concentraciones plasmáticas de CT, triglicéridos o de ambas a la vez, superiores a los valores considerados "normales" para la población general y por encima de las cuales la intervención es recomendable.[42]

La DLP más frecuente e importante por su trascendencia etiopatogénica en la ECV arteriosclerótica es la hipercolesterolemia, que se define como la elevación del CT y/o de las lipoproteínas que lo transportan en plasma. Así la hipercolesterolemia se define con valores de CT ≥250 mg/dl, y valores de LDL-C ≥ 160 mg/dl (Tabla 7). Esta elevación suele ocurrir por el incremento de CT unido a las LDL-C o lipoproteínas de muy baja densidad, y más raramente por quilomicrones, lipoproteínas de densidad intermedia y/o descenso del CT unido a las HDL-C.[43]

Tabla 7. Criterios de definición de hipercolesterolemia.[43]

	Normocolesterolemia	**CT < 200 mg/ dl** **LDL-C < 130 mg/ dl**
Prevención primaria	Hipercolesterolemia límite	CT 200-249mg/ dl LDL-C 130-159 mg/ dl
	Hipercolesterolemia definida	CT ≥250 mg/ dl LDL-C ≥160 mg/ dl
Prevención secundaria	Hipercolesterolemia definida	CT > 200 mg/ dl LDL-C ≥ 130 mg/ dl

CT, Colesterol total; LDL-C, lipoproteínas de baja densidad.

Las LDL-C se encargan del transporte de CT a los diferentes tejidos, pudiendo formar parte de la membrana plasmática o ingresando dentro de la célula para ser utilizado en la síntesis de compuestos derivados. El problema de las LDL surge cuando hay una gran cantidad de CT que no podemos utilizar, ni como parte de la estructura celular ni para formar derivados del mismo. Cuando esto sucede, el exceso de CT se acumula en las arterias dando lugar a problemas como artritis, arteriosclerosis, enfermedades cardiovasculares, cerebrales, entre otros.[44]

A causa de la hiperlipidemia se presenta la arteriosclerosis comunmente en la poblacion adulta. La arteriosclerosis es la enfermedad de las arterias que consiste en la pérdida de su elasticidad, convirtiéndose en vasos más gruesos y rígidos.[45] Los FRCV influyen enormemente en la aparición de este trastorno que se inicia ya en la infancia con la formación de las estrías grasas,

como lesiones iniciales, que se irán transformando a lo largo de la vida con la acción de los FR.[45,46]Al verse lesionada la pared de un vaso sanguíneo, se ponen en marcha una serie de acontecimientos que conducen a la acumulación de unas células sanguíneas encargadas de taponar la lesión, conocidas como plaquetas. La agrupación de las plaquetas, a su vez, favorece el depósito de grasa (CT) en las paredes de los vasos. De esta manera, se forman las llamadas placas de ateroma y la calcificación en arterias. Las primeras, provocan que las arterias se estrechen progresivamente. La consecuencia de todo esto es que la circulación sanguínea quede reducida de forma importante y, por lo tanto, exista un déficit en el aporte sanguíneo a los órganos y tejidos del cuerpo humano, que no reciben los nutrientes necesarios. Las segundas, son depósitos de calcio y otros minerales en las paredes de los vasos, lo que hace que haya una gran pérdida de flexibilidad con peligro de rotura. En otras palabras, este hecho provoca ECV, como son la cardiopatía isquémica, la enfermedad cerebrovascular, la enfermedad arterial periférica y los aneurismas de aorta.[45]

Hipertension arterial (HTA)

Diversos estudios[8,10] han examinado y evaluado el RCV que supone la presencia en mayor o menor medida de HTA. Se ha comprobado que la reducción de 20/10 mmHg en la PA habitual de hombres y mujeres con edades comprendidas entre los 40 y 89 años, está asociada con una disminución a la mitad de muertes debidas a eventos relacionados con accidentes cerebro vasculares o enfermedad isquémica de corazón, o que la reducción de 5, 7,5 y 10 mmHg en la PAS correlaciona con reducciones de accidente cerebro vascular del 34%, 46% y 56%, respectivamente, y reducciones de enfermedad coronaria del 21%, 29% y 37%, respectivamente.

La razon de la relación continua entre la PA y mayor RCV es a causa de que la HTA supone una mayor resistencia para el corazón, que responde aumentando su masa muscular (hipertrofia ventricular izquierda) para hacer frente a ese sobreesfuerzo. Este incremento de la masa muscular acaba siendo perjudicial ya que no viene acompañado de un aumento equivalente del riego sanguíneo y puede producir insuficiencia coronaria y angina de pecho. Además, el músculo cardiaco se vuelve más irritable y se producen más arritmias. Esto propicia la arterioesclerosis y fenómenos de trombosis (pueden producir infarto de miocardio o infarto cerebral). En el peor de los casos, la HTA puede reblandecer las paredes de la aorta y provocar su dilatación (aneurisma) o rotura (lo que inevitablemente causa la muerte). En aquellos individuos que ya han tenido un problema CV, la HTA puede intensificar el daño.[9]

1.3.2. Predicción de riesgo cardiovascular

Existen distintas escalas de predicción de RCV diseñadas para predecir la probabilidad de sufrir un evento CV a 10 años. Según la escala de medida del RCV se puede hablar de métodos cuantitativos; *i.e*., si dan un resultado numérico concreto (*e.g*., el 17%), o cualitativos; *i.e*., si nos dan un valor aproximado o categórico del riesgo (*e.g*., riesgo moderado).[47]

Un ejemplo del sistema cualitativo es el desarrollado por la Sociedad Europea de Hipertensión (ESH) y la Sociedad Europea de Cardiología (ESC) en el que dependiendo del grado de PA y añadiendo ciertos FR o enfermedades que aumentan el riesgo, obtenemos una calificación la cual nos indica el grado de riesgo (bajo, moderado, alto y muy alto) a padecer un evento CV. Cuantos más altos son los valores HTA y más FR añadidos se observen, mayor será el RCV (Tabla 8).[9,48]

Tabla 8. Estratificación del RCV en categorías bajo, moderado, alto y muy alto, en relación a la PA y otros FR.[10]

Otros factores de riesgo, LO asintomática o enfermedad	Presión arterial (mmHg)			
	Normal alta PAS 130-139 or PAD 85-89	**HTA grado 1 PAS 140-159 or PAD 90-99**	**HTA grado 2 PAS 160-179 or PAD 100-109**	**HTA grado 3 PAS≥180 or PAD≥110**
Sin otros factores de riesgo		RCV bajo	RCV moderado	RCV alto
1-2 factores de riesgo	RCV bajo	RCV moderado	RCV moderado-alto	RCV alto
3 o más factores de riesgo	RCV bajo-moderado	RCV moderado-alto	RCV alto	RCV alto
LO, ERC en fase 3, o diabetes	RCV moderado-alto	RCV alto	RCV alto	RCV alto-muy alto
ECV sintomática, ERC fase ≥ 4, o diabetes con LO/otros factores de riesgo.	RCV muy alto	RCV muy alto	RCV muy alto	RCV muy alto

ECV=enfermedad cardiovascular; ERC=enfermedad renal crónica; HTA=hipertensión arterial; LO=lesión de órganos; RCV=riesgo cardiovascular.

Dentro de los sistemas cuantitativos hay numerosos modelos para la estimación de la puntuación de RCV, así como las escalas procedentes del sistema SCORE (Systematic Coronary Risk Evaluation) que es aplicable en Europa, nace del estudio de Framingham y está calibrado de

acuerdo con las características de los europeos. El sistema posee limitaciones, la principal es que no tiene en cuenta la medicación de la PA.[9,48]

La escala más utilizada es la clásica escala de Framingham, inicialmente validada en 1998 para predecir ECV: muerte de causa cardíaca, infarto agudo de miocardio no fatal, angina estable e inestable. Esta escala fue revisada posteriormente en 2002 por el Third Adult Treatment Panel y por última vez en 2008.[49] Desde entonces ha sido validada para predecir ECV ateroscleróticas (*i.e.,* infarto agudo de miocardio fatal y no fatal, angina o insuficiencia coronaria, evento cerebrovascular isquémico/hemorrágico fatal y no fatal, accidente isquémico transitorio, claudicación intermitente) y no ateroscleróticas (*i.e,* insuficiencia cardíaca).[49] La ecuación de Framingham está basada en una población homogénea, geográficamente limitada, con un predominio de la raza blanca, de ahí que su uso en cohortes modernas haya sido ampliamente cuestionado. Recientemente la ACC y AHA desarrollaron las denominadas New Pooled Cohort Equations. Este nuevo instrumento está validado en una muestra multirracial diseñado para predecir ECV ateroscleróticas (*i.e.,* infarto agudo de miocardio fatal y no fatal, evento cerebrovascular fatal y no fatal), además de estar validado para la población afroamericana.[50-52]

Estos dos métodos cuantitativos que se utilizan en atención primaria establecen el perfil general del RCV. Sabiendo que una puntuación del 10% significa que hay un 10% de probabilidad de tener un ECV en los próximos 10 años.[49] El riesgo absoluto de cada persona puede situarse dentro de unos rangos según la puntuación conseguida; menos del 6% se considera bajo riesgo, entre 6 y 20% se considera de riesgo medio, y una puntuación de 20% o mayor ya se considera alto riesgo.[49] Estas ecuaciones se desarrollan a partir de modelos del riesgo proporcional específicos de sexo y raza, los cuales incluyen variables como la edad, nivel de PAS elevada o no elevada, CT y concentraciones de HDL-C, estado actual de tabaquismo y el historial de DM. Es de resaltar que el porcentaje RCV es siempre más elevado en hombres que en mujeres aun teniendo los mismos valores en el resto de los parámetros que definen el RCV.[49]

En los sistemas de cuantificación del RCV, la edad es el FRCV que más peso ejerce en el cálculo del RCV, de tal forma que personas jóvenes (por ejemplo, menores de 40 años) no alcanzan los umbrales de riesgo alto aun con valores muy elevados de CT y PAS. El problema con los jóvenes es especialmente importante porque dejaríamos de tratar a individuos en situación de riesgo importante hasta que no cumplieran cierta edad en la que alcancen el riesgo absoluto alto, cuando tal vez ya tengan repercusión orgánica y se haya perdido una oportunidad preventiva fundamental. Esta preocupación ya se expresó en la guía europea de prevención CV en 2003

proponiendo la extrapolación del riesgo a la edad de 60 años, y la valoración del riesgo relativo como alternativas complementarias a la valoración del riesgo absoluto en jóvenes.[53]

A pesar de que el método Framingham es el más difundido y utilizado y permite desarrollar modelos predictivos matemáticos[47], a día de hoy no existe una ecuación lo suficientemente precisa a la hora de estimar el RCV.[54,55]

1.3.3. Edad vascular (EV)

La EV según D'Agostino, es la edad cronológica de una persona con el mismo riesgo predicho, pero con todos los factores de riesgo en niveles normales.[53] La EV nos indica la edad que le corresponde a las arterias de un individuo. Es una herramienta para evaluar el RCV general, la cual se deriva de los datos del estudio de Framingham.[5] En comparación a la herramienta que se ha usado hasta ahora (proporción de riesgo de padecer un evento CV en los siguientes 10 años), la EV parece ser un instrumento más sencillo que simplifica la comunicación del estado de riesgo del individuo y podría mejorar la adherencia. Ilustra los años que el individuo puede ganar o perder según controle o no sus FR.[49] La conversión del riesgo absoluto en EV permite comparar la edad cronológica y la EV y obtener una interpretación del riesgo absoluto en el contexto de la edad: si la diferencia entre la edad cronológica y la EV es mínima la situación de riesgo del individuo es tolerable con independencia del valor del riesgo absoluto. Del mismo modo, si la diferencia es elevada, significa que la situación de la persona ocasionada por sus FR es preocupante independientemente de que el valor del riesgo absoluto sea mayor o menor.[53]

Para poder calcular la EV de una persona, se necesita conocer las variables: edad, HDL-C, CT, PAS, DM y tabaquismo. El valor de cada variable recibe un puntaje específico. La sumatoria de los puntos obtenidos con cada variable se puede luego traducir en riesgo de padecer un evento CV en 10 años, o bien, la EV.[49]

1.4. Condición física-Capacidad cardiorrespiratoria (CCR)

La condición física es un indicador muy valioso para hacer referencia al estado de salud de un individuo. Existe evidencia que entre otros FRCV es un predictor más para la ECV y se asocia directamente con una mayor esperanza de vida y longevidad.[56,57] La mejora de la condición física puede tener un rol fundamental en la prevención y tratamiento de la HTA, del sobrepeso y la obesidad y de los FRCV. De todas las cualidades que forman la condición física vinculada con la salud, la capacidad cardiorrespiratoria (CCR) ha sido la que más importancia científica ha adquirido.[58] La CCR se conoce como la capacidad que tienen los sistemas respiratorio y circulatorio de aportar oxígeno a la musculatura esquelética durante una AF continuada.[59,60]

La práctica regular de ejercicio físico mejora la CCR,[59] la cual está asociada con una disminución del RCV, a causa de diferentes adaptaciones fisiológicas a nivel cardiovascular. Por un lado, hay un aumento del tamaño de las cavidades del corazón, mejorando su capacidad de llenado por lo que se incrementa el volumen cardiaco. Como la capacidad de llenado se incrementa, incrementa el volumen sistólico, es decir, la cantidad de sangre que expulsa el corazón cada vez que se contrae. Por lo tanto, la cantidad de sangre que expulsa el corazón cada minuto (gasto cardiaco) también se incrementa. Teniendo en cuenta que en cada latido es capaz de expulsar más sangre aportando más oxígeno a la musculatura esquelética, hay un descenso de la frecuencia cardiaca (FC) de reposo y valores submaximos. Es decir, un mismo esfuerzo mecánico (por ejemplo, correr a 12 km/h) antes de una intervención no farmacológica podría suponer para el organismo un esfuerzo en cuanto a FC de 140 lat/min y después de 4 semanas de entrenamiento aeróbico suponer 130 lat/min. Además, hay disminución de la PA de reposo y PA valores submaximos, es decir, durante el ejercicio se experimentan incrementos más suaves. El ejercicio aeróbico produce una vasodilatación que tiende a disminuir las resistencias vasculares periféricas y en consecuencia disminuir la PA durante el ejercicio. [61]

Así, la valoración de la CCR resulta una información clínica importante en la evaluación del RCV. Recientemente, se ha considerado como signo vital, ya que es un predictor fuerte de mortalidad.[59] Resulta fundamental la valoración de la CCR como punto de partida para la evaluación y seguimiento del RCV, así como para programación de intervenciones no farmacológicas que combinen tratamiento dietético y ejercicio físico (EF).[9]

1.4.1. Valoración de la capacidad cardiorrespiratoria

Los parámetros estrella, conocidos como los "gold standard", para valorar la CCR, así como para la prescripción y diseño del EF son el consumo de oxígeno ($\dot{V}O_2$) máximo o pico ($\dot{V}O_{2max}$ o $\dot{V}O_{2pico}$) y el primer y el segundo umbral ventilatorio (UV1 y UV2) (es decir, los descriptores fisiológicos sobre el transporte y utilización de oxígeno en respuesta al ejercicio).[62,63,64] Estudios recientes demuestran que el VO_{2pico} es el mejor parámetro de referencia para valorar el nivel de salud. Así, las personas con mayor VO_{2pico} tienden a vivir más tiempo, incluso aunque muestren factores de riesgo ya establecidos asociados a ECV u obesidad.[65,66] La unidad de medida del $\dot{V}O_2$ puede expresarse de forma absoluta o de forma relativa a la masa corporal, indicando el consumo en volumen de oxígeno por minuto: $L \cdot min^{-1}$ y $mL \cdot kg^{-1} \cdot min^{-1}$, respectivamente.

Otra forma para expresar la CCR es el MET, del inglés "metabolic equivalent of task", que expresa el costo energético del EF y equivale a 3,5 $mL \cdot kg^{-1} \cdot min^{-1}$. El MET se usa como referencia de la intensidad del EF, que se calculará a partir del gasto metabólico de reposo, o lo que es lo mismo, el costo energético en METs cuando no se está practicando AF.[67,68] Se ha indicado que el incremento de 1 MET en el VO_{2pico} aumenta la esperanza de vida de las personas en un 10-25%.[59,69]

Existen numerosas pruebas de valoración directas e indirectas para determinar la CCR de una persona.[60] El método de referencia es a través de descriptores fisiológicos que determinan de forma directa la intensidad del esfuerzo metabólico, *i.e.* $\dot{V}O_{2pico}$ a través de una prueba cardiopulmonar limitada por síntomas. Sin embargo, no siempre se dispone de la instrumentación para realizar pruebas directas. Por ello, los métodos indirectos pueden monitorizar la carga metabólica durante una prueba de esfuerzo a través de la FC o FC de reserva (FCR=diferencia entre la FC basal y la pico).[59,64]

1.4.1.1. Método directo

Los métodos directos son los métodos más precisos para determinar el $\dot{V}O_{2pico}$ y se conoce a través de medición directa en una prueba de esfuerzo cardiopulmonar (CPET, del inglés *cardiopulmonary exercise test*). Este método tiene lugar bajo condiciones controladas en laboratorios y con aparatos de ergometría, supervisando la intensidad del EF mediante el análisis de gases ($\dot{V}O_2$ y producción de dióxido de carbono, $\dot{V}CO_2$) por la persona que realiza la prueba.[59] La CPET proporciona información sobre la respuesta al ejercicio. El rendimiento CV y los criterios ventilatorios se evalúan durante un estímulo de ejercicio de intensidad progresiva para

proporcionar un análisis integrado de las respuestas fisiológicas requeridas por los sistemas CV y respiratorio para satisfacer las demandas metabólicas del músculo esquelético (es decir, la demanda de O_2 durante el ejercicio).[70,71] La premisa fundamental de la CPET es que la evaluación del intercambio de gases ($\dot{V}O_2$ y $\dot{V}CO_2$) durante el EF proporciona una perspectiva sobre la fisiología general del cuerpo. La CPET refleja la capacidad de rendimiento del corazón, los pulmones, y la sangre para mantener el O_2 y eliminar CO_2 que son críticos para la homeostasis celular. Si hay patología presente que limita la CCR, la CPET puede ayudar a identificar qué partes del sistema fisiológico son las responsables.[70,71]

Las CPET mediante análisis de gases han aumentado significativamente la fiabilidad, reproducibilidad y utilidad clínica puesto que proporciona una cuantificación de la CCR significativamente más precisa.[72] La CPET mediante análisis de gases, nos lleva a la adquisición de VO_2 y proporciona la capacidad de medir tres respuestas durante la inspiración y la espiración: 1) la concentración de O_2; 2) la concentración de CO_2; y 3) una cuantificación de la ventilación, generalmente la ventilación minuto, es decir, la cantidad de gas inhalado o exhalado por minuto, que se consigue a partir de volumen corriente y frecuencia respiratoria. El intercambio de O_2 y CO2 se evalúa mientras se respira aire usando una máscara facial que cubre la nariz y la boca simultáneamente.[70] Los gases inhalados y exhalados se analizan en tiempo real utilizando analizadores de respuesta rápida, conectados al ordenador. Una interpretación de prueba válida depende crucialmente de la calibración del flujo de aire y los gases (O_2 y CO2) que se realiza antes de la prueba.[73] Los nuevos sistemas también se ajustan teniendo en cuenta las condiciones ambientales que afectan la concentración de O_2 en el aire inspirado (es decir, temperatura, presión barométrica y humedad).[70]

1.4.1.2. Método indirecto

El método indirecto para determinar el VO_{2pico} se basa en la presunción de que existe una relación directa entre la FC y el $\dot{V}O_2$. Por lo tanto, se estima que el $\dot{V}O_{2pico}$ se puede predecir con valores de la FC. El % de FCR ha sido adoptado por el Colegio Americano de Medicina del Deporte como el método de referencia para la evaluación indirecta y para establecer los rangos de diseño del EF (Tabla 9).[64]

Estos tipos de pruebas son más sencillas, requieren menos aparatos, son más económicas y tardan menos en ser preparadas y ejecutadas. Existen gran variedad de métodos para estimar la CCR o valores de $\dot{V}O_2$ submáximos sin medición directa, como pruebas de esfuerzo, diversos

test de campo que simulan el CPET, y ecuaciones de regresión para estimar el $\dot{V}O_{2pico}$. Los métodos alternativos al CPET son cada vez más utilizados y en poblaciones con características específicas. Por supuesto, el valor VO_{2pico} extraído de una prueba submáxima resultará menos exacto que aquel determinado en una prueba directa,[60] que conlleva un error de estimación entre 4,2 y 7,0 mL de$O_2 \cdot kg^{-1} \cdot min^{-1}$, por lo que se recomienda la obtención de esta información a través de un modo objetivo y directo cuando esté disponible, especialmente para la valoración de personas con RCV.[59]

Las pruebas de campo y demás métodos de estimación del $\dot{V}O_{2pico}$ resultan en una valoración eficaz que permite hacer seguimiento de la CCR a lo largo del tiempo, y en el caso de tratamientos con EF, facilitan el diseño de la intensidad de ejercicio.[60] Ejemplo de ello es la prueba incremental de ida y vuelta caminando (incremental shuttle walk test, ISWT),[74] o su variante (modified shuttle walk test, MSWT),[75] pruebas de campo de aplicación sencilla que han sido probadas y validadas para estimar el $\dot{V}O_{2pico}$ en distintas poblaciones a partir de la distancia recorrida y otras variables registradas en la misma prueba.[76]

Tabla 9. Rangos de intensidad y modalidades para el diseño de las zonas de entrenamiento del ejercicio físico aeróbico

RANGOS	FC o VO_2	%FCR	$\%FC_{pico}$	Escala RPE	Test del Habla	Modalidad de EF
R1-Ligero-moderado	<UV1	<50	<60	<12	Fácil llevar conversación	Continuo
R2-Moderado-alto	UV1-UV2	50-75	60-80	12-16	Conversación con esfuerzo. No se puede cantar	Continuo
R3-Alto-Severo	UV2-Pico	75-100	80-100	16-19	Sólo palabras sueltas	Interval
R4-Severo-Extremo	>Pico	>100	>100	>19	No se puede hablar	Interval

FC: frecuencia cardiaca; VO_2: consumo de oxígeno; FCR: frecuencia cardiaca de reserva; FC_{pico}: frecuencia cardiaca pico; RPE: valores escala de Borg (6-20); UV1: primer umbral ventilatorio: UV2: segundo umbral ventilatorio. Modificado de *Mezzani et al., 2012. Aerobic Exercise Intensity Assessment and Prescription in Cardiac Rehabilitation.*

1.5. Tratamiento no farmacológico

La HTA está íntimamente asociada al exceso de masa corporal, mientras que la pérdida de masa corporal se acompaña de reducciones significativas en la PA.[77,78] En un meta-análisis publicado en el año 2003 los autores concluían que una pérdida de masa corporal de 5,1 kg se asociaba con una reducción en la PAS y PAD media de 4,4 y 3,6 mmHg, respectivamente.[77] Los estudios indican que la HTA y la obesidad son dos de las causas de morbilidad y mortalidad prematura más prevenibles a nivel mundial, que pueden ser tratadas de forma efectiva, disminuyendo de esta forma la ocurrencia de las ECV, y que si la HTA no es tratada, está asociada a una elevación progresiva en la PA, a menudo culminando en estado resistente al tratamiento, debido a daño vascular y renal asociado.[8,10,78] Así, a los individuos con sobrepeso e HTA se les recomienda perder masa corporal para reducir el riesgo de morbi-mortalidad.[9,79] La ESH y ESC recomiendan mantener un IMC saludable (≤ 25 kg/m^2) y evitar la acumulación de grasa abdominal (perímetro de la cintura <102 cm en hombres y <88 cm en mujeres) tanto en la prevención, como en el tratamiento de la HTA. Además, la pérdida de masa corporal mejora la eficacia de la medicación antihipertensiva y el perfil cardiometabólico de los individuos.[9]

Como medida para la reducción del RCV, se proponen distintos tratamientos; dependiendo de la estratificación del RCV se recomiendan cambios en el estilo de vida, y adicionalmente tratamiento farmacológico.[9,10] Se calcula que el 80 % de ECV puede prevenirse mediante cambios en los estilos de vida.[19] La evidencia científica muestra que la combinación de EF y alimentación saludable podrían ser los mejores aliados en el tratamiento de la pérdida de

masa corporal, consiguiendo una mejora sustancial de la salud,[80] siendo la AF el mejor mecanismo en el mantenimiento de esta pérdida a lo largo del tiempo,[34] gracias a un aumento de la oxidación de las grasas preferentemente de la región central del cuerpo.[34]

Gran cantidad de literatura científica describe la relación entre PA elevada con el estilo y hábitos de vida. Las medidas de estilo de vida deben instaurarse en todas las personas con HTA con el objetivo de reducir la PA, controlar otros FR y trastornos clínicos, así como reducir el número de dosis de fármacos anti-hipertensivos que se podría tener que consumir.[9] Entre los múltiples factores de estilo de vida, que se asocian con la etiología o el tratamiento no farmacologico de la HTA así como del sobrepeso y la obesidad, destacan el EF y la alimentación saludable a través de un modelo de dieta específico. Se han encontrado reducciones de PA estadísticamente significativas, en intervenciones independientes de corta duración que mejoraban la calidad de la dieta, implementaban EF o terapias de relajación, y reducían la ingesta de sodio y el consumo de alcohol (Figura 1). Así, se estima que una intervención que combine tratamiento dietético y EF podría reducir la PAS y PAD alrededor de 5 mmHg de promedio.[8]

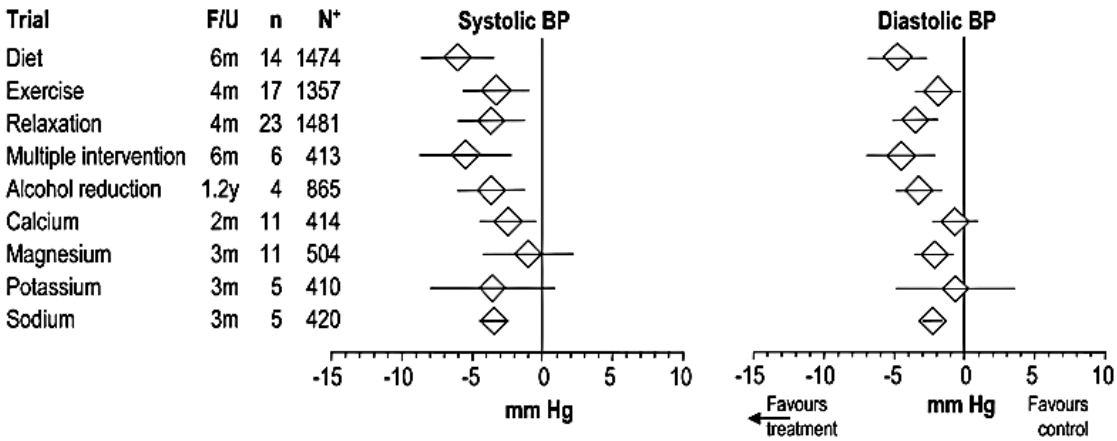

Figura 1. Visión general del efecto de los cambios en el estilo de vida sobre la presión arterial sistólica y diastólica en estudios realizados mediante ensayo aleatorizado en personas con presión arterial ≥140/85 mmHg.[8]

La PAS (y en menor medida la PAD) tiende a elevarse con la edad.[8] Analizar el estilo de vida ayuda a identificar posibles hábitos causantes de tener una PA elevada y a comenzar con una

vida más saludable retrasando el comienzo del tratamiento farmacológico, e incluso reducirlo o desecharlo por completo.

La toma de decisiones clínicas en relación con el inicio del tratamiento, la clase de tratamiento y el objetivo de PA que se desea alcanzar se deberá basar en la evaluación de la PA y RCV. El tratamiento tendrá como meta alcanzar la máxima reducción del riesgo de morbilidad y mortalidad CV a largo plazo; esta meta requiere un tratamiento de todos los factores de riesgo reversibles identificados.[9] En la Tabla 10 se muestra el tratamiento anti-hipertensivo recomendado, dependiendo de la PA y de otros factores que aumentan el RCV.[9]

Tabla 10. Inicio de cambios en el estilo de vida y tratamiento farmacológico. Se indican los objetivos del tratamiento. Recuperado de: *2013 ESH/ESC Guidelines for the management of arterial hypertension*

	Presión arterial (mmHg)			
Otros factores de riesgo, DO asintomático o enfermedad	Normal alta PAS 130–139 o PAD 85–89	HTA grado 1 PAS 140–159 o PAD 90–99	HTA grado 2 PAS 160–179 o PAD 100–109	HTA grado 3 PAS≥180 o PAD ≥110
SIN Otros FR	No intervención en PA	• Cambios en el estilo de vida durante varias semanas. Después añadir fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida durante varias semanas. Después añadir fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida • Tratamiento inmediato anti HTA con objetivo<140/90
1–2 FR	• Cambios en el estilo de vida • No intervención en PA	• Cambios en el estilo de vida durante varias semanas. Después añadir fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida durante varias semanas Después añadir fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida • Tratamiento inmediato anti HTA con objetivo<140/90
≥3 RF	• Cambios en el estilo de vida • No intervención en PA	• Cambios en el estilo de vida durante varias semanas. • Después añadir fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida • Fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida • Tratamiento inmediato anti HTA con objetivo<140/90
DO, ERC de grado 3 o diabetes mellitus	• Cambios en el estilo de vida •	• Cambios en el estilo de vida • Fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida • Fármacos anti HTA con objetivo <140/90	• Cambios en el estilo de vida • Tratamiento inmediato anti HTA con objetivo<140/90
ECV sintomática, ERC de grado ≥4 o diabetes con DO/FR	• Cambios en el estilo de vida • No intervenir sobre la PA	• Cambios en el estilo de vida • Tratamiento anti HTA con objetivo <140/90	• Cambios en el estilo de vida Tratamiento anti HTA con objetivo <140/90	• Cambios en el estilo de vida • Tratamiento inmediato anti HTA con objetivo<140/90

CV: Cardiovascular; DO: Daño orgánico; ECV: enfermedad cardiovascular; ERC: enfermedad renal crónica; FR: factor de riesgo; HTA: hipertensión arterial; PA: Presión arterial; PAD: Presión arterial diastólica; PAS: Presión arterial sistólica.

1.5.1 Tratamiento dietético

La reducción calórica es el componente más importante para lograr la pérdida de masa corporal, mientras que el aumento y mantenimiento de la AF es particularmente importante en el mantenimiento de la pérdida de masa corporal.[81] La pérdida de masa corporal depende principalmente de la reducción de la ingesta calórica total, no de las proporciones de hidratos de carbono, grasas y proteínas en la dieta.[81] La distribución de los macronutrientes, la proporción de calorías procedentes de hidratos de carbono, grasas y proteínas, serán determinadas por el nutricionista de acuerdo con la situación clínica del individuo.[26] Como se muestra en la Tabla 11, la prescripción dietética puede variar de acuerdo con el perfil metabólico de la persona y de los FRCV que presente.

Tabla 11. Recomendaciones dietéticas para los distintos componentes del síndrome metabólico en individuos con sobrepeso u obesidad.[82]

Componentes del síndrome metabólico	Recomendaciones dietéticas
Perímetro de cintura aumentada	Dieta hipocalórica
Tensión arterial elevada (sistolica≥130mmHg y/o diastólica ≥85mmHg)	Dieta DASH
Nivel de glucosa elevado en sangre ≥5,5mmol/L(100mg/dL)	Dieta hipocalórica controlada en hidratos de carbono
Nivel de triglicéridos elevado en sangre ≥1,7 mmol/L(≥150mg/dL)	Dieta hipocalórica mediterránea o cambios en el estilo de vida.
Bajo nivel de colesterol HDL-C <1,0 mmol/L(40mg/dL) hombres <1,3 mmol/L(50mg/dL) mujeres	Dieta hipocalórica mediterránea o cambios en el estilo de vida.

DASH, Estrategias Alimentarias para Detener la Hipertensión Arterial. Todas las dietasdeben ir acompañadas de ejercicio físico para obtener el maximo beneficio metabolico; HDL-C, lipoproteínas de alta densidad.

La calidad y la composición de la dieta es un factor de riesgo modificable que tiene efectos contrastados en la prevención de la ECV y la mortalidad. La modificación de los hábitos dietéticos y la adherencia a un patrón dietético saludable es particularmente importante en las personas de edad media consideradas como de alto riesgo.[83] En las dos últimas décadas, distintos trabajos han mostrado la eficacia de la adherencia al patrón dietético conocido como dieta DASH (del inglés, *Dietary Approaches to Stop Hypertension*, "Estrategias dietéticas para frenar la hipertensión arterial") en la reducción de la PA, la mejora del estado de salud y la calidad de vida, la prevención de la ECV, el síndrome metabólico, la DM y la mortalidad por todas las causas en distintas poblaciones.[81] La dieta DASH es muy rica en verduras y frutas y productos lácteos bajos en grasa e incluye productos de granos

entero, pescado y aves y frutos secos como las nueces. Sin embargo, es una dieta pobre en carnes rojas, dulces, azúcares añadidos y bebidas azucaradas. De esta forma, la dieta es baja en grasa (<30% de la energía), con predominio de la grasa insaturada y con un bajo aporte de grasa saturada (≤6% de la energía), tiene una mayor proporción de energía derivada de las proteínas que en las recomendaciones habituales (≈18% de la energía), y algo más alta de lo habitual también en hidratos de carbono (≈55% de la ingesta energética) y fibra. Entre los micronutrientes destacan por su abundancia el potasio, calcio y magnesio.[84]

Además, diferentes estudios han mostrado que la combinación de dieta DASH con reducción del aporte de sodio es el tratamiento dietético más efectivo para reducir la PA.[84] Así, las ESH/ESC recomiendan la reducción de los aportes de sodio en la dieta como estrategia complementaria para la reducción de la PA en personas con HTA.[9]

1.5.2. Tratamiento mediante ejercicio físico

Todas las guías internacionales[9,85-87] promueven la AF y la práctica de EF como una herramienta no farmacológica esencial para la prevención y el tratamiento de la HTA primaria y obesidad; así como y para reducir el RCV y mortalidad, induciendo mejoras sustanciales en la salud física y mental.[4] Son muchos los estudios realizados acerca del efecto que tiene el EF en la PA, tanto en personas con HTA como con normo-tensión, así como en la composición corporal de personas con distintos niveles de IMC. El EF afecta de forma favorable a los factores de RCV. Además de la reducción de la PA, trae consigo otros beneficios para la salud CV, como reducción de la masa corporal, de la adiposidad visceral y total, del perímetro de cintura, de la resistencia a la insulina, de concentraciones de LDL-C y aumento de concentraciones de HDL-C y CCR.[9] El RCV se ve también disminuido por la mejora de la CCR, por pequeña que esta sea;[88] el riesgo resulta menor cuanto mayor es la CCR, llegando a considerar que las personas en baja forma física tienen el doble de riesgo de muerte, independientemente del IMC.[89]

Para el tratamiento de la obesidad, la dosis de EF recomendada no varía en exceso de unas guías a otras.[24,49] La combinación de EF y dieta según la evidencia científica son los mejores aliados de la pérdida de masa corporal, siendo la AF el mejor mecanismo en el mantenimiento de esta pérdida a lo largo del tiempo,[34] gracias a un aumento de la oxidación de las grasas preferentemente de la región central del cuerpo.[34] Prescribir programas de EF en esta dirección constituye un enfoque fundamental para conseguir éxito en la población obesa.[90]

Se ha analizado la respuesta de la PA, composición corporal y CCR frente a los principios FITT (*i.e.,* frecuencia, intensidad, tiempo y tipo) con el fin de encontrar la dosis óptima de EF y poder diseñar de una forma sistemática, progresiva e individualizada. La frecuencia del ejercicio (número de sesiones por semana) y la duración o volumen (duración de cada sesión o ejercicio) son características importantes de un programa de ejercicios, pero un factor igualmente importante es la intensidad (el grado del esfuerzo al que se realiza la actividad) y el tipo de ejercicio (patrón de entrenamiento).[18] A continuacion se presentan las recomendaciones de ejercicio fisico junto a las investigaciones que reafirman el efecto del EF en la HTA.

Frecuencia

Todas las organizaciones profesionales[91-95] recomiendan hacer EF el mayor número de días a la semana, preferiblemente todos los días de la semana ya que la PA es menor en los días que las personas hacen EF en comparación con los días que no hacen EF. Esta respuesta fisiológica se conoce como hipotensión post-ejercicio, y sucede con tan solo una sesión de EF aeróbico.[96,97] La hipotensión es la reducción inmediata de la PA de 5-7 mmHg en personas con HTA que ocurre después de una única sesión aislada de EF aeróbico de diferentes duraciones (10-50 min) e intensidades (40%-100% VO_{2pico}).[98] Durante el EF, la PAS se eleva progresivamente a medida que la carga de entrenamiento aumenta. En esfuerzos pico la PAS alcanza aproximadamente 200 mmHg, aunque en algunas personas se puede elevar sustancialmente más, como en el caso de las personas hipertensas, que parten de una PA de base más elevada. La PAD, en cambio, permanece alrededor de los valores de reposo.[88] Una vez cesa el estímulo de entrenamiento, el efecto anti-hipertensivo del EF aeróbico es inmediato: la PAS y la PAD disminuyen y se pueden mantener durante más de diez horas por debajo de los valores pre-ejercicio. [98] (Figura 2). Los méritos de la hipotensión post-ejercicio como estilo de vida antihipertensiva están respaldados por estudios recientes que han mostrado que cuando se realiza EF aerobico de forma regular durante meses la PAS y PAD de reposo reduce hasta 8,3 y 5,2 mmHg, respectivamente,[88,99] y mejora la salud general y los FRCV.[100] Además de la hipotensión post-ejercicio, otra razón para la recomendación de hacer EF el mayor número de días de la semana es que los adultos con HTA a menudo tienen sobrepeso u obesidad, y una alta frecuencia (días por semana) o volumen (minutos por semana) de EF es necesario para lograr el gasto calórico requerido para la pérdida de masa corporal inicial y el mantenimiento prolongado de esa pérdida de masa corporal.[101] En este sentido, realizaron un estudio en 201 mujeres con sobrepeso, durante un periodo de dos años, las cuales fueron divididas en diferentes grupos, combinando EF y dieta. La AF fue de 150, 200 o 275 minutos a la semana. Los resultados mostraron que las mujeres que realizaron una media de 275 minutos de EF a la semana mantenían la masa corporal perdida. Además, la pérdida de masa corporal (13 kg) fue significativamente

superior comparando con los otros dos grupos con 200 (6,5 kg) y 150 (3,5 kg) minutos respectivamente de EF por semana. Observando los efectos a largo plazo, las mujeres que realizaron EF durante 200 minutos/semana, mostraron tendencia a recuperar la masa corporal.[102]

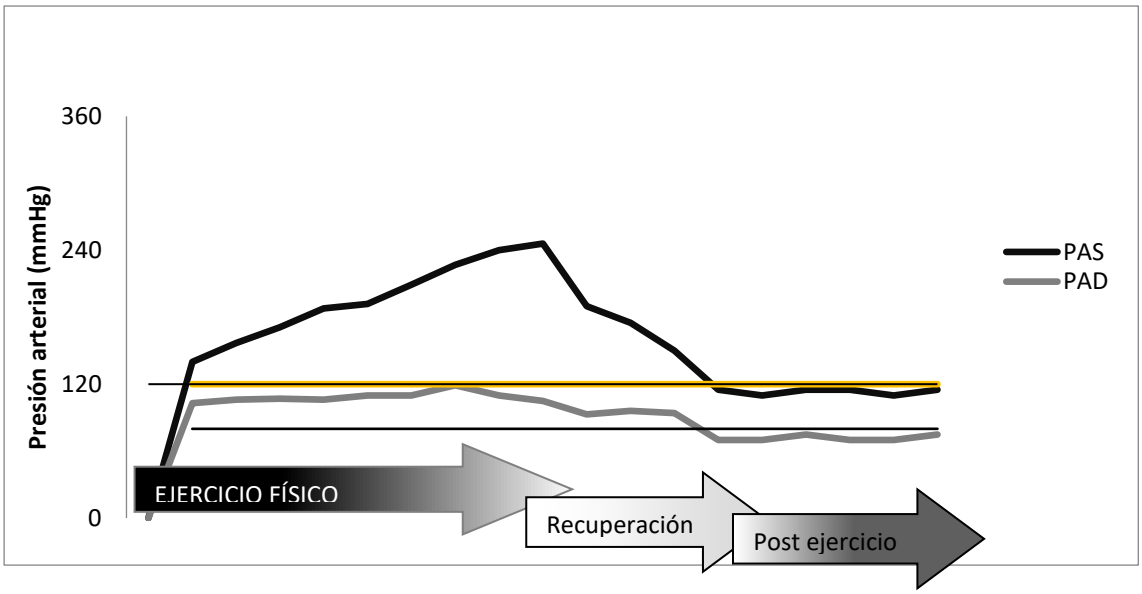

Figura 2: Respuesta característica de la tensión arterial durante el ejercicio físico, periodo de recuperación y post ejercicio (aproximadamente 10h). PAS: presión arterial sistólica; PAD: presión arterial diastólica. Datos reales estudio EXERDIET-HTA *(Maldonado et al., 2016. Effects of different aerobic exercise programs with nutritional intervention in primary hypertensive and overweight/obese adults: EXERDIET-HTA controlled trial)*

Intensidad

El Comité Nacional Conjunto[91] y Grupo de trabajo Estilo de Vida,[92] AHA,[93] Colegio Americano de Medicina del deporte (ACSM),[103] ESH/ESC[9] y Programa de Educación de Hipertensión Canadiense[95] están de acuerdo que una sesión de EF aeróbico a intensidad moderada, durante 20-40 minutos reduce sistemáticamente la PAS/PAD en los adultos hipertensos.[98] Asimismo, se estima que la AF regular de baja intensidad y duración se asocia con una reducción de la mortalidad del 20%.[104] Cabe destacar que distintos estudios muestran que el EF aeróbico a intensidad vigorosa (como por ejemplo, EF aeróbico interválico) reducen la PA.[98,105-108]

El entrenamiento aeróbico continuo se refiere cuando la persona es capaz de llevar a cabo un EF aeróbico en un periodo de tiempo determinado de forma continua con una intensidad ligera-moderada-alta. En cambio el entrenamiento aeróbico interválico, consiste en alternar periodos intensos de EF aeróbico con periodos de recuperación activos de moderada intensidad o pasivos (Figura 3).[18] La proporción de alta intensidad/ligera-moderada intensidad es la base del diseño del EF interválico. Así,

se pueden diseñar entrenamiento interválico de baja intensidad (*low intensity interval training, LIIT*) y entrenamiento interválico de alta intensidad (*high intensity interval training, HIIT*).[18] Los programas HIIT presentan una proporción superior en volumen de tiempo en el intervalo a intensidad alta con respecto al tiempo en el intervalo en la intensidad de recuperación. Como, por ejemplo, 4 minutos en alta intensidad alternado con cargas de recuperación de 3 minutos a moderada intensidad (*i.e.* SERIE 1=4/3minutos, Figura 4). Por el contrario, los programas LIIT presentan una proporción inferior en volumen de carga en minutos a intensidad alta con respecto al tiempo de recuperación. Asimismo, el protocolo más utilizado, suele ser 30 seg en intensidad alta y 60 seg en intensidad moderada (*i.e.* SERIE 1=30/60seg, Figura 5).[18]

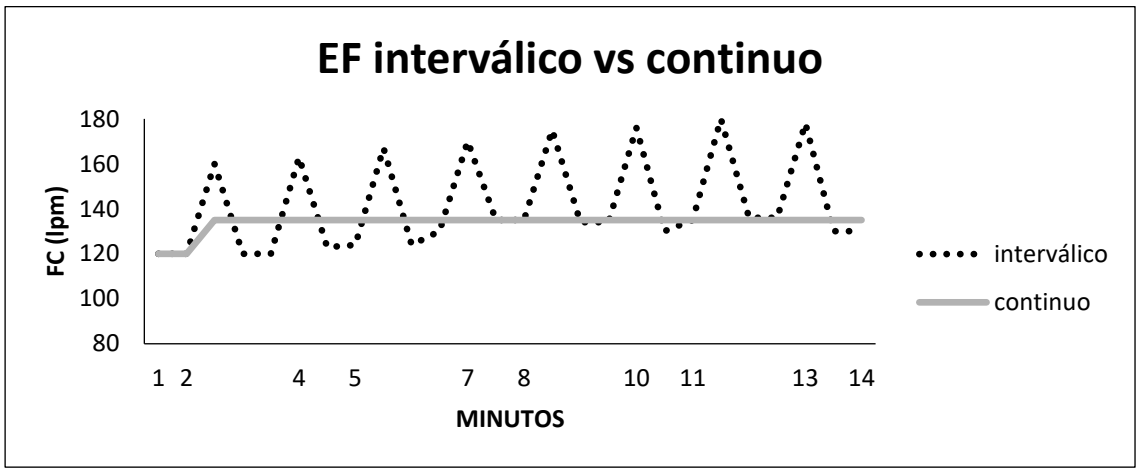

Figura 3. Respuesta de la frecuencia cardiaca (FC) en latidos por minuto (lpm) a un ejercicio interválico (alternancia de intensidades altas y moderadas) y un ejercicio continuo (intensidad moderada). Datos reales estudio EXERDIET-HTA *(Maldonado et al., 2016. Effects of different aerobic exercise programs with nutritional intervention in primary hypertensive and overweight/obese adults: EXERDIET-HTA controlled trial)*

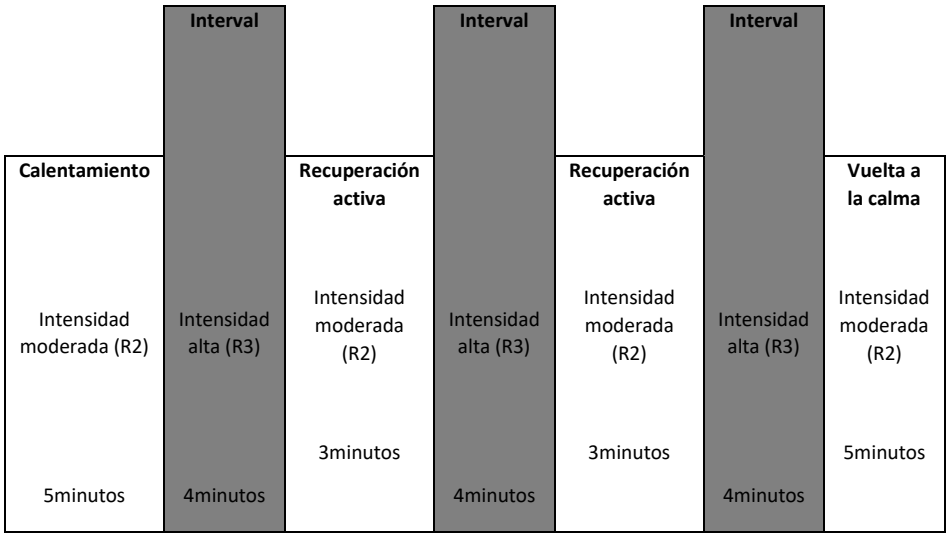

Figura 4. Protocolo tradicional de "High Intensity Interval Training (HIIT, 4/3minutos). Adaptado de *Mezzani et al. 2012. Aerobic Exercise Intensity Assessment and Prescription in Cardiac Rehabilitation*

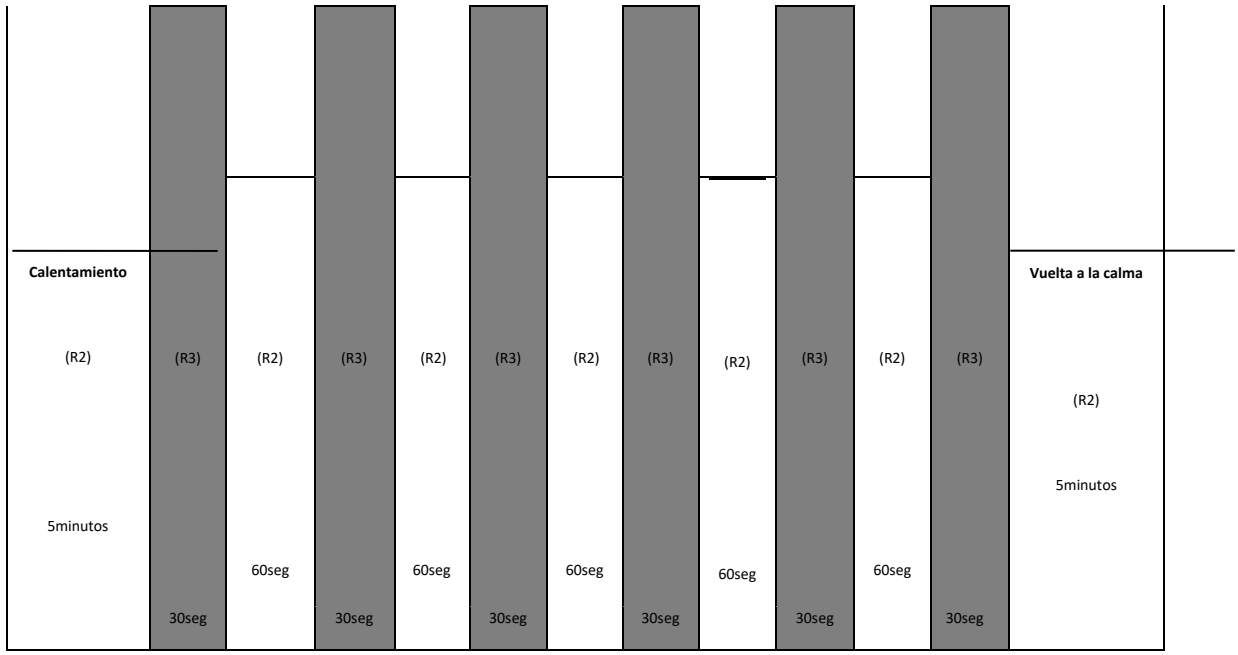

Figura 5. Protocolo tradicional de *Low Intensity Interval Training (*LIIT, 30/60seg). Adaptado de *Guiraud et al. 2012. High-Intensity Interval Training in Cardiac Rehabilitation.*

En cuanto al ejercicio de alta intensidad, algunos autores como Pescatello et al. (1991),[109] no encontraron diferencias entre distintas intensidades de EF.[109] Quinn et al.(2000),[110] sin embargo, analizaron el efecto en la PA después de una sesión de ejercicio aeróbico a dos intensidades diferentes (50% *vs*. 75% VO_{2max},) y en contraste con los hallazgos previos, los resultados mostraron que la reducción de la PA después de una sesión de EF aeróbico dependía de la intensidad, observando disminuciones de la PA más pronunciadas con intensidades de EF mayores. Los participantes hipertensos promediaron una disminución de la PAS y PAD de 4 y 5 mmHg al 50% VO_{2max}, y una disminución de 9 y 7 mmHg al 75% VO_{2max}, respectivamente.[110] Además, Quinn et al. (2000),[110] observaron que el efecto hipotensivo del EF dura más cuando mayor es la intensidad, 4 h al 50% VO_{2max} y hasta 13 h al 75% VO_{2max}.[98] Acorde a este último, Eicher et al.,[111] Morais et al.,[112] y Lima et al.,[113] afirmaron que el ejercicio a una intensidad igual o superior al 75% VO_{2max} produce efectos de hipotensión mayores en comparación con una intensidad baja o moderada en individuos hipertensos y prehipertensos.

No obstante, ya son varios los estudios realizados acerca del efecto que tiene el entrenamiento aeróbico interválico en la PA y CCR. Gunjal et al.[114] estudiaron los efectos de 12 semanas de HIIT en 30 personas con HTA y después de la intervención, la PAS y PAD disminuyeron 12mmHg y 8 mmHg, respectivamente (Tabla 12). Del mismo modo, Nemoto et al.,[115] analizaron a 24 personas durante cinco meses desarrollando un entrenamiento de HIIT y vieron que el grupo que realizó entrenamiento

aeróbico interválico obtuvo una reducción significativa de la PA y además una mejora del 9% de la CCR (Tabla 12). Esto ha sido reforzado por otros autores, como, Tjonna et al.,[116] Guimaraes et al.[117] y Molmen-Hansen et al.[118] que examinaron el efecto de HIIT en adultos hipertensos en comparación con entrenamiento aeróbico continuo. Por ejemplo, Molmen-Hansen et al.[118] concluyeron que después de 12 semanas de EF, la PAS/PAD se redujo 12/8 mmHg en el grupo HIIT y 4,5/3,5 mmHg en entrenamiento aeróbico continuo y que solo en el grupo HIIT se encontró una resistencia vascular reducida.[118] Sin embargo, Guimares et al, no observaron diferencias entre ambos grupos en la reducción de la PA, pero la rigidez arterial, se redujo solo en el grupo HIIT.[117]

Tabla 12: resumen de diferentes estudios que analizan el efecto que tiene el entrenamiento aeróbico interválico en la PA y CCR

Estudio	PAS (mm Hg)	PAD (mm Hg)	Medicación	Tipo de HIIT	Duración	Intensidad del ejercicio(%$VO_{2max/pico}$)	Mejora de la CCR
Gunjal et al.,[114]	↓12	↓8	U	3X (4'/4'RA) Cinta	12sem	75-80%	NA
Nemoto et al.,[115]	↓10	↓5	U	5x(3'/3'RA)	20 sem	70-80%	NA ↑9%
Tjonna et al.,[116]	↓9	↓6	U	4X(4'/3'RA)	16 sem	80%	↑35%
Munk et al.,[119]	↔	↓4	T	4X(4'/3'RA)	24 sem	70-80%	↑17%
Rognmo et al.,[120]	↔	↔	U	4X(4'/3'RA)	10 sem	80-90%	↑18%
Wisloff et al.,[121]	↔	↔	T	4X(4'/3'RA)	12 sem	85%	↑46%
Guimaraes et al.,[117]	↓2	↓2	T	13 x (1'/2'RA)	16 sem	80-90%	NA
Molmen-Hansen et al.,[118]	↓12	↓8	U	4X(4'/3'RA)	12 sem	80-90%	↑15%

CCR, Capacidad cardiorrespiratoria; HITT, high intensity Interval training; PA, presión arterial; PAS, presión arterial sistólica; PAD, presión arterial diastólica; RA, Recuperación activa.

Por otro lado, los protocolos HIIT de bajo volumen resultan estrategias más eficientes en el tiempo que han demostrado que "menos" puede ser "más", mostrando mejoras tanto en poblaciones sanas[122-124] como en individuos con HTA primaria, DM,[125,126] y ECV.[127] Teniendo en cuenta que la "falta de tiempo" es una de las barreras más comunes para las personas, un HIIT de bajo volumen podría ser una estrategia interesante al inicio de un programa de EF supervisado, si los beneficios fisiológicos son comparables a los HIIT de alto volumen. Parece que las cargas cortas e intensas de actividad con HIIT de bajo volumen podrían inducir un estímulo efectivo para los componentes centrales (cardiovasculares) y periféricos (músculo esquelético) que conducen a una mejora rápida en la CCR.[128] Sin embargo, aún no se sabe si el HIIT de bajo volumen, que implica un menor gasto de energía derivado del entrenamiento

y compromiso de tiempo, puede ser tan eficaz como el HIIT de alto volumen para mejorar la HTA, ECV y la composición corporal.

Los estudios afirman que el efecto reductor del EF en la HTA depende de la intensidad del ejercicio y que el HIIT es un método efectivo para disminuir la PA, aumentar la CCR y disminuir la resistencia vascular.[114-116,118-120] A pesar de todo, la frecuencia, la intensidad, la duración y la modalidad de HIIT óptima para diferentes grupos de individuos hipertensos todavía está sin establecerse.

Tiempo

Todas las guías internacionales[9,85-87] recomiendan realizar al menos 30 minutos de ejercicio físico al día como tratamiento no farmacológico esencial para la prevención y el tratamiento de la HTA y obesidad. Como en el caso de la frecuencia, de realizar ejercicio el mayor número de días por semana, preferiblemente todos los días, existe unanimidad entre las organizaciones profesionales, que la duración de los ejercicios debe alcanzar un total de 150 o más minutos por semana; una cantidad que es equiparable con las recomendaciones para la población general.[101,129] Hay suficiente evidencia que afirme que el EF aeróbico realizado de forma continua en una sola sesión o acumulando en series más cortas durante todo el día tiene un efecto hipotensivo similar en adultos con HTA.[130-132] Por ejemplo, Bhammar et al.,[133] compararon los efectos del EF aeróbico fraccionado (3 series de 10 minutos) intercaladas durante el día (mañana, mediodía y tarde) y el ejercicio aeróbico continuo (una sesión de 30 minutos) en la PA entre 11 participantes jóvenes con prehipertensión y descubrieron que el EF fraccionado era tan eficaz como el EF continuo para producir un efecto hipotensivo post-ejercicio hasta la mañana siguiente. [133] Acorde a este último, Miyashita et al.,[134] encontraron que incluso series más cortas de EF aeróbico (10 series de 3 min) intercaladas a lo largo del día fueron tan efectivas como una sesión de 30 minutos de EF aeróbico continuo para provocar una reducción de la PA.[134] Algo similar ocurre con la masa corporal, algunos autores se cuestionan realizarlo en pequeños bloques de 10 a 15 minutos.[90] A priori, no hay evidencia científica de que esto ayude o colabore a una mayor o menor reducción de la masa corporal. De hecho, se compararon el ejercicio continuo e intermitente, durante un periodo de 18 meses, y su efecto sobre diferentes parámetros, no observando diferencias en cuanto a la pérdida de masa corporal durante los 18 meses de estudio. Un grupo de mujeres realizó 3 veces por semana, 30 minutos al 60-75% de su máxima capacidad aeróbica; y otro grupo, realizó 5 veces por semana, paseos a un buen ritmo, dos veces al día, 15 minutos cada vez. Los resultados marcaban mejoras del 8 y 6 % para el grupo de trabajo continuo e intermitente respectivamente, aunque las diferencias para el grupo de trabajo continuo fueron superiores.[102,135]

Ya que la "falta de tiempo" es una de las barreras más comunes para las personas para comenzar y mantener un programa de EF de forma regular, la realización del EF fraccionado (series de ejercicios de corta duración acumuladas a lo largo del día), parece ser una opción terapéutica atractiva entre los adultos con HTA.[130-132] No obstante, un trabajo físico de carácter intermitente, puede estar justificado en población obesa, dado que suelen ser individuos con cierta aversión por el ejercicio en general, o por el ejercicio continuo en particular. [102,135]

Tipo

Existe un amplio consenso respaldado por una fuerte evidencia científica de que el EF aeróbico debe prescribirse como el tipo de EF principal para la prevención, el tratamiento y el control de la HTA y obesidad. Esta recomendación es hecha por todas las organizaciones y guías internacionales debido a que se ha demostrado constantemente de que el EF aeróbico desciende la PA 5-7 mmHg en personas con HTA, efectos hipotensivos que son dos veces mayores en comparación con el efecto reductor del entrenamiento de fuerza.[94] La AHA,[93] ACSM,[103] ESH/ESC[9] y el Programa de Educación de Hipertensión canadiense[95] recomiendan que los adultos con HTA realicen entrenamientos de fuerza como complemento del entrenamiento aeróbico, mientras que otros como, Comité Nacional Conjunto,[91] y el Grupo de trabajo Estilo de Vida,[92] no hacen recomendaciones específicas sobre el entrenamiento de fuerza. El entrenamiento de fuerza no disminuye la masa corporal, pero resulta en cambios de la composición corporal, aumentando la masa muscular y disminuyendo la masa grasa.[25] Por otro lado, las guías[24,49] para el manejo de la obesidad, aconsejan combinar el entrenamiento aeróbico con tres sesiones no consecutivas de entrenamiento de fuerza a la semana. El entrenamiento de fuerza no disminuye la masa corporal, pero resulta en cambios de la composición corporal, aumentando la masa muscular y disminuyendo la masa grasa.[25]

El nivel de evidencia sobre el cual las recomendaciones sobre el entrenamiento de fuerza sean mínimas, puede contribuir a la falta de consenso entre las organizaciones respecto a la efectividad del entrenamiento de fuerza como terapia antihipertensiva. Una posible razón por la cual se debilita la evidencia se puede atribuir principalmente a la escasez de estudios que hayan examinado el entrenamiento de fuerza como tratamiento no farmacológico de la HTA.[10,99,103,106,130] De hecho, diferentes estudios han examinado el efecto de una sesión ejercicio de fuerza dinámica en la PA de hipertensos adultos. Por ejemplo, Hardy y Tucker[136] administraron un programa de fuerza dinámica en adultos hipertensos y encontraron un pequeño efecto de hipotensión post-ejercicio sobre la PAS que duraba hasta 1 hora. Resultados similares fueron encontrados por Morlaes et al.[137] y Melo et al.[138] que encontraron un efecto de hipotensión post-ejercicio que duraba hasta 10 h. Sin embargo, según las investigaciones sobre la práctica regular de un entrenamiento de fuerza dinámica regular a largo plazo

no influye en la PA de los hipertensos[106,107]. Hasta el momento carecemos de datos científicos que reafirmen estas teorías ya que el número de estudios que han examinado el efecto del entrenamiento de fuerza en la PA de adultos hipertensos es mínimo.[108]

1.5.2.1 Recomendaciones actuales de ejercicio físico

Las personas con HTA y sobrepeso u obesidad deben recibir consejo y asesoramiento para realizar AF al menos 30 minutos a intensidad moderada (60-70% de FC máxima objetiva) diariamente.[103,106] Aunque existe un consenso general para recomendar el EF continúo de intensidad moderada-alta como terapia antihipertensiva, las diferentes asociaciones internacionales integran también el ejercicio de intensidad alta-severa a través del entrenamiento HIIT, debido a que la reciente evidencia científica muestra su eficacia en la reducción de la PA.[9,10]Las guías de práctica clínica citadas[6,16] se centran primordialmente en los indicadores de RCV más conocidos, como la PA y composición corporal, y consideran otros indicadores como la CCR para barajar comorbilidades, y para evaluar y hacer seguimiento de la condición física.[120,130,139]

Se ha analizado la respuesta de la PA, composición corporal y CCR frente a los principios FITT (*i.e.,* frecuencia, intensidad, tiempo y tipo) con el fin de encontrar la dosis óptima de EF y poder diseñar de una forma sistemática, progresiva e individualizada. La frecuencia del ejercicio (número de sesiones por semana) y la duración (duración de cada sesión) son características importantes de un programa de ejercicios, pero un factor igualmente importante es la intensidad y el tipo de ejercicio.[18]

Las más recientes recomendaciones de EF aeróbico existentes para la prevención de FRCV[6], como la PA y exceso de masa grasa, concretan de la siguiente forma en términos del principio *FITT*:

- **Frecuencia:** mínimo 3 sesiones por semana, preferiblemente a diario.
- **Intensidad:** moderada (64-76 % de la FC máxima) o vigorosa (77-93 % de la FC máxima).
- **Tiempo:** al menos 150 minutos de AF moderada o 75 minutos de AF vigorosa por semana, que se pueden acumular en sesiones de más de 10 minutos. También se pueden combinar distintas intensidades.
    - Para un control más exhaustivo de la masa corporal se recomienda mayor volumen, en sesiones de mayor duración (60-90 minutos al día).
- **Tipo:** EF aerobico (caminar, jogging, nadar…); EFC al menos 30 minutos al día y en la guía de practica clínica de la ESH y en la ESC tambien se cita el modo interválico debido a la reciente evidencia científica. Además del entrenamiento aeróbico, se recomiendan

al menos dos sesiones semanales de trabajo de fuerza muscular dinámica (bandas elásticas, calistenia, trabajo físico intenso), realizando en cada sesión 2-3 series de 8-12 repeticiones al 60-80 % de la repetición máxima individual, y ejercicios de equilibrio, agilidad, coordinación y marcha para los que no especifica la dosis recomendada.

1.6. What is known and not known about this topic?

Hypertension (HTN), overweight/obesity and low cardiorespiratory fitness (CRF) are associated with an increased risk of a cardiovascular event. Both exercise training and diet are recommended to prevent and control HTN and overweight/ obesity. During the last two decades, several studies have shown the effectiveness of adherence to the Dietary Approaches to Stop Hypertension (DASH) dietary pattern.[5,140,141] In a population with HTN, the combination of the DASH diet with aerobic exercise has resulted in a greater reduction in blood pressure (BP) and improved cardiovascular biomarkers than DASH diet alone.[142] Exercise guidelines recommend that both moderate-intensity and high-intensity aerobic training should be used to treat and reduce HTN.[9] However, there is currently a discordance amongst studies, which have used similar methodologies to compare the effects of physical activity interventions on BP reduction.[98,118] The guidelines for the prevention of cardiovascular disease, and the treatment of HTN and obesity recommend using different physical activity doses for different modalities of exercise. Thus, the types of exercise, and maximum and minimum limits of intensity, and duration vary from one to the other. As such, there appears to be contradictions in terms of recommended or not recommended practices.[9,10,130] Due to the lack of sufficient scientific evidence in aspects related to the design of the exercise and cardiovascular risk (CVR), the adequate characteristics for an exercise program remains discordant,[130] since it is difficult to draw conclusions about which is the best combination of the components of the FITT principle (*F*requency, *I*ntensity, *T*ime, and *T*ype).[94] In other words, the quantification of the dose of exercise is needed, so that the benefit transferred to health will be optimal and/or provide the lowest risk.[118]

The biggest challenge for patients with HTN and overweight/obesity who wish to exercise, is to make an optimum intervention for each case. Therefore, various combinations of FITT principle components should be compared in order to specify the optimum intervention program that may positively affect variables such as BP, body composition, CRF, CVR, and vascular age.[88] Currently, no research has determined the effects of different exercise intensities and volumes combined with a hypocaloric diet intervention in overweight/ obese, sedentary adults diagnosed with HTN.

Capítulo 2 / Chapter 2

Objetivos e hipótesis

2. OBJETIVOS E HIPÓTESIS DE LA INVESTIGACIÓN / Objectives and hypotheses

2.4. Objetivos

- Evaluar el estado de salud mediante algunos marcadores físicos, fisiológicos, clínicos y nutricionales clave en personas adultas con sobrepeso u obesidad e HTA primaria caracterizadas por sexo y CCR. antes de comenzar una estrategia terapéutica no farmacológica.
- Estimar el perfil de RCV y EV en personas con HTA primaria a través del método Framingham y New Pooled Cohort Equations caracterizadas por sexo y CCR antes de comenzar una estrategia terapéutica no farmacológica.
- Evaluar el efecto de distintos programas de EF aeróbico en la PA, composición corporal y CCR en individuos adultos con sobrepeso u obesidad con HTA primaria tratados con dieta hipocalóra.
- Evaluar la influencia de una intervención de dieta y ejercicio físico aeróbico en los FRCV, RCV y EV, en personas adultas con sobrepeso/obesidad e HTA, así como analizar las diferencias entre sexos en la predicción de RCV y EV.

2.5. Hipótesis

- La población estudiada presentará patrones físicos, fisiológicos, clínicos y nutricionales específicos que sugerirán comportamientos clave tales como mejorar la calidad nutricional y la CCR a través de la AF regular.
- Los resultados mostrarán un RCV y una EV relativamente altos. El riesgo en los hombres será mayor que el riesgo en las mujeres. La EV de las personas será superior a su edad cronológica. Una nivel favorable de CRF contribuira a la atenuación del RCV.
- El tratamiento con dieta y EF aeróbico provocará mejoras superiores en la PA, composición corporal, condición cardiorespiratoria, RCV y EV en personas adultas con sobrepeso u obesidad e HTA primaria en comparación con un tratamiento exclusivamente dietético.
- El programa de EF de mayor intensidad (interválico) provocará mejoras superiores en variables de la condición física en comparación con el EF de intensidad moderada en modo continuo. Además, un programa de EF aeróbico de mayor intensidad y volumen corto podría resultar más eficiente afirmando que “menos” puede ser “más”.

Capítulo 3 / Chapter 3

Methods

3. METHODS / Métodos

3.4. Study design

The design, selection criteria and procedures for the EXERDIET-HTA study have been previously detailed.[143] The study protocol was approved by the Ethics Committee of the University of the Basque Country (UPV/EHU, CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital (2015-030), and all participants provided written informed consent before any data collection.

After baseline measurements, they were randomly allocated to one of the four intervention groups. The participants were followed for 16 weeks. All follow-up, examinations were performed in the same laboratory (laboratory of Sport Performance Analysis, Department of Physical Education and Sport, UPV/EHU) setting and by the same researchers as in the baseline measurements. Figure 6 presents a flow diagram of the study process.

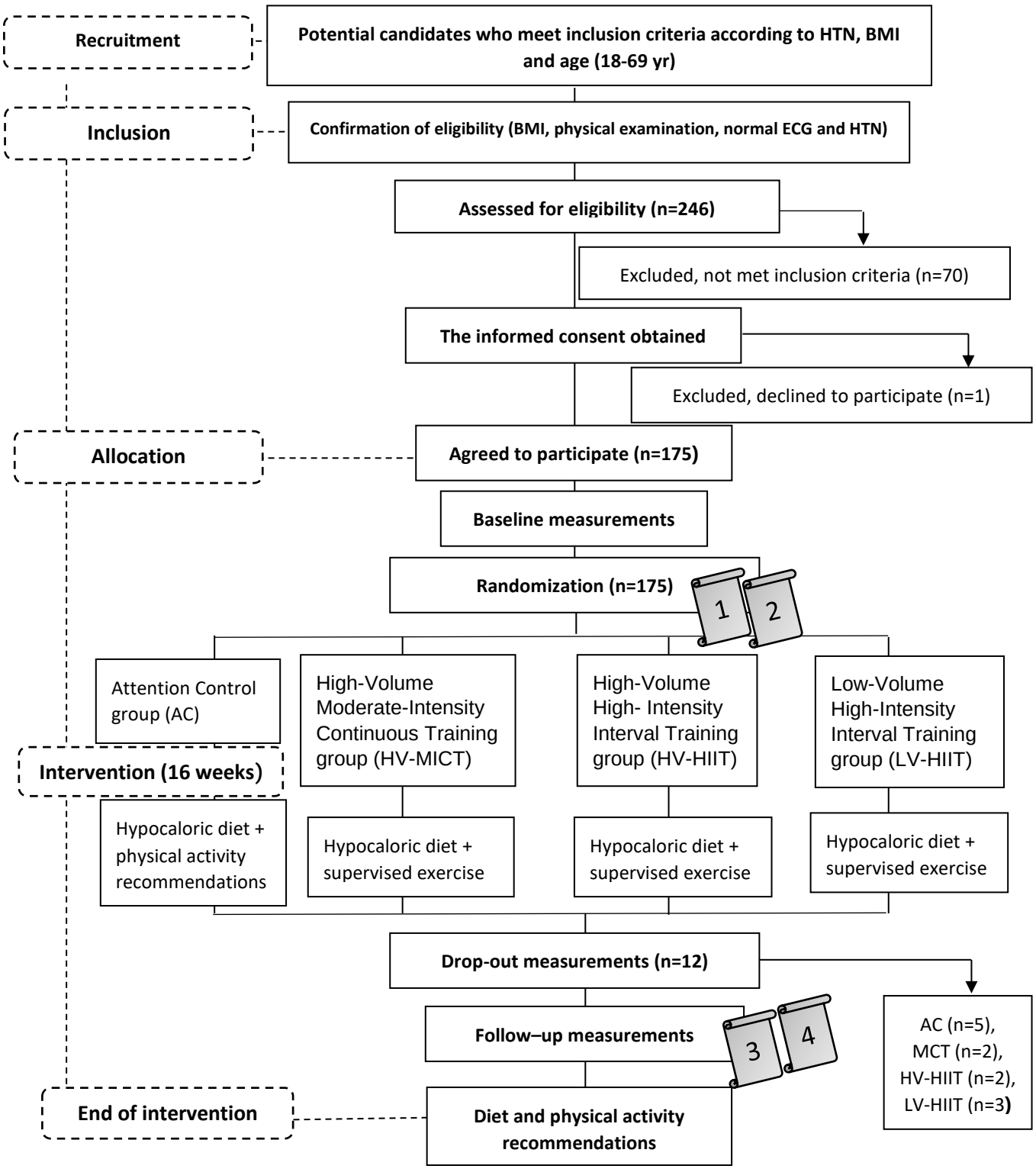

Figure 6: shows flow diagram of the EXERDIET-HTA study from recruitment to the end of intervention and relation to the articles published and presented in chapters 4-6.

DIVULGACIÓN

1

Ilargi Gorostegi-Anduaga et al. (2018)

Clinical, physical, physiological, and dietary patterns of obese and sedentary adults with primary hypertension characterized by sex and cardiorespiratory fitness: EXERDIET-HTA study. Clinical and Experimental Hypertension 2018, 40(2):141–149

Capítulo 4

2

Ilargi Gorostegi-Anduaga et al. (2017)

Assessment of cardiovascular risk and vascular age in overweight/obese adults with primary hypertension: the EXERDIET-HTA study. Blood Pressure Monitoring 2017, 22:154–160

Capítulo 5

3

Ilargi Gorostegi-Anduaga et al. (2018)

Effects of different aerobic exercise programmes with nutritional intervention in sedentary adults with overweight/obesity and hypertension: EXERDIET-HTA study. European Journal of Preventive Cardiology 2018, 25(4):343-353

Capítulo 6

4

Ilargi Gorostegi-Anduaga et al. (2018)

Effects on cardiovascular risk scores and vascular age after aerobic exercise and nutritional intervention in sedentary and overweight/obese adults with primary hypertension: EXERDIET-HTA study. HIGH Blood Pressure & Cardiovascular Prevention 2018, Sept 24. doi: 10.1007/s40292-018-0281-0.

Capítulo 7

3.5. Participants and selection criteria

One hundred and seventy-five non-Hispanic white participants (n=120 men and n=55 women) with primary HTN and overweight or obesity were enrolled in the study from September 2013 to June 2016 in Vitoria-Gasteiz (Basque Country, Spain). All participants were recruited from the cardiology services, from the physician specialists, and from local media. Interested individuals were invited to contact the research team. Before starting the study, a screening was performed for all candidates. After completion of the informed consent process, participants underwent anthropometric assessment (stature, total body mass, waist, and hip circumferences) and were selected for inclusion if they were classified as overweight (body mass index (BMI)>25kg/m2) or obese (BMI>30kg/m2).[34] Likewise, sedentary behavior was determined through the International Physical Activity Questionnaire (IPAQ) to ensure personal compliance with "Global Recommendations on Physical Activity for Health" by the World Health Organization.[144] Moreover, all participants were assessed with a 12-lead electrocardiogram (ECG) in order to detect left ventricular hypertrophy or any other predictor of cardiovascular events. Echocardiography was indicated by the cardiologist when more sensitive diagnosis was needed for the inclusion. Participants taking medication with beta-blockers were eligible only if the treatment allowed a peak cardiopulmonary test at baseline. Otherwise, the cardiologist advised the most suitable pharmacological treatment. Participants with no diagnosis of HTN were assessed with ambulatory blood pressure monitoring (ABPM) to confirm the HTN status by the cardiologist, defined as systolic blood pressure (SBP) of 140–179mmHg and/or diastolic blood pressure (DBP) of 90–109mmHg and/ or under antihypertensive pharmacological treatment.[9] The inclusion and exclusion criteria for EXERDIET-HTA study are shown in Table 13.

Table 13: Inclusion and exclusion criteria for EXERDIET-HTA study.

Inclusion criteria
- Age: 18-70 years old.
- Diagnosis of primary HTN, 1-2 stage defined as SBP 140-179 mmHg and/or DBP of 90-109 mmHg.
- Overweight or obese (BMI ≥25 kg/m^2).
- Sedentary lifestyle according to IPAQ scale.
-Time availability (90 min, two days a week for 16 weeks) to carry out the exercise program.
Exclusion criteria
- Secondary HTN.
- Left ventricular hypertrophy (estimated left ventricular mass up to 103 g/m^2 for men and up to 89 g/m^2 for women).
- The presence of one severe or, uncontrolled, cardiovascular risk factor, or diabetes mellitus more than 10 years since diagnosis, or with associated organopathy.
- Other significant medical conditions: Including but not limited to chronic or recurrent respiratory, gastrointestinal, neuromuscular, neurological, or psychiatric conditions; musculoskeletal problems interfering with exercise; autoimmune or collagen vascular diseases; immunodeficiency diseases or a positive HIV test; anemias, bleeding disorders, chronic thrombotic disorders, or hypercoagulable states; malignancies in the past 5 years, with the exception of skin cancer therapeutically controlled; endocrine and metabolic disorders, including type 1 DM; any other medical condition or disease that is life-threatening or that can interfere with or be aggravated by exercise.
- Pregnancy or breast-feeding.
- Plans to be out of the city more than 2 weeks.
- To have participated in a diet-weight-loss program during the last year

3.6. Measurements

The measurements used in the protocol were taken before and after the intervention period (16-weeks) (Figure 6). The post-intervention test was scheduled the following week after finishing the 16-week intervention period. The primary outcome variable is BP. The secondary outcome variables included body composition, physical fitness, and cardiovascular risk factors (Table 14). Both the baseline and follow-up measurements were divided into four sessions (Table 14).

Table 14. Overview of the assessment schedule at baseline and follow-up in the EXERDIET-HTA study

Session	Measurement	Methodology
DAY 1	PHYSICAL MEASUREMENTS	
	Stature (cm)	Stadiometer
	Body mass (kg)	Scale
	Waist and hip circumferences (cm)	Non-elastic tape
	Fat-free mass, fat mass, total body water	Bioelectrical impedance
	Systolic and diastolic blood pressure	Oscillometric monitor device
	Rest electrocardiogram	12-lead electrocardiogram
	PHYSICAL ACTIVITY & SEDENTARY BEHAVIOUR	
	International Physical Activity Questionnaire	Questionnaire
DAY 2	BLOOD PRESSURE ASSESSMENT	
	Mean systolic and diastolic blood pressures, mean arterial pressure, pulse pressure (24 h)	Ambulatory blood pressure monitor
DAY 3	PHYSICAL FITNESS	
	Cardiorespiratory fitness	Modified Shuttle Walking Test Cardiopulmonary exercise test (bike)
	DIETARY ASSESSMENT	24 h recalls and food frequency questionnaires
DAY 4	BIOCHEMICAL MEASURES	
	Glucose (mg/dL)	Enzymatic spectrophotometry
	Insulin	Immunoassay chemiluminescent
	Haemoglobin A1c (%)	High-performance liquid chromatography ion exchange (HPLC)
	Total-, HDL- and LDL-cholesterol (mg/dL)	Enzymatic spectrophotometry
	Tryglicerides (mg/dL)	Enzymatic spectrophotometry
	Alanine aminotransferase (U/L)	Enzymatic spectrophotometry
	Aspartate aminotrnsferase (U/L)	Enzymatic spectrophotometry
	C-reactive protein (g/dL)	Enzyme immunoassay
	Uric acid (mg/dL)	Enzymatic spectrophotometry

Blood pressure

Ambulatory BP monitoring was performed with an oscillometric ABPM 6100 recorder (Welch Allyn, New York, USA).[145] We followed the report's recommendations by the ESH/ESC guidelines[9] to ensure the best methodology. The device measured BP at 30-minute intervals during the daytime and at 60-minute intervals during night-time. Participants had previously self-disclosed their typical bedtime and wake-up time, and it was used to define the assessments per 30 min intervals, and the beginning per 60 min intervals. Recorded data were downloaded with participant's attendance in order to correct the actual bedtime and wake-up time in case of change. The recording was accepted if at least 75% of the recordings were obtained. If the ABP failed to measure the BP, another ABP was performed.

Physical fitness

Physical fitness includes the Modified Shuttle Walking test (MSWT) and a peak, symptom-limited CPET.

The MSWT required the participant to walk up and down a 10 m course and it was performed as previously described by Singh et al.[74] Participants walked along a flat, indoor 10 m course marked by two cones placed 0.5 m in from each end of the course (Figure 7). A shuttle refers to one 10 m lap. Standardized pre-recorded instructions for the test were played from a digital recording immediately prior to beginning the test. The test was externally paced, with signal beeps at regular intervals to indicate when the participant should be turning around the cone to commence the next shuttle. A triple beep signaled the next level and an increase in walking speed. Participants commenced the test at a walking speed of 0.5 m/seconds (level 1), allowing the participant 20 seconds to complete each of the three shuttles in level 1. There was a speed increment of 0.17 m/seconds each minute for a maximum of 15 minutes. The test was stopped when the participant could no longer maintain the required pace or was more than 0.5 m from the cone before the signal beep after one opportunity to catch up or if the test was completed. Additional criteria for early termination of the test included patient distress, dizziness, angina, or onset of severe musculoskeletal pain, failure of the heart rate (HR) to increase with exercise or attainment of 85% of the maximum HR. The number of shuttles completed were recorded at the completion of each test and converted to the distance walked. Prior to commencing the test, with the participant in a seated position, baseline HR and BP were recorded. Heart rate and Borg scale (6 to 20) were monitored throughout the test, and BP and HR were continued to be recorded five more minutes after completion of the test.[146,147]

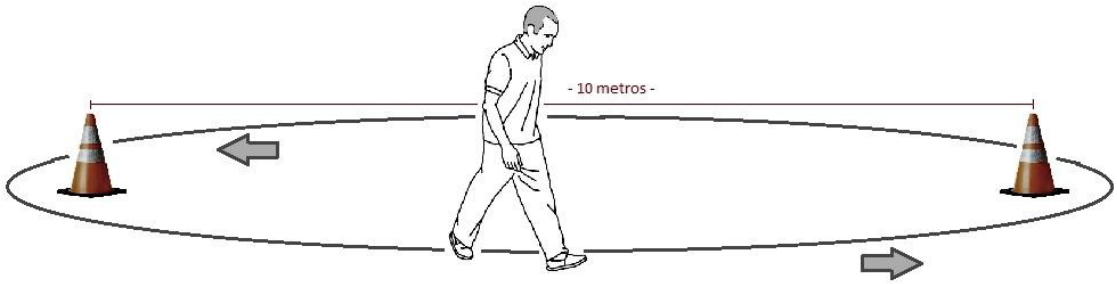

Figure 7. Graphic diagram of MSWT

Participants were allowed a 30-minute rest break, or longer if needed, prior to commencing the CPET test in order to get baseline HR and BP values.

The CPET was performed in the upright position on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). Testing protocol started with 40W with gradual increments of 10W every minute to exhaustion with continuous ECG monitoring (Table 15). Each participant's bike setup (*i.e.,* saddle height, reach, and handlebar height) was recorded and registered to replicate at follow-up. The test was not preceded by any type of warm-up, and participants cycled at least at 70 rpm. During the test, participants were encouraged verbally by the laboratory technician and medical doctor. Expired gas analysis was conducted using a commercially available system (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) that was calibrated before each test with a standard gas of known concentration and volume. Breath-by-breath gas exchange data were measured continuously during exercise and averaged every 60 seconds. Peak oxygen uptake was defined as the highest oxygen uptake (VO_{2peak}) value attained toward the end of the test. Achievement of true peak effort was assumed in the presence of two or more of the following criteria: 1) volitional fatigue (>18 on BORG scale), 2) peak respiratory exchange ratio (VCO_2/VO_2) ≥1.1, 3) achieving >85% of age-predicted HR_{max}, and 4) failure of VO_2 and/or HR to increase with further increases in work rate.[64]

A self-reported Borg rating of perceived exertion (6 to 20 scale) was recorded at the end of each stage. Blood pressure was measured every two minutes throughout the test. Ventilatory thresholds (*i.e.,* VT1 and VT2) were assessed by standardized methods using the V-slope and ventilatory equivalents. First ventilatory threshold (VT1) was identified as the point of transition in the carbon dioxide production (VCO_2) *vs*. VO_2 slope from less than 1 to greater than 1, or VT1 is also identifiable as the nadir of the ventilatory equivalent (VE) of VO_2 *vs.* work rate relationship. Second ventilatory threshold (VT2) was identifiable as the nadir of the VE/VCO_2 *vs.* work rate relationship.[64] After completion of the test, participants remained on the bike five more minutes for recovery with ECG and BP monitoring. Absolute and relative indications for terminating the exercise test were taken into account.[148] The identification of the two VT determined the three different exercise intensity domains or ranges for exercise design

(R1, R2, R3): R1) **light** to moderate exercise intensity with HR values below VT1; R2) **moderate** to high or vigorous exercise intensity with HR values between VT1 and VT2, and R3) **high** to severe intensity exercise intensity with HR values up to VT2 to peak intensity. When it was not possible to identify the VT2, exercise intensity domains were established considering percentages of HR reserve, *i.e.,* moderate intensity is defined between 50-75% of HR reserve, high intensity from ≥76% to <95% of HR reserve. [148]

Table 15. CPET protocol features in Cycle Ergometer

Time (min)	Power (W)
1	40
2	50
3	60
4	70
5	80
6	90
7	100
8	110
9	120
10	130
11	140
12	150
13	160
14	170
15	180
16	190
17	200
18	210
…	…

Anthropometry and body composition

Anthropometry included stature (SECA 213, Hamburg, Germany), total body mass (SECA 869, Hamburg, Germany), body mass index calculated as [total body mass (kg)/stature (m^2)], and waist and hip circumferences (SECA 200) to calculate waist to hip ratio. All measurements were taken in accordance with guidelines from International Society for the Advancement of Kinanthropometry.[149] Furthermore, fat-free mass, total body water, and fat mass were estimated with bioelectrical impedance analysis (Tanita, BF 350).

Biochemical profile

Morning fasting blood samples were obtained from each participant by experienced nursing staff in the Clinical Trials Unit of Tecnalia (HUA, Vitoria-Gasteiz). This procedure permitted measurements of glucose, insulin, haemoglobin A1c (HbA_{1c}), lipid profile (total-, high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol, and triglycerides), liver enzymes (ALT, AST), C-reactive protein and uric acid. Insulin resistance was determined by the homeostasis model assessment for insulin resistance (HOMA-IR).[150]

Physical activity and sedentary behaviour

Physical activity and sedentary behaviour were subjectively assessed by *(IPAQ*. The short version of IPAQ was used to assess sedentary behaviour. This questionnaire is an instrument developed to enable the estimation of the level of physical activity in populations across different countries. The short version is composed of eight questions that are used to estimate the time spent per week performing different physical activity intensities. The short IPAQ record the activity at four intensity levels: (1) vigorous-intensity, (2) moderate-intensity, (3) walking or light activity and (4) sitting. For all intensity levels, the participants were asked how many days per week and minutes per day, they performed the activity for ≥10-min continually.[151] To quantify the physical activity levels, the product of the duration (min/day) and frequency (days/week) were used to estimate light, moderate-to-vigorous and total physical activity.

Dietary assessment

Habitual food consumption and nutrient intake were evaluated using three questionnaires: the dietary history, food frequency questionnaire and 24h recall questionnaire**.**

3.7. Intervention

After baseline testing, participants were randomized to one of the four intervention groups (AC, MCT, HV-HIIT, LV-HIIT) stratified by gender, SBP, BMI and age using a time-blocked computerized randomization program. Medical staff was blinded to participant randomization assignment.

Attention Control group (AC). The AC group received treatment only with hypocaloric diet and also a standard recommendation for patients with primary HTN, including regular physical exercise. In this sense, hypertensive patients were advised to participate, without supervision, in at least 30 min of moderate-intensity dynamic aerobic exercise (walking, jogging, cycling or swimming) 5-7 days per week. Aerobic interval training including high-intensity exercise and dynamic resistance exercise (force development associated with movement) was also be recommended.[9] Participants received information related to HR values regarding moderate and high exercise intensity domains for the self-monitoring of exercise intensity.

Exercise groups received double treatment (*i.e.,* hypocaloric diet + supervised exercise):

1) MCT group: Moderate (HR values between VT1 and VT2 or 50-75% of HR reserve) continuous exercise and high volume increasing gradually from 20 to 45 min;

2) HV-HIIT group: high-intensity (HR values up to VT2 to peak intensity or ≥76% to <95% of HR reserve) interval training and high-volume increasing gradually from 20 to 45 min and alternating high and moderate intensities at different protocols; and

3) LV-HIIT group: high-intensity interval training and low-volume (20 min) alternating high and moderate intensities at different protocols.

3.7.1. Exercise intervention program

The participants exercised two nonconsecutive days per week for 16 weeks under supervision by exercise specialists. All the exercises sessions started and finished with BP monitoring and training intensity was controlled by HR monitoring (Polar Electro, Kempele, Finland) and through the rate of perceived exertion using the Borg's original scale (6-20 point). Each session included a 10 min warm-up with joint mobility and coordination exercises with continuous leg movement to facilitate the venous return and a 10 min cool-down period with basic core strengthening exercises and passive stretching exercises on the floor to ensure a progressive return to the resting values of both HR and BP. The main portion of the training session consisted of aerobic exercises (*i.e.,* one day of the week on the treadmill,

and the second one on the bike) developing progressively both the volume (*i.e.,* 20 to 45 min in MCT and HV-HIIT, whereas in LV-HIIT the duration was always of 20 min) and intensity. Intensity was individually tailored to HR at moderate or vigorous intensities, adjusting the speed and incline of the treadmill or the power and speed on the bike, to achieve the planned target HR (Tables 16-18). The exercise specialists kept detailed records of all the exercise sessions reporting the HR and Borg scale values of every interval. The importance of targeting moderate and high intensity was emphasized.

Several strategies were implemented to maximize adherence, including music in all sessions, individualized attention at the intervention sessions and telephone calls following missed sessions.

Table 16. Intervention program for Moderate-intensity Continuous Training (MICT) group. Volume and intensity progression.

	MICT	
Weeks	**Total Volume (min)**	**INTENSITY (%HR res)**
1-2	20	50%
3-4	25	60%
5-6	30	65%
7-8	35	70%
9-10	40	75%
11-12	45	75%
13-16	45	75%

Table 17. Intervention program for High-Volume & High-Intensity (HV-HIIT) and Low-Volume & High-Intensity (LV-HIIT) groups on the treadmill. Volume- and intensity-progression.

	HV-HIIT				**LV-HIIT**			
	HIGH-INTENSITY INTERVAL		**MODERATE INTENSITY INTERVAL**		**HIGH-INTENSITY INTERVAL**		**MODERATE INTENSITY INTERVAL**	
Weeks	Volume (min)	Intensity (%HRres)	Volume (min)	Intensity (%HRres)	Volume (min)	Intensity (%HRres)	Volume (min)	Intensity (%HRres)
1-2	8	80	12	60	8	80	12	60
3-4	12	80	13	60	8	80	12	60
5-6	16	85	14	65	8	85	12	65
7-8	16	85	19	65	8	85	12	65
9-10	16	95	24	70	8	95	12	70
11-12	16	95	29	70	8	95	12	70
13-16	16	95	29	70	8	95	12	70

Table 18. Intervention program for High-Volume & High-Intensity (HV-HIIT) and Low-Volume & High-Intensity (LV-HIIT) groups on the bike. Volume- and intensity-progression.

	HV-HIIT				LV-HIIT			
	HIGH-INTENSITY INTERVAL		MODERATE INTENSITY INTERVAL		HIGH-INTENSITY INTERVAL		MODERATE INTENSITY INTERVAL	
Weeks	Volume (min)	Intensity (%HRres)	Volume (min)	Intensity (%HRres)	Volume (min)	Intensity (%HRres)	Volume (min)	Intensity (%HRres)
1-2	2	80	18	60	2	80	18	60
3-4	3	80	22	60	3	80	17	60
5-6	4	85	26	65	4	85	16	65
7-8	5	85	30	65	4:30	85	15:30	65
9-10	6	95	34	70	4:30	95	15:30	70
11-12	7	95	38	70	4:30	95	15:30	70
13-16	9	95	37	70	4:30	95	15:30	70

High-intensity interval training protocol on the treadmill

The high intensity aerobic exercise groups carried out a 5-min warm-up period at a moderate-intensity (*i.e.,* HR values between VT1 and VT2 or 50-75% of HR reserve) on the treadmill, before walking two intervals of 4 min at high-intensity (*i.e.,* HR values up to VT2 to peak intensity or ≥76% to <95% of HR reserve). The participants exercised at the lower intensity limit for the first two weeks of the training period before increasing the intensity towards the upper limit. Between the high-intensity intervals, 3 min of walking at moderate-intensity was conducted. The training session ended with a 1-4 min cool-down period at moderate-intensity.[120] This gave a total exercise time of 20 min. Meanwhile, this protocol was kept in the LV-HIIT group; every two weeks the HV-HIIT progressed to four intervals of 4 min at high intensity and 45 min of total volume (Table 17).

High-intensity interval training protocol on the bike

The high-intensity aerobic exercise groups carried out a 10-min warm-up period on the bike for the high-volume group and 5-10 minutes for the low-volume group. After that participants cycled for 30 s at high-intensity (*i.e.,* HR values up to VT2 to peak intensity or ≥76% to <95% of HR reserve) followed by 60 s at moderate-intensity (*i.e.,* HR values between VT1 and VT2 or 50-75% of HR reserve). Four repetitions (1rep = 30 s high-intensity followed by 60 s moderate-intensity) were initially performed in both groups and gradually increased to 18 repetitions in the high-volume group, while 9 repetitions

were completed (Table 18) in the low-volume group. The training session ended with a 5-10 min cool-down period at moderate-intensity.

3.7.2. Diet intervention

Diet was calibrated with the Easy Diet program (www.easydiet.es) by the Spanish Foundation of dieticians and nutritionists) obtaining caloric intake and macronutrient distribution. The resting energy expenditure was calculated by the Mifflin St Jeor equation to be the most appropriate for individuals who are overweight or obese[79,152], and the coefficient of 1.5 corresponds to the factor of physical activity for light physical activity level or sedentary individuals. All participants were treated with a diet designed to provide 25% less energy than their daily energy expenditure. Approximately 30% of their energy intake came from fat, 15% from protein, and 55% from carbohydrates designed to achieve a weekly loss of body mass between 0.5 and 1.0 kg in accordance with the recommendations of the American Diabetes Association and the Spanish Society for the Study of Obesity.[153,154] From a qualitative point of view, the diet was designed following the proportions and amounts of foods/food groups recommended by the dietary pattern of the DASH diet.[140] In addition, participants received nutritional advice regarding the restriction of foods high in sodium according to the recommendations of the European Societies of Hypertension and Cardiology.[9] The diet was also accompanied by guidance menus and the most appropriated culinary techniques to facilitate compliance and dietary adherence. Participants were encouraged, weighed and receive advice and nutritional counseling every two weeks to help in their compliance with the dietary recommendations and requirements.

Capítulo 4 / Chapter 4

Clinical, physical, physiological, and dietary patterns of obese and sedentary adults with primary hypertension characterized by sex and cardiorespiratory fitness: EXERDIET-HTA study.

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4.1. Abstract

The main purpose of this study was to determine some key physical, physiological, clinical and nutritional markers of health status in obese and sedentary adults (54.0±8.1 years, 141 men and 68 women) with primary hypertension (HTN) characterized by sex and cardiorespiratory fitness (CRF) level. The studied population showed a high cardiovascular risk (CVR) profile including metabolically abnormal obese, with poor CRF level (22.5±5.6 $mL \cdot kg^{-1} \cdot min^{-1}$), exercise-induced HTN (Systolic Blood Pressure>210 mmHg in men and >190 mmHg in women at the end of the exercise test) and with non-healthy adherence to dietary pattern (Dietary Approaches to Stop Hypertension, 46.3%; Mediterranean Diet, 41.1%; and Healthy Diet Indicator, 37.1%). Women showed a better biochemical and dietary pattern profile than men (lower values, *P*<0.05, in triglycerides, mean difference=26.3; 95% CI=0.9-51.7 mg/dL, aspartate transaminase, mean difference=4.2; 95% CI=0.3-8.0 U/L; alanine transaminase, mean difference=8.2; 95% CI=1.6-14.8 U/L; gamma-glutamyl transpeptidase, mean difference=11.0; 95% CI=-1.1-23.2 U/L and higher values, *P*=0.002, in high-density lipoprotein cholesterol, mean difference=5.0, 95% CI=-13.3-3.3 mg/dL), but physical and peak exercise physiological characteristics were poorer. A higher CRF level might contribute to the attenuation of some CVR factors, such as high body mass index, non-dipping profile, and high hepatic fat. The results strongly suggest that targeting key behaviors such as improving nutritional quality and CRF via regular physical activity will contribute to improving the health with independent beneficial effects on CVR factors.

Trial Registration: NCT02283047

Keywords: cardiovascular risk, metabolically abnormal obese, cardiorespiratory fitness, dietary pattern, sex differences

4.2. Introduction

The 2013 guidelines on hypertension (HTN) of the European Society of Hypertension and the European Society of Cardiology[9] and the guidelines of the American College of Cardiology and the American Heart Association for the management of overweight and obesity in adults[34] presented new evidence on several diagnostic and therapeutic aspects of HTN and overweight/obesity, including lifestyle modification to reduce cardiovascular risk (CVR). Obesity and HTN frequently coexist in the same individual, and they have been recognized as a pre-eminent cause of CVR.[78,155] It is well known that blood pressure (BP) and cardiovascular (CV) damage are related, and how CV mortality is modified

by the concomitance of other CVR factors.[156] Prevalence of HTN, defined as values ≥140 mmHg systolic BP (SBP) and/or ≥90 mmHg diastolic BP (DBP) and/or prescription of antihypertensive drug therapy, appears to be around 30-45% of the general population.[9]

Specifically, in the Spanish population, HTN was found in 42.6% aged ≥18 years and it was more common among men (49.9%) than women (31.5%).[17] In addition, current estimates suggest that 69% of adults are either overweight or obese, with approximately 35% obese.[34] Hence, for the management of HTN and the prevention of coronary heart disease, it is mandatory to quantify the total CVR, since only a small fraction of the hypertensive population has an elevation of BP alone, with the main portion exhibiting additional CVR factors, thereby increasing the total CVR.[9] Accordingly, BP measurements (*i.e.* daytime, night-time and 24-h BP), medical history (*i.e.* first diagnosis of HTN, biochemical profile, medications, concomitant diseases, smoking habit, family history), physical examination (*i.e.* electrocardiography and body composition), laboratory investigation with BP during exercise and lifestyle assessment (*i.e.* physical activity and dietary pattern) should be implemented.[9,34]

Experimental studies indicate that sex affects the developmental programming of BP and CVR. Thus, testosterone appears to serve as a pro-hypertensive factor, whereas estrogen is suggested to contribute an anti-hypertensive influence and sensitivity to vasoactive factors.[157] However, whether gender differences in prognosis represent a true result from differences in patient management and diagnostic approach is not yet clarified.[158]

On the other hand, cardiorespiratory fitness (CRF) is considered a vital sign and its strong association with CVR is well known (*i.e.,* poor CRF level corresponds with a substantially increased mortality risk.[159] A previous meta-analysis also indicated that the risk of death was dependent upon CRF level and not body mass index (BMI); thus, it was asserted that fit individuals who were overweight/obese were not automatically at a higher risk for all-cause mortality.[89] Therefore, it should be of interest to assess the characteristics of overweight/obese individuals with HTN diagnosis taking into account different CRF levels.

An unhealthy dietary pattern is also considered a CVR factor.[160] Hence, nutrition research is focusing more on the impact of dietary pattern on disease risk rather than on individual food groups or nutrients.[161] The Healthy Diet Indicator (HDI), Mediterranean Diet (Med) and The Dietary Approaches to Stop Hypertension (DASH) are the most well-known dietary guidelines that specifically target lowering CV disease risk. However, to the best of our knowledge, no reports are available on the adherence to dietary guidelines by overweight/obese individuals with HTN.

The main purpose of this study was to determine some key physical, physiological, clinical and nutritional markers of health status in obese and sedentary adults with primary HTN characterized by sex and CRF before starting a non-pharmacological therapeutic strategy.

4.3. Methods

Study participants

The EXERDIET-HTA study was conducted between September 2012 and June 2016 in Vitoria-Gasteiz (Basque Country, Spain). The current baseline study comprised a total of 209 participants aged between 24 and 70 years (mean 54.0±8.1 years), 141 men (67.5%) and 68 women (32.5%). All participants were overweight/obese, sedentary and had been diagnosed of HTN. Participants were considered to have HTN if they had a mean SBP≥140 mmHg and/or DBP≥90 mmHg or used antihypertensive medications. All other inclusion and exclusion criteria have been specified in the protocol of the study.[143] The ethics committee of the University of the Basque Country (UPV/EHU, CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital (2015-030) approved the study design, study protocols, and informed consent procedure. (Clinical Trials.gov identifier, NCT02283047).

Measures

Stature and body mass were measured, and BMI was calculated as total body mass divided by height squared (kg/m^2). Waist and hip circumferences were taken, and waist to hip ratio (WHR) was defined as waist circumference divided by hip circumference both in centimeters. Moreover, the estimation of fat-free mass (FFM), total body water (TBW) and fat mass (FM) was made by bioelectrical impedance (Tanita, BF 350).

Blood pressure measures were obtained by wearing an ambulatory BP monitoring (ABPM) 6100 recorder (Welch Allyn, New York, USA). The device measured BP an entire day, at 30-minute intervals during the daytime and at 60-minute intervals during night time. The variables taken into account from the ABPM measures were mean values of SBP and DBP, mean BP (MBP), pulse pressure (PP) and heart rate (HR). Blood pressure mean dipping pattern was the percent of the nocturnal reduction in SBP in relation to diurnal mean SBP, and it was calculated as ([daytime SBP-nighttime SBP]/daytime SBPx100).[162] Based on the % decline in nocturnal BP participants were grouped as dippers ≥10% or non-dippers≤10%.[9]

All medications prescribed to participants were recorded and classified in their group: angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), diuretics, calcium channel blockers (CCB,) beta-blockers (BB), statins, hypoglycemic agents, antiplatelets, and anticoagulants.

Physical fitness measures included the Modified Shuttle Walking Test (MSWT)[75] and a peak, symptom-limited cardiopulmonary exercise test (CPET). Walked distance (m) was recorded at the completion of each MSWT. The CPET was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, Netherlands) starting at 40W with a gradual increment of 10W each minute in ramp protocol. Expired gas was analyzed with a system (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) that was calibrated before each test for the determination of peak oxygen consumption ($\dot{V}O_{2peak}$).[143]

The distributions of $\dot{V}O_{2peak}$ were divided into tertiles (low, moderate and high CRF) in each sex. The details regarding the range in each group were as follows; the lowest tertile (Low-CRF group): $\dot{V}O_{2peak} \leq 21$ mL·kg^{-1}·min^{-1} in men and $\dot{V}O_{2peak} \leq 16$ mL·kg^{-1}·min^{-1} in women; the medium tertile (Moderate-CRF group): $21 < \dot{V}O_{2peak} \leq 26$ mL·kg^{-1}·min^{-1} in men and $16 < \dot{V}O_{2peak} \leq 21$ mL·kg^{-1}·min^{-1} in women; the highest tertile (High-CRF group): $\dot{V}O_{2peak} > 26$ in men and $\dot{V}O_{2peak} > 21$ mL·kg^{-1}·min^{-1} in women.

A blood sample (12.5mL) was collected from each participant in the Clinical Trials Unit of Tecnalia (HUA, Vitoria-Gasteiz) after an overnight fast to determine the biochemical profile including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose, insulin, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT) and C-Reactive Protein (CRP)[75]. Type 2 Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL.[163] HOMA-IR was used to evaluate insulin resistance [fasting serum insulin (μU/mL) x fasting plasma glucose (mg/dL)/405].[150]

For the dietary assessment, face-to-face two non-consecutive 24-h recalls were used to examine dietary habits by trained dieticians, allowing for important correction for within-subject variability in nutrient intake.[164] This is considered the most cost-effective method to implement within a pan-European dietary survey.[165] Moreover, statistical methods suggest that to achieve detailed dietary data at least two measurements are required and also to get an equal distribution of the different days of the week.[166] Fixed instructions to the interviewers were done to minimize the time between registrations days and emphasizing that participants were not allowed to choose the most convenient days for them.[165] All dietary data were calibrated in Easy Diet computer program and dietary nutritional composition was obtained. Adherence to the Med was obtained based on the score proposed by

previous studies.[167] Nevertheless, instead of median cut-offs, mean cut-offs were used because of the low consumption in some food groups. A sum of nine food groups and nutrients were included in calculating the Med score. Intakes of vegetables, legumes, fruits and nuts, cereals, fish and seafood and monounsaturated to saturated fats ratio were considered as positive dietary components, whereas, dairy, meat products, and alcohol were considered as negative. Sex-specific mean intakes were calculated as a cut-off in each food group to recode the components. A value of 1 was given when the positive dietary components were above the mean and when the negative ones were below the mean. In contrast, a value of 0 was given either when food groups considered as positive were below the mean or when the negative components were above the mean. However, when alcohol consumption among men and women was ≤2 drinks per day and ≤1 per day respectively, a value of 1 was given, whereas a value of 0 was given with higher intakes of alcohol. Therefore, with the sum of all the recoded dietary elements, the adherence to the Med score was ranged from 0 (minimal adherence) to 9 points (maximal adherence). The adherence to the DASH dietary pattern was calculated with the sum of eight dietary elements, considering the consumption of fruits, vegetables, nuts and legumes, whole grains and low-fat dairy products as positive components and intakes of sodium, red and processed meat and sweetened beverages as negative.[161] As above, values of 0 or 1 were given when the intakes were above or below the sex-specific means. Thereby, the adherence to the DASH dietary pattern was ranged between 0 and 8 (from lowest to highest adherence). The adherence to HDI proposed by the World Health Organization was calculated following healthy diet recommendations for the general population.[161] This score is composed of seven dietary nutrients, and food groups and values of 1 or 0 were also given depending on the meeting established criteria. The components of this dietary pattern were the following: saturated fatty acid (≥10% of total energy intake = 0, <10% of total energy=1), polyunsaturated fatty acids (<6% or >10% of total energy =0, 6-10%=1), cholesterol (≥ 300 mg=0, ≤300 mg=1), protein (<10% or >15% of total energy=0, 10-15% of total energy=1), fiber (<25g= 0, ≥25g = 1), fruits and vegetables (<400 g=0, ≥400 g=1) and free sugars (≥10% of total energy= 0, <10% of total energy=1).

Statistical analyses

Descriptive statistics were calculated for all variables. Data are expressed as mean±standard deviation (SD). All variables were deemed normally distributed using a Kolmogorov-Smirnov apart from age, BMI, waist circumference, WHR, FM, TBW, FFM, DBP means, %BP dipping, $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$ and $mL \cdot kg^{-1} \cdot min^{-1}$), metabolic equivalent of task (MET), TC, HDL, TG, glucose, AST, ALT and GGT which had a skewed distribution and were therefore log transformed prior to any analysis. The Chi-square test was used to test differences in

categorical variables between sexes. An independent samples *t*-test was used to determine whether there was a significant sex difference for all parametric variables. Analysis of covariance (ANCOVA) was used to examine dependent variables of the participants classified by CRF level (low, medium and high), adjusting the analysis for age, sex and body mass. A Bonferroni post-hoc test was used to determine the level of significance when a significant main effect was found. Cohen's d was calculated to describe the standardized mean difference between sex effect sizes. Omega squared (ω^2) was calculated to describe the standardized mean difference of an effect between CRF groups. The effect sizes were interpreted as small (d=0.2), medium (d=0.5), and large (d=0.8) based on benchmarks suggested by Cohen.[168] Statistical significance was set at $P<0.05$. The statistical analyses were performed with the SPSS version 22.0 software package.

4.4. Results

Characteristics of the study population are shown in Table 19. Although one of the inclusion criteria was to be overweight/obese, after statistical analysis the mean BMI>30 kg/m^2, what is considered obesity and the mean WHR was 0.96±0.11 which is considered a CVR factor in accordance with guidelines for the management of overweight and obesity in adults.[34] Significant differences were observed between men and women in body mass, WHR and body composition variables ($P<0.001$). Men showed a higher proportion of FFM ($P<0.001$, Δ=16.1%) and TBW ($P=<0.001$, Δ=17.7%) compared to women, whereas women had a higher proportion of FBM ($P=<0.001$, Δ=32.2%) compared to men.

No differences were found in mean SBP between sexes. However, mean DPB values were significantly higher in men ($P=0.001$, Δ=5.0%) compared to women. Consequently, MBP was significantly lower in women ($P=0.027$, Δ=-3.14%) compared to men. Mean HR was lower ($P=0.005$, Δ=-5.6%) in men compared to women, showing 4.1 beats less per minute. Taking into account the mean of sleep–time-relative SBP decline (*i.e.,* ≥%10), all individuals were broadly classified as BP dippers in accordance with ESH/ESC Guidelines for the management of arterial HTN.[9]

Related to **medication-pharmacological therapy**, 87.1% of participants received antihypertensive and/or other medications, while 12.9% did not. The percentage of participants who took one, two, three or four, or more medications was 40.2%, 27.3%, 12.9% and 6.7%, respectively. Referring to the antihypertensive drugs, 36.8% of participants took ACEI, 43.5% ARB, 32.1% diuretics,

17.7% CCB and 9.57% BB. Chi-square test analysis revealed no significant differences between sexes (Table 19).

Table 19. Characteristics of the study population and medication-pharmacological therapy.

Variables	AP (*n*=209)	Men (*n*=141)	Women (*n*=68)	*P* M-W	*d* Cohen
Age (yrs)	54.0±8.1	54.3±7.9	53.4±8.6	0.4	0.1
Body mass (kg)	90.1±15.5	95.0±14.07	80.0±13.5	<0.001***	1.1
BMI (kg/m^2)	31.3±4.6	31.3±4.3	31.5±5.2	0.9	0.04
WHR (cm)	0.96±0.1	1.0±0.1	0.9±0.1	<0.001***	1
FFM (%)	66.7±8.7	69.9±8.0	60.2±5.9	<0.001***	1.4
TBW (%)	48.7±6.6	51.2±5.5	43.5±5.5	<0.001***	1.4
FBM (%)	33.3±8.7	30.1±8.0	39.8±5.9	<0.001***	1.4
SBP (mmHg)	135.9±14.1	136.4±12.9	134.8±16.3	0.4	0.1
DBP (mmHg)	78.9±8.6	80.1±7.8	76.3±9.6	<0.001***	0.5
Mean HR (beats·min^{-1})	71.0±10.0	69.8±9.9	73.9±9.7	0.005**	0.4
MBP (mmHg)	97.9±9.5	98.9±8.7	95.8±10.9	0.027*	0.3
PP (mmHg)	57.0±10.4	56.3±9.5	58.5±11.9	0.2	0.2
BP Dipping (%)	11.4±7.0	11.6±7.0	11.0±7.0	0.6	0.1
Cigarette smoking (%)	11.4	10.6	13.2	0.6	
DM (%)	4.5	5	3	0.5	
ACEI (%)	36.8	34.8	41.2	0.4	
ARB (%)	43.6	45.4	39.7	0.4	
DIURETICS (%)	32.1	31.2	33.8	0.7	
CCB (%)	17.7	21.3	10.3	0.05	
BB (%)	9.6	8.5	11.8	0.4	
STATINS (%)	12.9	12.8	13.2	0.9	
HYPOGLYCEMIC AGENTS (%)	5.3	6.4	2.9	0.3	
ANTIPLATELETS (%)	3.9	4.3	2.9	0.6	
ANTICOAGULANTS (%)	1	0.7	1.5	0.6	

Abbreviations: AP, all participants; BMI, body mass index; WHR, waist to hip ratio; FFM, fat free mass; TBW, total body water; FBM, fat body mass; SBP, systolic blood pressure; DBP diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; PP, pulse pressure; BP, blood pressure; DM, diabetes mellitus. ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; BB, beta-blockers. P<0.05: Significant difference between men (M) and women (W)

*P<0.05, ** P<0.01, *** P<0.001

When **exercise capacity** was objectively analyzed (*i.e.,* through CEPT), all participants made an exhaustive exercise effort (RER=1.1±0.1). According to the American College of Sport Medicine, participants of the present study were classified as "very poor" CRF level[169] taking into account $\dot{V}O_{2peak}$ values (22.5±5.6 and mL·kg^{-1}·min^{-1}), and presented "exercise HTN" with SBP values higher than 210 mmHg in men and >190 mmHg in women at the end of the exercise test.[170] Higher values in men compared to women were observed in peak workload (W, *P*<0.001, Δ=47.3%), $\dot{V}O_{2peak}$ (L·min^{-1}, *P*<0.001, Δ=53.3% and mL·kg^{-1}·min^{-1}, *P*<0.001, Δ=24.2%), $\dot{V}CO_{2peak}$ (L·min^{-1}, *P*<0.001, Δ=38.9%), RER, and MET. However, no differences (*P*=0.3) were found for MSWT distance between sexes (Table 20).

Table 20. Participants' peak exercise function.

Variables	AP (*n*=209)	Men (*n*=141)	Women (*n*=68)	*P* M-W	*d* Cohen
Workload (W)	131.1±39.6	146.4±36.1	99.4±25.0	<0.001***	1.5
SBP (mmHg)	211.6±29.9	210.7±31.6	213.6±26.1	0.7	0.1
DBP (mmHg)	101.00±18.5	99.9±16.9	105.7±21.1	0.05	0.3
HR (beats·min^{-1})	151±19.2	150.3±20.0	154.8±17.3	0.2	0.2
$\dot{V}O_{2peak}$ (L·min^{-1})	2.0±0.5	2.3±0.4	1.5±0.3	<0.001***	2.3
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	22.5±5.6	24.1±5.4	19.4±4.6	<0.001***	0.9
$\dot{V}CO_{2peak}$ (L·min^{-1})	2.23±0.6	2.5±0.5	1.8±0.4	<0.001***	1.6
RER	1.1±0.1	1.1±0.1	1.2±0.1	<0.001***	1
MET	6.4±1.7	6.8±1.6	5.5±1.3	<0.001***	0.9
MSWT (m)	834.1±265.0	848.3±264.8	804.7±265.0	0.3	0.2

Abbreviations: AP, all participants; SBP, systolic blood pressure; DBP diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; PP, pulse pressure; $\dot{V}O_{2peak}$, peak oxygen uptake; $\dot{V}CO_{2peak}$, peak carbon dioxide production; RER, respiratory exchange ratio; MET, metabolic equivalent of task; MSWT, modified shuttle walk test distance. P<0.05: Significant difference between men (M) and women (W)

*** *P*<0.001

Regarding participants' **biochemical profile** characteristics and according to the Adult Treatment Panel III[42], LDL-C values were upper to optimal values (<100 mg/dL), TC showed higher values than desirable (<200 mg/dL), and also "cholesterol ratio" (*i.e.,* TC/HDL-C) presented values above the ideal (<3.5). On the other hand, there were normal triglycerides (<200 mg/dL) and HDL-C (>40 mg/dL) values. Furthermore, according to the new International Diabetes Federation definition,[171] participants showed slightly raised fasting glucose (>100mg/dL). The 90th percentile for the HOMA-IR was lower than 3.8, which is not considered diagnostic of IR.[172] Although evidence has shown that CRP concentrations, a proinflammatory biomarker, could be modulated by dietary fatty acid intake,[173] levels of CRP>3mg/L were considered cardiometabolic abnormal[174]. Therefore, taking into account Wildman Modified criteria, participants of the present study were classified as metabolically abnormal obese (*i.e.,*

BMI≥30kg/m^2 and ≥2 cardiometabolic abnormalities).[175] Furthermore, among the three hepatic enzymes, which are indices for the diagnosis of non-alcoholic fatty liver disease (*i.e.,* AST; ALT; and GGT), only ALT showed abnormal criteria (>30 U/L)[176] (Table 21). Triglycerides (mean difference=26.3; 95% CI=0.9-51.7 mg/dL), AST (mean difference=4.2; 95% CI=0.3-8.0 U/L), ALT (mean difference=8.2; 95% CI=1.6-14.8 U/L), GGT (mean difference=11.0; 95% CI=-1.1-23.2 U/L) and AST/ALT (mean difference=-0.1; 95% CI=-0.2-0.0) were significantly lower in women than men. Moreover, HDL-C was higher (*P*=0.002) in women than in men (mean difference=5.0, 95% CI=-13.3-3.3 mg/dL) (Table 21), but both sexes presented healthy values.

Table 21. Biochemical profile characteristics of study's participants.

Variables	AP (*n*=209)	Men (*n*=141)	Women (*n*=68)	P_{M-W}	*d* Cohen
TC (mg/dL)	213.0±134.1	214.1±162.8	210.8±34.0	0.2	0.03
HDL-C (mg/dL)	50.7±33.2	49.1±39.2	54.1±13.9	0.002**	0.2
LDL-C (mg/dL)	127.7±32.2	124.8±33.6	133.5±28.8	0.1	0.3
Triglycerides (mg/dL)	133.9±78.4	142.5±85.4	116.1±57.9	0.03*	0.4
TC/HDL-C ratio	4.7±4.1	5.0±5.3	4.1±1.1	0.1	0.2
Glucose (mg/dL)	106.4±82.4	108.7±100.0	102.1±20.6	0.9	0.1
Insulin (µU/mL)	9.8±5.4	9.4±5.3	11.0±6.0	0.2	0.3
HOMA-IR	2.5±1.6	2.2±1.1	3.0±2.3	0.3	0.4
CRP (mg/L)	4.5±4.5	4.1±4.3	5.4±4.9	0.4	0.3
AST (U/L)	25.3±12.0	26.6±13.0	22.5±9.4	0.01*	0.4
ALT (U/L)	31.9±20.7	34.6±21.2	26.4±18.7	0.01*	0.4
GGT (U/L)	37.3±38.5	40.6±42.8	29.5±25.2	0.006**	0.3
AST/ALT (U/L)	0.9±0.5	0.9±0.5	1.0±0.3	0.029*	0.2

Abbreviations: AP, all participants; TC, Total cholesterol; HDL-C*,* High-*density lipoprotein* cholesterol; LDL-C, Low-*density lipoprotein* cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; CRP, C-Reactive Protein; AST, Aspartate Transaminase; ALT, Alanine Transaminase; GGT, Gamma-glutamyl transferase. P<0.05: Significant difference between men (M) and women (W)
P*<0.05, ** *P*<0.01, * *P*<0.001

The adherence to different healthy **dietary patterns** was calculated to examine the diet quality of the participants (Table 22). The highest adherence was observed in DASH dietary pattern (46.3%), followed by Med (41.1%), and HDI (37.1%) dietary pattern. A higher adherence to Med (*P*=0.022) was shown in women compared to men, with no significant differences between sexes concerning DASH (*P*=0.464) and HDI dietary (*P*=0.406) pattern.

Table 22. Adherence to the Mediterranean (Med), Dietary Approaches to Stop Hypertension (DASH) and Healthy Diet Indicator (HDI) dietary patterns among participants of the study.

Variables	AP (*n*=165)	Men (*n*=114)	Women (*n*=51)	*P* M-W	*d* Cohen
Med-score (0-9)	3.7±1.7	3.5±1.5	4.2±1.8	0.022*	0.4
Adherence (%)	41.1	38.9	46.7		
DASH score (0-8)	3.7±1.7	3.6±1.6	3.8±1.7	0.5	0.1
Adherence (%)	46.3	45	47.5		
HDI score (0-7)	2.6±1.3	2.6±1.3	2.4±1.4	0.4	0.2
Adherence (%)	37.1	37.1	34.3		

*$P<0.05$

Characteristics of all participants divided by **CRF levels** are indicated in Table 23. Significant differences were found in age between high and low CRF level participants ($P<0.05$, Δ=-9.7%). High CRF level participants had lower BMI than those with medium or low CRF level ($P<0.001$, Δ=-8.7% and $P<0.01$, Δ=-16.2%, respectively). Although no significant differences were found in mean SBP and DBP, there were differences in % of BP dipping ($P=0.048$). Those with low CRF level were broadly designated as non-dippers, whereas those in medium and high CRF level were designated as dippers in accordance with ESH/ESC Guidelines for the management of arterial HTN.[9] According to biochemical profile, significant differences were found in ALT, GGT and AST/ALT ratio. Thus, participants with low CRF level showed elevated ALT, GGT and lower AST/ALT ratio ($P=0.001$, $P=0.030$, and $P=0.018$ respectively) compared to medium (ALT: $P<0.05$, Δ=50.8%, and GGT: $P=0.085$, Δ=41.2%) and high (ALT: $P<0.001$, Δ=118.8%, GGT: $P=0.035$, Δ=76.4% and AST/ALT ratio: $P=0.014$, Δ=27.3%) CRF level. No significant differences were observed in the rest of biochemical parameters among CRF levels.

Table 23. Characteristics of the study population classified by cardiorespiratory fitness level (low, medium, high).

	Cardiorespiratory fitness groups				
Variables	**Low (M=48,W=24)**	**Medium (M=51,W=23)**	**High (M=42,W=21)**	***P*-value**	***ω-squared***
Age (yrs)	56.7±1.0	53.8±0.9	51.2±1.1	0.003**	0.00995
BMI (kg/m^2)	34.0±0.5	31.2±0.5	28.5±0.5	<0.001***	0.206
WHR (cm)	0.97±0.1	0.98±0.13	0.95±0.08	0.8	-0.0807
SBP (mmHg)	136.6±1.8	135.8±1.6	135.2±1.9	0.9	-0.005
DBP (mmHg)	78.4±1.0	78.6±0.9	79.7±1.1	0.7	0.0006
BP DIPPING (%)	9.7±7.3	12.5±6.8	12.1±6.6	0.048*	0.0228
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	17.8±0.5	22.6±0.5	27.7±0.6	<0.001***	0.6739
MET_{peak}	5.0±0.2	6.5±0.2	7.5±0.2	<0.001***	0.59183
TC (mg/dL)	202.4±19.2	233.5±20.2	206.0±22.1	0.7	-0.0024
HDL-C (mg/dL)	48.9±4.6	46.8±4.6	57.2±5.2	0.4	-0.08124
LDL-C (mg/dL)	127.6±4.5	120.8±4.7	134.9±5.1	0.1	0.01376
Triglycerides (mg/dL)	134.0±10.6	144.2±10.6	122.7±12.0	0.3	0.00191
TC/HDL-C	4.4±1.2	5.6±7.8	4.1±1.4	0.3	0.012357
Glucose (mg/dL)	117.6±11.5	101.0±11.1	99.1±12.7	0.7	0.00255
Insulin (µU/mL)	7.9±1.3	11.8±1.2	9.4±1.5	0.2	0.97905
HOMA-IR	1.9±0.4	3.1±0.4	2.3±0.4	0.1	0.000739
CRP (mg/L)	5.9±5.3	4.2±4.3	2.5±1.6	0.5	0.0565
AST (U/L)	28.4±2.2	25.3±2.3	25.5±2.8	0.5	-0.0032
ALT (U/L)	46.6±4.4	30.9±4.5	21.3±5.1	0.001**	0.06250
GGT (U/L)	49.4±59.02	33.1±21.0	28.0±14.4	0.030*	0.04139
AST/ALT ratio	0.8±0.3	0.9±0.2	1.1±0.8	0.018*	0.04567

Abbreviations: BMI, body mass index; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP diastolic blood pressure; MBP, mean blood pressure.; VO_{2peak}, peak oxygen uptake; TC, Total cholesterol; HDL-C, High-*density lipoprotein* cholesterol; LDL-C, Low-*density lipoprotein* cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; CRP, C-Reactive Protein; AST, Aspartate Transaminase; ALT, Alanine Transaminase. P<0.05: Significant difference between men (M) and women (W)

*P<0.05, ** P<0.01, *** P<0.001

4.5. Discussion

This was the first study showing the clinical, physical, physiological and dietary patterns of overweight/obese and sedentary adults diagnosed with primary HTN characterized by sex and CRF level. The data collected provide a thorough understanding of the physiopathology of the studied population and emphasize the importance of CVR screening for CV disease prevention in clinical practice. Overall, the assessed individuals suffered from resting HTN, were metabolically abnormal obese with poor CRF level, exercise-induced HTN, and the majority of them lacked a healthy dietary pattern, which confirms a high CVR profile. Specifically, women showed a better biochemical and dietary pattern profile than men, but physical and exercise physiological characteristic were poorer; hence, calling into attention the sex differences in physiology between women and men. Finally, a favorable CRF level seems to contribute to the attenuation of some CVR factors, such as high BMI, non-dipping profile, and high hepatic fat.

All population. In addition to HTN and obesity, the results of the present study clearly showed additional CVR factors, which may potentiate each other, leading to a total CVR that may be greater than the sum of its individual components.[9] Potentially, some of the modifiable risk factors were very present in the studied population (*i.e.,* HTN, obesity, physical inactivity, atherogenic diet) along with non-modifiable risk factors related to age (men ≥45 years, women ≥55years).[42] As a result, although the population of this study presented favorable metabolic features such as low levels of HOMA-IR and fasting triglycerides as well as normal HDL-C, a clustering of cardiometabolic risk factors are shown (*i.e.,* BMI ≥30 kg/m^2 and ≥2 cardiometabolic abnormalities: HTN, elevated glucose level and systemic inflammation) along with non-healthy levels of TC, ALT and TC/HDL-C ratio. These results lead to categorizing the individuals as metabolically abnormal obese according to Wildman Modified criteria.[175] Indeed, both inflammation (exemplified by high C-reactive protein levels, 4.5±4.5 mg/dL), and TC/HDL-C ratio (4.7±4.1) are factors associated with the development of atherosclerosis and the pathogenesis of CV disease in the general population.[38] Furthermore, previous studies have also shown that high ALT values (31.9±20.7 U/L, in the present study) were related to higher levels of hepatic fat, abdominal fat, and insulin resistance,[176] and it was also independent predictor of Diabetes Type II.[177] Adding to that, knowing that the risk of CV disease and death is often more related to fitness level than BMI,[178] the very poor CRF level in this population could be another important, yet not recognized, clinically risk marker.[38] On the other hand, even though there is currently no consensus on the normal BP response during dynamic exercise testing, participants of the present study showed “exercise-induced HTN” (*i.e.,* SBP peak values >210 mmHg for men and >190mmHg for women).[170] Related to that, proposed pathophysiologic factors include excessively high sympathetic tone during exercise, decreased aortic

distensibility, increased left ventricular mass, and endothelial dysfunction.[170,179] These results may identify those individuals that are not well controlled in resting HTN in clinical practice and could present a cardiac "end-organ" manifestation of HTN in the future. Thus, some authors have even proposed exercise SBP as being an effective and more convenient technique than ABPM for identifying the prehypertensive state and to predict future risk for adverse CV events.[170]

There is increasing evidence that **sex differences** are important in pathophysiology treatment, and more relevant for noncommunicable diseases as HTN. With regards to body composition, the heterogeneity by sex in the relationship between hormones and body composition is well known. Thus, women present increased subcutaneous fat accumulation promoted by estrogen, and men feature a greater trunk and visceral and liver fat.[180] The aforementioned was corroborated by the results of the present study in relation to a "better" body composition in men (*i.e,* higher FFM and lower FBM, Table 19) compared to women, but women showing a better metabolic profile (higher values in HDL-C, and lower triglycerides and hepatic enzymes, Table 21) than men. However, taking into account the percentage of FBM, both sexes were obese according to cut off points for body fat percentage (*i.e.,* ≥25.0% for men and ≥35.0% for women).[28] Hence, men could present a higher CV or metabolic risk profile mainly due to the higher liver enzyme activities (*i.e.,* ALT, ALT, GGT and AST/ALT ratio), and specifically with ALT values upper to healthy cutoff (<30 U/L), which is closely associated with non-alcoholic fatty liver disease.[181] Furthermore, even though both sexes presented HDL-C and triglycerides values within the normal healthy range, the indirect vascular effect of estrogen in women may have had an influence on serum lipid concentrations with better values compared to men (Table 21), leading to a cardioprotective effect.[182] Likewise, circulating estrogen in women may potentiate the vasodilatory effect of β-adrenergic activation by a nitric oxide mechanism causing vasodilation and favoring a lower resting DBP (P=0.001) compared to men (Table 19).[183]

Regarding the **exercise function**, this study showed that there are natural physiological differences between men and women when objective variables are considered (*i.e.,* $\dot{V}O_{2peak}$), but not when the physical capacity is evaluated through a field test (*i.e.* MSWT) (Table 20). These results may question the validity of using this or similar field tests to evaluate CRF in this population. Thus, sex differences in body fat, hemoglobin, dimensions of the oxygen transport system and musculature could account for the different CRF level.[184] However, according to ACSM´s Guidelines for Exercise Testing and Prescription,[169] both sexes presented "very poor" CRF level (Table 20), which is associated with a high risk of CV disease and all-cause mortality.[59]

The **adherence to healthy dietary patterns** in relation to CV disease has been previously examined. In this way, the Med pattern, which shares many of the characteristics of the DASH diet, was

inversely associated with arterial BP,[185] knowing that a higher adherence leads to 70% less prevalence of HTN.[186] However, in a representative Spanish population, only 17.3% of those diagnosed with HTN had a DASH-accordant diet and 17.2% Med-accordant diet.[187] These results are in keeping with other population studies showing that a lower adherence to HDI and DASH diet was associated with the prevalence of HTN.[188,189] A similar adherence to the Med compared to the present study (41.1%, Table 22) was observed in a Balearic adult population (43.1±5.8%),[190] thus confirming the association between adherence to a healthy diet and HTN, and the higher adherence to Med diet in women with better metabolic profile than men.

It has been proposed that **CRF** should be incorporated as a vital sign in CV disease risk factor evaluation and management[159] and that the addition of CRF to traditional risk factors would significantly improve the classification of risk for adverse outcomes.[59] Previous studies have suggested that low CRF appeared to have an indirect effect on the risk for subsequent CV events moderated through higher metabolic risk.[191] In the current study, similarly, it was found that CRF could significantly moderate some CVR factors. Thus, the low CRF group was older (P=0.003), had higher BMI (P<0.001), no-dipping profile (P=0.048), and higher hepatic fat (ALT, P=0.001; GGT P=0.030; AST/ALT ratio P=0.018) compared to moderate and high CRF level (Table 23). Taking into account that other studies have also demonstrated that the least fit individuals (<6 METS for those without CV disease) had >4-fold increased risk of all-cause mortality compared with the fittest,[56] it could be stated that the addition of CRF to established risk scores would further improve risk prediction.[59] Results of the present study reinforce previous investigations showing that worse CRF was associated with increasing non-alcoholic fatty liver disease represented by non-healthy values of ALT, GGT and AST/ALT ratio.[176] Furthermore, previous studies also showed that an absent normal dipping BP pattern (*i.e.,* <10% fall in nocturnal BP relative to diurnal BP) was independently predicted by increasing age, BMI and treated HTN (among other factors). These results confirm that non-dipping BP pattern, 1) is associated with increased CV mortality risks[192] and 2) is determined mainly by non-genetic factors.[193]

This study has limitations. Firstly, although our sample size was sufficient as an initial investigation for the EXERDIET-HTA study; it would not be comparable with that of larger epidemiological studies. Secondly, the current study only had 32.5% of women, which does not represent an equal gender split of the sample. However, even though female is usually lower than male enrolment in clinical trials, we have got significant differences, which adds knowledge in the gap for BP management to improve women' health.

4.6. Conclusions

In summary, the studied population diagnosed with primary HTN presented a high CVR profile showing the following characterization: obesity metabolically abnormal with poor CRF level, exercise-induced HTN and non-healthy dietary pattern. Specifically, women showed a better biochemical and dietary pattern profile than men did, but physical and exercise physiological characteristics were poorer. Furthermore, a favorable CRF level seemed to contribute to the attenuation of some CVR factors, such as high BMI, non-dipping profile, and high hepatic fat.

In closing, by analyzing a hypertensive, obese and sedentary population, we have identified specific clinical, physical, physiological and dietary patterns that strongly suggest that targeting key behaviors such as improving nutritional quality and CRF through regular physical activity will contribute to getting a “healthy population” with independent beneficial effects on CVR factors.

Capítulo 5 / Chapter 5

Assessment of cardiovascular risk and vascular age in overweight/obese adults with primary hypertension: the EXERDIET-HTA study.

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5.1. Abstract

Objectives: Hypertension (HTN), obesity and low cardiorespiratory fitness (CRF) are associated with an increased risk of a cardiovascular event. Taking part overweight/obese individuals with HTN the aims of the current study were: to estimate cardiovascular risk (CVR) and vascular age (VA) profiles analyzing potential sex differences; to determine whether VA is higher than chronological age (CA) and, whether CVR is associated with a low level of CRF.

Methods: Overweight/obese non-Hispanic white participants (n=209; 141 men and 68 women) with primary HTN had their CVR and VA determined using the New Pooled Cohort Risk Equations and The Framingham method, respectively. Considering values of peak oxygen uptake, participants were divided into tertiles for each sex.

Results: The CVR, but not VA (p=0.339), was higher (p<0.001) in men compared to women irrespective of age. Irrespective of sex VA was higher than CA (p<0.001). Age and body mass index were higher (p<0.05) in the low CRF group compared to other groups. There were no differences in CVR (p=0.907) and VA (p=1.643) when values were separated into CRF groups.

Conclusions: Pooled Cohort Equations could underestimate the risk of suffering a cardiovascular event in the following 10 years in overweight/obese non-Hispanic white women with HTN compared to men. The VA appears to be a useful tool in communicating CVR in this population irrespective of sex. The CRF alone may not be enough to moderate the CVR.

Trial Registration: NCT02283047

Keywords: Cardiovascular disease; Chronological age, Cardio-respiratory fitness.

5.2. Introduction

Cardiovascular disease (CVD) is the leading cause of early morbidity and hospitalization in the world.[5] According to World Health Organization, 17.5 million people died from CVD in 2012, representing 31% of all deaths, of which 7.4 and 6.7 million were due to coronary heart disease and cardiovascular (CV) events, respectively.[194] Furthermore, a large number of individuals have a heightened risk of CVD because they have two or more associated risk factors.[4,5,9]

Several attempts have been made to determine CV risk (CVR) factors associated with having a cardiac event. Guidelines indicate that age, sex, diabetes, smoking, cholesterol, and hypertension (HTN) have a causal relationship with CV events and premature death.[4,9,195] High blood pressure (BP), often referred to as HTN, is the most common CVR factor that leads to heart failure, stroke, angina, and premature death if not detected early and treated adequately.[91] Additionally, population-based research suggests that obesity is directly related to HTN.[155] An appreciation of the clinical significance of obesity-related HTN has since grown substantially over time. As such, obesity is now recognized as a major cause of HTN (at least 75% of all cases), and the combination of both are well known to increase CVR.[155] Additionally, CVR factors, associated with the development of CVD, are similar in both sexes.[196] However, with the same risk factors, CVR is two to five times more common in men than in women, *i.e*., women have a lower predicted 10-year risk.[3] It has previously been suggested that this discrepancy may be due to the protective action of estrogens[196] or because substantial disparities exist in the prevention, recognition, management and clinical outcomes of CVD in women.[197] A CVR score can be used to determine CVD using the Pooled Cohort Equations and the Framingham Heart Study, which are tools commonly, used to define the 10-year risk of developing CVD.[3] An additional tool for evaluating the overall CVR is vascular age (VA). This is a quite novel concept derived from Framingham CVR tables, which indicates the biological age of an individual's arteries (*i.e.,* the age of the vascular system of a person with different CVR factors).[5,49] This process is accelerated with the presence of additional CVR factors and is associated with changes in the mechanical and the structural properties of the vascular wall, which leads to poor endothelial health and the loss of arterial elasticity.[5,155]

The relationship between poor lifestyle and increased CVR is well documented. As such, there is a persistent need to discuss cardio metabolic lifestyle factors with all patients, in order to reduce CVD and control the CVR factors. Cardiovascular risk factors can be classified as modifiable and non-modifiable. Non-modifiable risk factors are (but not limited to) age, sex and family history. Modifiable CVR factors are cardio metabolic lifestyle factors and can be altered during the cause of one life; these include but are not limited to smoking, alcohol, diet and importantly physical activity.[38] Higher levels of

physical activity can improve the CVR in diseased or at-risk patients. Cardio-respiratory fitness (CRF) can be used to quantify these positive effects as it is negatively associated with a reduction in CV morbidity and mortality.[38]

Currently, there is no known research that measures CVR and VA and its association with CRF in primary hypertensive and overweight/obese adults. Considering the importance of CVR factors and the limited scientific literature, the aims of the study were: 1) to estimate CVR and VA profiles of overweight/obese patients with HTN, analyzing potential sex differences, (2) to determine whether VA is higher than chronological age (CA) and, (3) to determine whether CVR is associated with a low level of CRF.

5.3. Methods

Study design

Baseline data from EXERDIET-HTA randomized controlled experimental trial were taken for the purpose of this study.[143] The design, selection criteria, and procedures for the EXERDIET-HTA study have been previously detailed.[143] The study protocol was approved by The Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital (2015-030), and all participants provided written informed consent prior to any data collection.

Participants

Non-Hispanic white participants (n=209) with primary HTN (≥140 Systolic BP (SBP) and ≥90 diastolic BP)[9], who were classified as being overweight (body mass index, BMI≥25) or obese (BMI≥30)[34] were recruited from the cardiology services and local media.

Cardio-respiratory fitness

Cardio-respiratory fitness was determined using a cardiopulmonary exercise test to assess $\dot{V}O_{2peak}$. Briefly, the test was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). The testing protocol was started at 40W (70 rpm) with gradual increments of 10W every minute until exhaustion with continuous electrocardiogram monitoring. Expired gas analysis was determined using a commercially available metabolic cart (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) which was calibrated before each test with a standard gas of known concentration and volume. Breath by-breath data were measured continuously during exercise before

being averaged over each 60 second periods. Blood pressure was measured every two minutes throughout the test. At the end of each stage, the rate of perceived exertion (6 to 20) was recorded (Borg Scale). Peak oxygen uptake was defined as the highest oxygen uptake value attained toward the end of the test. Achievement of $\dot{V}O_{2peak}$ was assumed with the presence of two or more of the following criteria: 1) volitional fatigue (>18 on Borg scale), 2) peak respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) ≥1.1, 3) achieving >85% of age predicted maximum heart rate, and 4) failure of $\dot{V}O_2$ and/or heart rate to increase with further increases in work rate.[143]

The distributions of $\dot{V}O_{2peak}$ were divided into tertiles for each sex: The lowest tertile (Low-CRF group); $\dot{V}O_{2peak}$ ≤21 in men and $\dot{V}O_{2peak}$ ≤16 in women; the intermediate tertile (Medium-CRF group); 21.1<$\dot{V}O_{2peak}$ ≤26 in men and 16.1<$\dot{V}O_{2peak}$≤21 in women and the highest tertile (High-CRF group); $\dot{V}O_{2peak}$>26 in men and $\dot{V}O_{2peak}$>21 mL·kg·min^{-1} in women.

Measurement of CVD Risk Factors

Established CVR factors used in the present study to determine the CVR and VA of participants were defined as follows:

Blood pressure. Ambulatory BP monitoring was conducted over a 24 hour period using an oscillometric ABPM 6100 recorder (Welch Allyn, New York, USA) to evaluate SBP (as used to determine CVR).[3] The device was used in line with the recommendations set by the ESH/ESC guidelines. As such BP was measured at 30-minute intervals during the awake-time and at 60-minute intervals during periods of sleep. Data were only used if at least 75% of the awake-time and sleep periods were successfully recorded.[143]

Blood sampling. Fasting venous blood (12.5ml) was obtained from each participant. Diabetes mellitus (DM) was defined as a fasting glucose of ≥126 mg/dL. Additionally, measurements of glucose and lipid profile (total-, HDL- and LDL-cholesterol) were assayed.

Self-report. Age and cigarette smoking status were assessed by self-report. All medicines were ascertained from the participant's physician.

Cardiovascular risk. The Framingham Heart Study is a quantitative method used in primary care for assessment of general CVR profile. The absolute risk applies to the individual, a score of 10% means that there is a 10% chance of having a CV event within the next 10 years.[3,49] Under 6% is considered low risk; between 6 and 20% medium risk, and ≥20% high risk.[49] Recently, New Pooled Cohort Risk Equations have been developed from the Framingham Heart Study.[3,49] The equation to estimate the 10-year risk

of developing a first atherosclerotic CVD event was developed from sex- and race-specific proportional-hazard models that included the covariates of age treated or untreated high SBP level, total cholesterol and HDL-C concentrations, current smoking status, and history of DM. For the equation, the values for age, lipids, and SBP were log transformed. Interactions between age and lipids or age and SBP used the natural log of each variable. Calculation of the 10-year risk estimate for hard atherosclerotic CVD is described as a series of steps.[3]

Vascular age. The Framingham method was used to determine the VA of all participants.[49] The VA indicates the biological age of the individual's vascular system, as the age a person would be with the same calculated CVR but whose risk factors were all within normal ranges. The sex-specific risk factors considered were age, HDL-C, total cholesterol, SBP, DM, and smoking status. Each variable received a weighted score; the sum of the score for each variable was then translated to the risk of a CV event in 10 years and the VA.[49]

Statistical analysis

Descriptive statistics were calculated for all variables. Data are expressed as mean±standard deviations (SD). All variables were deemed normally distributed using a Kolmogorov-Smirnov apart from, age, total cholesterol, HDL-C, CVR and VA which had a skewed distribution and were. Therefore, log transformed prior to any analysis.

A 2 sample *t*-test was used to determine whether there was a significant sex difference for the variables: age, BMI, SBP, total cholesterol, HDL-C, antihypertensive medication, cigarette smoking, and DM. Analysis of covariance (ANCOVA) was used to examine the dependant variables (age, BMI, SBP, total cholesterol, HDL-C, antihypertensive medication, cigarette smoking, DM, CVR, and VA) of the participants classified by CRF level (low, medium and high). A Bonferroni test was used to determine the level of significance when a significant main effect was found. Statistical significance was set at $p<0.05$. The statistical analyses were performed with the SPSS version 22.0 software package.

5.4. Results

The characteristics of CVR factors classified by sex are presented in Table 24. The mean age (±SD) of participants was 54.0±8.1 yrs with 67.5% and 32.5% being men and women, respectively. All participants were classified as obese (BMI>30 kg/m^2) in accordance with AHA/ACC/TOS guidelines for the Management of Overweight and Obesity in Adults.[34] Although 87.1% of all participants were taking anti-hypertensive medication, mean SBP suggested that all participants irrespective of sex were pre-hypertensive. However, there was a trend to suggest that women had a lower SBP compared to men

(mean difference=1.6; 95%, confidence interval (CI)=-2.5-5.7 mmHg). Mean total cholesterol was similar in men and women with both sexes exceeding cut-off values set by the ESH/ESC guidelines,[9] but there was also a trend to suggest that women had lower total cholesterol than men (mean difference=3.3; 95% CI=-30.6-37.3 mmHg). Moreover, HDL-C was significantly higher (p=0.002) in women than men (mean difference=5.0, 95% CI=-13.3-3.3 mg/dL), but both were inside the healthy cut-off values suggested by the ESH/ESC guidelines.[9] Smoking was present 11.4% of the participants and 4.5% of the sample was suffering from DM.

Table 24. Characteristics of risk factors and cardiovascular risk classified by sex. Values are mean±SD or percentage (%)

Dependant variable	All participants (n=209)	Men (n=141)	Women (n=68)	P_{M-F}
Age (yrs)	54.0±8.1	54.3±7.9	53.4±8.5	0.426
BMI (kg/m^2)	31.3±4.6	31.3±4.3	31.5±5.2	0.873
SBP (mmHg)	135.9±14.1	136.4±12.9	134.8±16.3	0.433
Total cholesterol (mg/dL)	213.0±126.1	214.1±162.8	210.8±34.0	0.245
HDL-C (mg/dL)	50.7±33.1	49.1±39.2	54.1±13.8	0.002*
Antihypertensive medication (%)	87.1%	85.1%	91.2%	0.220
Cigarette smoking (%)	11.4%	10.6%	13.2%	0.581
DM (%)	4.5%	5%	3%	0.500
Cardiovascular risk (%)	8.1±6.3	10.0±6.5	4.3±3.6	<0.001*

BMI, body max index; SBP, systolic blood pressure; HDL-C *H*igh-density lipoprotein cholesterol; DM, diabetes mellitus.
*Significant difference (p<0.05) between men and women.

The absolute CVR was significantly different (p<0.001) between sexes with women having a lower CVR than men (mean difference 5.8, 95% CI=-3.8-7.7 %, Table 24). Additionally, in accordance with the Framingham study and ACC/AHA Guideline on the Assessment of CVR[3,49] men were considered to be at medium risk whereas women were considered low risk. As shown in Table 25, there were no sex differences in VA (mean difference=1.4, 95% CI=-2.4-5.1 yrs). However, VA was significantly higher (p=0.001) than CA (mean difference=8.8, 95% CI=7.2-10.3 yrs).

Table 25. Results of vascular and chronological age. Values are mean ± SD.

Dependant variable	VA (y)	CA(y)	PVA-CA
Total (n=209)	61.7±9.5	54.0±8.1	<0.001*
Men (n=141)	62.1±8.5	54.3±7.9	<0.001*
Women (n=68)	60.8±11.1	53.4±8.5	<0.001*
P M-F	0.339	0.426	

Y, years old; VA, vascular age; CA, chronological age.
*Significant difference (p<0.05) between vascular and chronological age.

Characteristics of the participants separated into CRF groups are presented in Table 26. Bonferroni analysis revealed that age was higher (p<0.05, Δ=-9.7%) in the low CRF group compared to

the high CRF group. Moreover, BMI was higher in the low CRF group compared to the medium CRF group (34.0±0.5 *vs.* 31.2±0.5 kg/m^2; mean difference=2.8, 95% CI=1.1-4.4 kg/m^2) and to the high CRF group (34.0±0.5 *vs.* 28.5±0.5 kg/m^2; mean difference=5.5, 95% CI=3.8-7.2 kg/m^2). No significant differences were observed among CRF groups for SBP, total cholesterol, antihypertensive medication, smoking, DM or HDL-C (p>0.05).

Bonferroni analysis revealed that no significant differences were observed in CVR (p=0.907) and VA (p=1.643), when values were separated into CRF groups (Table 26). However, the low CRF group showed an upward trend in VA with higher values than those with medium CRF group (mean difference=0.5, 95% CI=-4.1-5.0 yrs) or higher CRF group (mean difference=3.4, 95% CI=-1.5-8.4 yrs).

Table 26. Cardiovascular risk factors, cardiovascular risk and vascular age classified by fitness level. Values are mean ± SD or percentage (%)

	Cardiorespiratory fitness groups			**One-way ANOVA**		
Dependant variable	Low (M=48,W=24)	Moderate (M=51,W=23)	High (M=42,W=21)	*P-value*	*F-value*	*%Variance*
Age (yr old)	56.7±1.0	53.8±0.9	51.2±1.1	0.003*****	6.5	6.0
SBP (mmHg)	136.6±1.8	135.8±1.6	135.2±1.9	0.882	0.126	0.1
BMI (kg/m^2)	34.0±0.5	31.2±0.5	28.5±0.5	<0.001*****	29.631	22.5
Total cholesterol (mg/dL)	202.4±19.2	233.5±20.2	206.0±22.1	0.744	0.272	1.0
HDL-C (mg/dL)	48.9±4.6	46.8±4.6	57.2±5.2	0.363	1.185	1.5
Antihypertensive medication (%)	88.9%	86.5%	85.7%	0.845		
Cigarette smoking (%)	15.3%	10.8%	8%	0.400		
DM (%)	1.4%	6.7%	4.8%	0.273		
Cardiovascular risk (%)	8.1±0.6	8.4±0.6	7.9±0.7	0.907	0.253	0.4
Vascular age (y)	62.9±1.3	62.5±1.3	59.4±1.4	1.643	1.710	2.9

% variance is the estimated variance explained by the mean effects within each group for the named variable.
M, men; W, women; SBP, systolic blood pressure; BMI, body max index; HDL-C, *H*igh-density lipoprotein cholesterol; DM, diabetes mellitus.
***** Shows the significantly different (p<0.05) among groups.

5.5. Discussion

To our knowledge, this is the first known study to estimate the CVR and VA in overweight/obese people with HTN and its association with CRF level using the recently developed Pooled Cohort Equations[3] and the original 2008 Framingham model. The main findings of this study were: 1) CVR is

significantly higher in men than in women despite them having same CVR values, and this is not effected by age; 2) predicted VA is significantly higher than CA in overweight/obese people with primary HTN with no sex differences, and 3) CRF alone did not appear to significantly moderate CVD. These findings highlight the importance of being able to determine the CVR and VA of overweight/obese people with primary HTN. Considering the known increase in CVD in hypertensive patients and the relative ease of predicting 10-year CVR; defining CVR and VA in a hypertensive population would likely be a useful tool for clinicians.

Although the role of major CVR factors in the development of CVD and VA were similar in both sexes, Table 24 shows that CVR is 57% higher in men than in women (p=0.001), with an estimated 10-year risk of hard atherosclerotic CVD event of 10% in men and 4.3% in women, which represents medium and low risk, respectively. As such, it is likely that men have a higher risk of suffering a CV event in the following 10 years. The difference in the HDL-C level could be one of the determinants of the sex difference in CVR profile in the present study, with women showing higher concentrations compared to men. It is well known that high concentrations of HDL-C prevent the development of atherosclerosis and CVD. In particular, the transport of reserve cholesterol and the inhibition of oxidized LDL-induced monocyte infiltration can avoid this development.[198] In addition, the Framingham Heart Study showed that HDL-C was the most powerful lipid predictor of CHD risk in both sexes >49 yr old. For every 1mg/dL increment in HDL-C, there was an associated 2% decrease in the risk of CHD in men, and a 3% decrease in women.[199] Previous studies have shown that the increased CVR in men was hidden behind an almost-normal classic lipid profile, being total cholesterol, LDL-C, and TG higher, and HDL-C concentrations significantly lower than women (pre or post menopausal status), with all values within the normal range.[200] In our study, both sexes presented hyperlipidemia values (total cholesterol>190mg/dL) and prehypertensive SBP values with slight, but concomitant variation (*i.e.,* an upward trend in men compared to women), which has been shown to increase the risk of coronary heart disease and promotes a poor cardio metabolic profile.[200] It seems that there is a cardio protective effect of endogenous estrogens in premenopausal women, when compared with age-matched men, due to an enhanced HDL quality. However, in postmenopausal women, there is a trend to present with a significantly increased BMI, BP, LDL-C, and total cholesterol, along with a reduction of absolute HDL-C concentration, with changes in the composition of HDL particles.[182,200] In the present study, 51.5% of women were premenopausal state. Therefore, it should take into account that in the current study: 1) both men and women were in normal HDL-C values (>40 mg/dL for men, and >46 mg/dL for women),[9] along with obesity, hyperlipidemia and primary HTN diagnostic, 2) almost half of the women were on postmenopausal state, and 3) the sex-specific risk prediction model used in the Pooled Cohort Equation always calculates a higher risk in men compared to women, despite them having the same CVR values

and regardless of age.[3] As such, women could show an underestimated CVR profile with less aggressive treatment strategies. Nowadays, a greater number of women die annually from CVD compared with men.[201] Thus, although sex differences are well documented in the prevalence of the[202] factors, the clinical manifestation and incidence of CVD and the impact of risk factors on outcomes in women is often underestimated due to the misperception that females are "protected" against CVD.[203]

As expected, VA was significantly higher (p=0.001) than CA (Table 25) (VA=62 *vs.* CA=54 yrs). As such, people with primary HTN and obesity are "older" for their VA when compared with their CA. It is, therefore, likely that the health of the heart and blood vessels are more deteriorated than they should be in this population.[49] There is good evidence that CA is strongly and independently related to CVR, but this is not necessarily so for the VA. Repeated exposure to CVR factors across the lifespan leads to between-subject differences in VA and CA.[204] Previous research has shown that in apparently healthy and asymptomatic people, 72.45% of the individuals had a greater VA than the CA, suggesting that this risk may be underestimated.[205] The current study suggests that key contributors of an increased VA in a hypertensive population are dyslipidemia, SBP, treatment for HTN, obesity, and smoking (87.2% of them showing a greater VA than CA). Thus, VA seems to be a useful tool in communicating about risk to individuals, such as hypertensive and obese patients, who are at a greater risk of a CVD event and warrant early intervention of modifiable CVR factors (*i.e.,* healthy eating, increasing physical activity, cessation of cigarette smoking and alcohol).

It is well recognized that physical activity is an important factor for reducing CVR and CVD.[3,38] Previous research has suggested that people with sedentary behaviors are at a higher risk of all-cause mortality compared with those who do at least 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity aerobic physical activity per week, as recommended by WHO.[38] In the current study, it was found that CRF alone does not significantly moderate CVR, due to no differences among the three CRF groups (Table 26). However, mean difference and CI suggest that those who are in the low CRF group, have meaningfully higher VA (although no significant) (Table 26); which suggests that CVR may in-part be moderated by CRF but in conjunction with other CVR factors such as BMI and age. Aging and inactivity are associated with a decrease in both CRF and morphological changes in all layers of the vascular tree, and these are accompanied by increased arterial stiffness and aortic pressure, leading to a higher VA.[206] Furthermore, in the present study, BMI explained the 22.5% and age 6% of the variance between the CRF groups. The current study reinforces the evidence linking obesity, age and CRF level with VA in primary hypertensive population,[78,155] suggesting that low CRF could potentially be used in conjunction with other CVR factors to help determine predisposal of CVD, but not as a factor in its own right. Previous studies have concluded that physical activity is associated with beneficial changes in

circulating lipids and lipoproteins, body weight, BP and insulin sensitivity, having a significant reduction in CVR.[38,78] In line with that, the last 2016 European Guidelines on CVD prevention in clinical practice highlight the CRF as a factor that might influence the relationship between adiposity and clinical prognosis in the "obesity paradox". Thus, normal-weight individuals with a low CRF have a higher risk of mortality than fit individuals, regardless of their BMI.[5,89]

Although our study has highlighted the importance of determining CVR factors in a hypertensive population, several limitations should be acknowledged. Firstly, although our sample size was sufficient as an initial investigation into CVR and HTN; it would not be comparable with that of larger epidemiological studies, and future studies should consider large-scale investigations as well as determining the short and long-term effects of different interventions. Secondly, the current study only had 32.5% of women, which does not represent an equal gender split. As this poses statistical issues, future studies, particularly those using interventions should look to recruit equal numbers. Lastly, although CRF did not sufficiently moderate CVR in the current study, the effects of physical activity in hypertensive patients with a broader range of $\dot{V}O_{2peak}$ should be further investigated in conjunction with other modifiable risk factors to determine the effectiveness of moderating CVR and VA. Additionally, future studies should look to determine whether VA and CVR can be used to more easily inform patients of their cardiovascular health than current methods.

5.6. Conclusions

Findings suggest that male non-Hispanic white overweight/obese individuals with diagnosed HTN have a higher risk of suffering a CV event in the following 10 years compared to females according to the greater CVR assessed using the Pooled Cohort Equations. However, CVR in women could be underestimated when both sexes present with the same CVR values and age. Those who are overweight/obese with HTN have an "older" VA compared to their CA irrespective of sex. Finally, although CRF alone did not moderate CVR in the current study, further research into the effect of physical activity alongside additional modifiable CVR factors in HTN populations, particularly those who are the least active is warranted. Predictions of CVR and VA estimation may represent as a useful clinical tool for detecting patients at risk of a cardiac event, but estimation equations should be more focused on sex-related differences.

Capítulo 6 / Chapter 6

Effects of different aerobic exercise programmes with nutritional intervention in sedentary adults with overweight/obesity and hypertension: EXERDIET-HTA study

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6.1. Abstract

Background: Both exercise training and diet are recommended to prevent and control hypertension (HTN) and overweight/obesity.

Purpose: To determine the effectiveness of different 16-week aerobic exercise programs with hypocaloric diet on blood pressure (BP), body composition, cardiorespiratory fitness (CRF) and pharmacological treatment.

Methods: Overweight/obese, sedentary participants (n=175, 54.0±8.2 yrs) with HTN, were randomized into attention control group (AC, physical activity recommendations) or one of three supervised exercise groups [two days/week: high-volume with 45 min of moderate-intensity continuous training (HV-MICT), HV and high-intensity interval training, alternating high and moderate intensities (HV-HIIT), and low volume-HIIT (LV-HIIT, 20 min)]. All variables were assessed pre and post intervention. All participants received the same hypocaloric diet.

Results: Following the intervention, there was a significant reduction in BP and body mass in all groups with no between-group differences for BP. However, body mass was significantly less reduced in the AC group compared with all exercise groups (AC=-6.6%, HV-MICT=-8.3%, HV-HIIT=-9.7%, LV-HIIT=-6.9%). HIIT groups had significantly higher CRF than HV-MICT, but there were no significant between-HIIT differences (AC=16.4%, HV-MICT=23.6%, HV-HIIT=36.7%, LV-HIIT=30.5%). Medication was removed in 7.6% and reduced in 37.7% of the participants.

Conclusions: The combination of hypocaloric diet with supervised aerobic exercise 2 days/week offers an optimal non-pharmacological tool in the management of BP, CRF and body composition in overweight/obese and sedentary individuals with HTN. HV-HIIT seems to be better for reducing body mass compared to LV-HIIT. The exercise-induced improvement in CRF is intensity dependent with LV-HIIT as a time-efficient method in this population.

Trial Registration: NCT02283047

Keywords: Obesity; hypertension; high-intensity interval training; low-volume training; blood pressure; cardiorespiratory fitness; body composition

6.2. Introduction

Due to the recent changes in both eating habits and lifestyles (*i.e.,* the abandonment of traditional dietary patterns and culinary techniques, increased sedentary time, and decreased volume and intensity of physical activity, which results in an imbalance in the energy balance), primary hypertension (HTN), overweight/obesity, and being sedentary often coexist in the same person.[78,155] Obesity has been considered the driving force of this response culminating in a significant increase in direct and indirect healthcare costs.[34] It is, therefore, important to develop cost-effective strategies for the treatment of obesity in order to reduce the prevalence of obesity-related HTN.[5,78] The European Societies of Hypertension (ESH) and Cardiology (ESC) recommend appropriate lifestyles changes for the prevention and treatment of HTN, alongside the use of drug therapy in individuals at a high risk.[9] One benefit of losing body mass is the concomitant reduction in blood pressure (BP),[9,34,78] especially in individuals taking antihypertensive medication.[77] Although individual BP responses to a reduced body mass are variable depending on "fat-sensitive" or "fat-resistant" BP,[155] it has been demonstrated that combining exercise and diet may be the most effective treatment for reducing body mass. Consequently, the combination appears to be a logical step in facilitating a substantial improvement in cardiometabolic health, including HTN.[9,78]

During the last two decades, several studies have shown the effectiveness of adherence to the Dietary Approaches to Stop Hypertension (DASH) dietary pattern.[5,140,141] In a population with HTN, the combination of DASH diet with aerobic exercise has resulted in a greater reduction in BP and improved cardiovascular biomarkers than DASH diet alone.[142] Exercise guidelines recommend that both moderate-intensity and high-intensity aerobic training should be used to treat and reduce HTN.[9] However, there is currently no agreement with respect to the optimal *F*requency, *I*ntensity, *T*ime, and *T*ype (FITT principle) of exercise prescription.[94] Previously, aerobic high-intensity interval training (HIIT) produced a significant improvement in BP and cardiorespiratory fitness (CRF) compared to moderate-intensity continuous training (MICT).[118,207,208] Additionally, a dose-response curve for physical activity volume and intensity has previously been reported, this is especially important for sedentary individuals and those with a moderate level of physical condition,[209] suggesting that "*some is good but more is better.*" There is also evidence to support the use of low-volume HIIT (LV-HIIT) (*i.e.,* ≤10 min of high-intensity effort) *vs.* high-volume (HV) as a potent and time-efficient training method suggesting "*less is more*".[128]

Currently, no research has determined the effects of different exercise intensities and volumes combined with a hypocaloric diet intervention in overweight/obese, sedentary adults diagnosed with HTN. Therefore, the aim of this study was to determine changes in BP, body composition, CRF and

pharmacological treatment following three different (HV-MICT, HV-HIIT, LV-HIIT) 16-week aerobic exercise programs performed twice a week, all combined with hypocaloric diet.

6.3. Methods

Study design

EXERDIET-HTA study is a multi-arm parallel, randomized, single-blind controlled experimental trial comparing the effects of different 16-weeks aerobic exercise programs (performed two days per week) combined with a dietary intervention in sedentary, overweight/obese individuals suffering HTN (www.clinicaltrials.gov, number NCT02283047). The study protocol was approved by The Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) and Clinical Investigation of Araba University Hospital (2015-030), and all participants provided written informed consent before any data collection. Medical staff were blinded to the participant randomization process. The design, selection criteria, and procedures for the EXERDIET-HTA study have been previously detailed.[143]

Participants

One hundred and seventy-five non-Hispanic white participants (n=120 men and n=55 women) were enrolled in the study from September 2013 to June 2016 in Vitoria-Gasteiz (Basque Country, Spain). Figure 8 presents a flow diagram of the study process. All participants were classified as overweight (body mass index, BMI>25 $kg \cdot m^{-2}$) or obese (BMI>30 $kg \cdot m^{-2}$)[34] and diagnosed with stage 1 or 2 HTN, defined as a systolic blood pressure (SBP) of 140-179 mmHg and/or a diastolic blood pressure (DBP) of 90-109 mmHg and/or under antihypertensive pharmacological treatment[9]. Physical activity behavior was determined by the International Physical Activity Questionnaire (IPAQ), and only participants who did not comply with the *"Global Recommendations on Physical Activity for Health*[144] by the World Health Organization were selected.

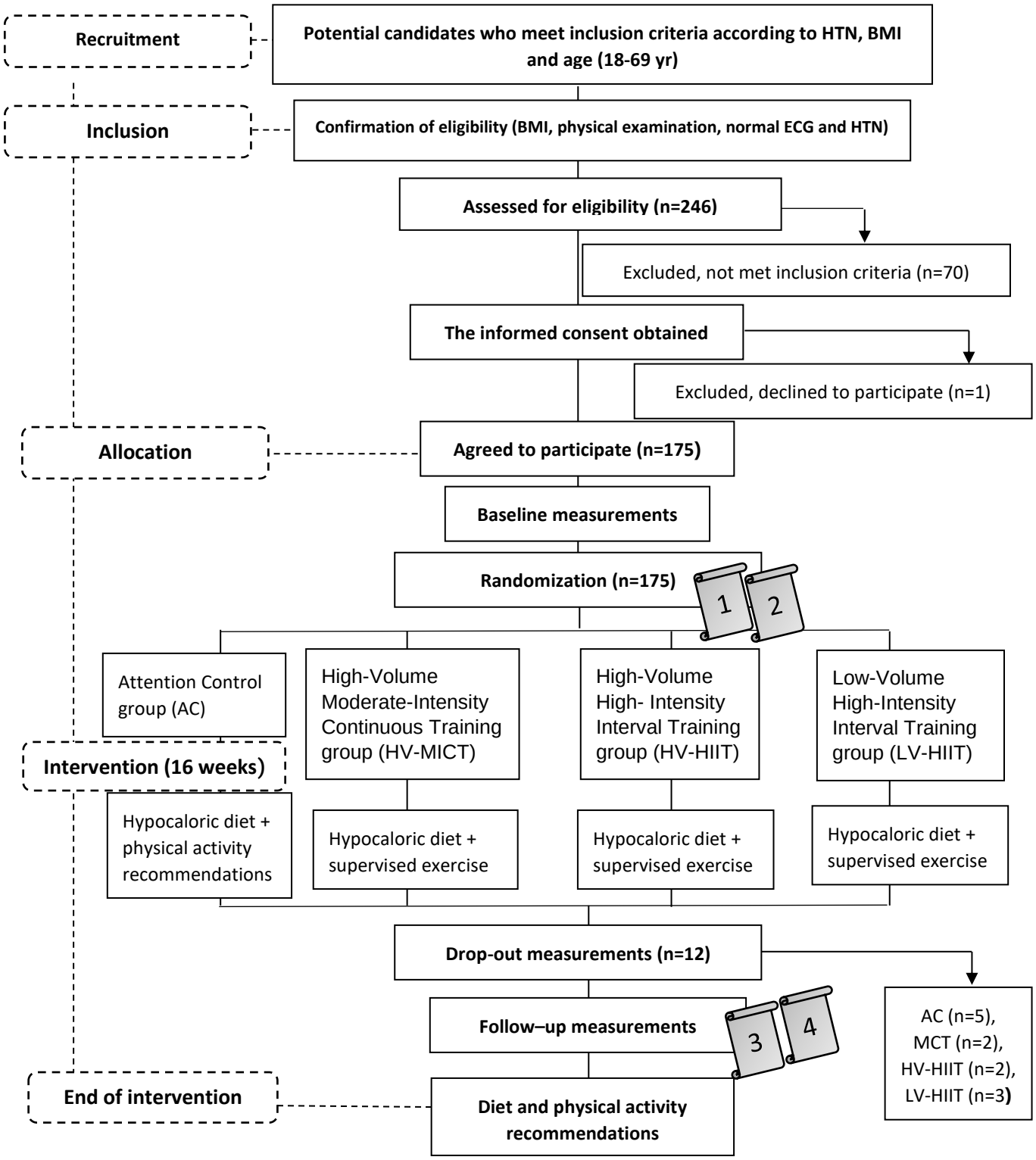

Figure 6: shows flow diagram of the EXERDIET-HTA study from recruitment to the end of intervention and relation to the articles published and presented in chapters 4-6.

Measurements

The measurements for the study were taken pre (T0) and post (T1) each 16-week intervention period.

Blood Pressure. Ambulatory BP monitoring (ABPM) was conducted over a 24-hour period using an oscillometric ABPM 6100 (Welch Allyn, New York City, NY, USA) device to evaluate BP in line with the guidelines set by the ESH/ESC.[9] Blood pressure (ABPM) values are displayed as the mean of the day.

Cardiorespiratory fitness. A cardiopulmonary exercise test (CPET) was used to determine peak oxygen uptake ($\dot{V}O_{2peak}$) and ventilatory thresholds (VT). The CPET was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). The test protocol started at ~70 rpm and 40W, with gradual increments of 10W every minute applied until volitional exhaustion occurred. Continuous electrocardiogram monitoring was conducted throughout each test. Expired gas analysis was assessed using a commercially available metabolic cart (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0). Achievement of $\dot{V}O_{2peak}$ criteria has been previously defined.[64] Ventilatory thresholds (*i.e.,* VT1 and VT2) were assessed by standardized methods using the ventilatory equivalents.[64] After completion of the test, participants remained stationary on the bike for five minutes recovery with electrocardiogram and BP monitoring throughout. The identification of the two VT determined the three different exercise intensity domains, or ranges for the exercise intervention design (*i.e.,* R1, **light** to moderate; R2, **moderate** to high; R3, **high** to severe).[64]

Dietary assessment. Habitual food consumption and nutrient intake were evaluated using three questionnaires: a dietary history, food frequency questionnaire and two face-to-face non-consecutive 24-h recalls. Trained dieticians conducted the necessary correction for within-subject variability in nutrient intake.[164] All nutritional data were calibrated in the Easy Diet computer program. Resting energy expenditure was calculated by the Mifflin St Jeor equation, which has previously been deemed the most appropriate for individuals who are overweight or obese.[152]

Medication. Prescribed medications were recorded and classified into the groups: angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), diuretics, calcium channel blockers (CCB,) beta-blockers (BB), statins, hypoglycemic agents, antiplatelets, and anticoagulants. Medical staff controlled all necessary changes to medication pre, during and post-intervention.

Intervention

All participants underwent a hypocaloric diet. Following baseline data collection, participants were randomly allocated to one of the four intervention groups: the Attention Control (AC) group, or the

three supervised exercise groups (HV-MICT, HV-HIIT, or LV-HIIT). Each group was stratified by gender, SBP, BMI, and age. All participants were asked to continue with their normal physical activity patterns outside of the study protocol. However, in addition to treatment for the hypocaloric diet, the AC received the standard guidelines for physical activity recommendations in order to comply with ethical procedures regarding health.[9]

Intervention procedures. All exercise groups trained for two nonconsecutive days per week under the supervision of exercise specialists. All sessions started and finished with BP monitoring, and training intensity was dictated by individual heart rate (HR) responses (Polar Electro, Kempele, Finland) and rate of perceived exertion (Borg's 6-20 point). Each session included a 5-10 min warm-up and a 10 min cool-down. The core part of each training session consisted of a range of aerobic exercises; *i.e.,* one day of the week on the treadmill, and the second one on the bike (BH Fitness equipment™). The HV-MICT group performed 45 min aerobic exercise, whereas the HV-HIIT and LV-HIIT conducted 45 and 20 min, respectively. The intensity was individually tailored to each participant's HR at moderate (R2) or vigorous intensities (R3), adjusting the speed and/or incline of the treadmill or the power and speed on the exercise-bike. The rationale of mixing stationary exercise-bike and treadmill was to avoid the osteoarticular impact of two treadmill days taking into account the nature of the HIIT program and the impact derived from overweight/obese participants. The HV-MICT group performed 45 min continuous steady training at R2. Supervised exercise-training protocols have been previously explained in full.[143]

Considering the average $\dot{V}O_{2peak}$ at baseline for all participants (2.01±0.5 L·min^{-1}), the total work performed by the three exercise groups was calculated using the $\dot{V}O_2$-time relationship. As such, the moderate intensity at R2 was taken as 65% of $\dot{V}O_{2peak}$ (1.3 L·min^{-1}) and the high intensity at R3 as 90% of $\dot{V}O_{2peak}$ (1.8 L·min^{-1}). Thus, the HV-MICT performed 45 min at R2 twice per week representing ~117 L. The HV-HIIT performed 45 min twice per week, one day on the treadmill (4x4 min at 1.8 L·min^{-1} at R3 and 29 min at 1.3 L·min^{-1} at R2, representing ~66.5 L), and one day on the exercise-bike (18x30 s at R3 and 36 min at R2 representing ~63 L·min^{-1} resulting a total work of ~129.5 L). The LV-HIIT group performed 20 min twice per week, exercising one day on the treadmill (2x4 min at R3 and 12 min at R2 representing ~30 L) and one day on the exercise-bike (9x30 s at R3 and 15:30 min at R2 representing ~28 L resulting a total work of ~58 L). A criterion for completing the study was set at 100%. Thus, all participants in the supervised-exercise groups performed 32 sessions; if a session was missed (a maximum of four were allowed), these were added on to the end of the 16-week program, maintaining the two sessions per week.

Diet intervention. Hypocaloric and controlled sodium diet (3-6 g/d) was prescribed for each participant. The diet was designed to provide 25% less energy than their daily energy expenditure and

to achieve a weekly loss in body mass of between 0.5 and 1.0 kg in accordance with the recommendations of the American Diabetes Association and the Spanish Society for the Study of Obesity.[153] The diet contained ~30% fat, 15% protein, and 55% carbohydrates and was designed in accordance with the DASH diet.[140] Every two weeks participants were weighed and received encouragement and advice alongside nutritional counseling in order to aid compliance.

Statistical analysis

Descriptive statistics were calculated for all variables. Data are expressed as mean±standard deviations (SD) and the range. All variables that were not normally distributed using a Kolmogorov-Smirnov test and so they were log transformed prior to any analysis. Analysis of variance (ANOVA) was used to determine if there were significant pre-intervention between-group differences. The comparison of frequencies in categorical variables among groups was performed using Chi-Square test. A 2 sample *t*-test was used to determine whether there was a significant difference in the recorded data between pre and post intervention within each group. Analysis of covariance (ANCOVA) was used to examine the delta (Δ) score for each group (AC, HV-MICT, HV-HIIT, LV-HIIT), adjusting for age, sex, changes in body mass and the initial value of each of the dependent variables. Helmert contrasts were performed to analyse the difference between the three exercise groups pooled together and AC group. Bonferroni correction was used to determine the level of significance when a significant main effect was found. Data were analysed according to the intention-to-treat principle. Statistical significance was set at $P<0.05$. All statistical analyses were performed with the SPSS version 22.0. Power calculation was completed using G*Power 3 analysis program.[210] The required sample size was determined for the primary outcome variable (SBP). It was identified that adequate power (0.80) to evaluate differences in our design consisting of four experimental groups would be achieved with 164 people (41 each group, $\alpha=0.05$, effect size f=0.27) based on the pilot study with an SD of 9 mmHg.

6.4. Results

Baseline characteristics. Participants and medications were classified by groups and presented in Table 27. Baseline data for all participants have been previously published.[211] At baseline, 86.9% of participants were taking medication irrespective of group. The percentage of participants who took one, two, three or >four medications were 40%, 26.3%, 13.1%, and 7.4%, respectively. With respect to medication type, 32.3% of participants took ACEI, 41.1% ARB, 34.3% diuretics, 15.4% CCB, 9.8% BB, 13.7% statins, 6.3% hypoglucemic, 4.6% antiplatelets, and 1.1% anticoagulants. There were no significant between-group differences observed for anthropometric, body composition, hemodynamic,

cardiorespiratory and pharmacological treatment at baseline. No major complications or cardiac events occurred during any part of the study.

Table 27. Physical, physiological and pharmacological therapy characteristics at baseline for each group of participants (N=175). Values are mean±SD, percent (%) or number.

	AC (N=45)	HV-MICT (N=42)	HV-HIIT (N=44)	LV-HIIT (N=44)	*P*
Sex (men/women)	30/15	28/14	32/12	30/14	0.9
Age (yrs)	53.1±8.3	54.7±7.6	53.5±9.1	54.7± 8.8	0.7
Body mass (kg)	91.2±15.9	93.4±16.4	90.3±15.6	91.6±14.6	0.8
BMI (kg m^{-2})	31.9±4.6	32.2±4.4	31.2±3.6	32.0±4.6	0.7
Waist (cm)	103.1±11.6	105.5±12.6	102.0±11.0	103.5±10.4	0.6
Hip (cm)	107.5±9.7	108.8±9.4	106.2±7.6	108.9±10.7	0.5
Waist/hip ratio	0.96±0.7	0.97±0.1	0.96±0.8	0.96±0.1	0.8
FFM (%)	66.2±8.1	64.6±8.6	67.7±6.3	67.0±8.1	0.3
FBM (%)	33.7±8.1	35.4±8.6	32.3±6.4	32.9 ±8.1	0.3
FFM/FBM	2.14±0.8	1.98±0.7	2.2±0.6	2.18 ±0.7	0.5
Rest SBP (mmHg)	139±13	133±12	133±10	135±13	0.06
Rest DBP (mmHg)	79±8	76±8	79±7	77±9	0.1
Rest HR (beats·min^{-1})	69±10	74±9	70±11	69±10	0.08
Rest MBP (mmHg)	99±9	94±8	97±7	97±10	0.1
$\dot{V}O_{2peak}$ (L min^{-1})	2.04±0.59	2.01±0.55	2.0±0.5	2.01±0.5	0.9
$\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1})	22.5±6.0	21.6±5.2	22.4±4.8	22.0±5.6	0.9
VT1 (mL kg^{-1} min^{-1})	13.1±5.8	12.2±3.9	12.7±4.6	12.7±4.4	0.8
VT2 (mL kg^{-1} min^{-1})	17.1±6.6	17.7±5.6	17.9±6.5	17.8±6.4	0.9
MET	6.4 ±1.7	6.13±1.4	6.4±1.4	6.3±1.6	0.8
Medication (%)	84	93	82	89	0.6
ACEI (%)	37.8	45.3	40.9	29.5	0.5
ARB (%)	46.7	40.5	27.3	50.0	0.1
Diuretics (%)	33.3	38.1	34.1	31.8	0.9
CCB (%)	8.9	21.4	13.7	18.2	0.4
BB (%)	13.3	11.9	9.1	4.5	0.5
Statins (%)	11.1	16.7	16.0	11.4	0.8
Hypoglycemic (%)	6.7	2.4	2.3	13.6	0.09
Antiplatelets+anticoagulants (%)	4.4	9.5	2.3	2.3	0.3
Cigarette smoking (%)	2.2	9.8	20.9	9.3	0.08
DM (%)	4.4	4.9	7.0	11.6	0.5

BMI, body mass index; FFM, fat free mass; FBM, fat body mass; SBP, systolic blood pressure; DBP diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; $\dot{V}O_{2peak}$, peak oxygen uptake; VT, ventilatory threshold; MET, metabolic equivalent of task; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; BB, beta blockers; DM, diabetes mellitus. BP values show the mean BP calculated by 24 hours ambulatory blood pressure monitoring. P<0.05. AC, attention control group; HV-MICT, high-volume and moderate-intensity continuous training group; HV-HIIT, high-volume high-intensity training group; LV-HIIT, low-volume high-intensity training group.

Physiological changes (Table 28). Following the 16-week intervention, resting SBP, DBP, mean BP and HR decreased (*P*<0.05). Further, in all groups, CRF expressed as $\dot{V}O_{2peak}$ (L min^{-1}) (AC, Δ=10%; *P*<0.05; HV-MICT, Δ=15%; HV-HIIT, Δ=25%; and LV-HIIT, Δ=25%; *P*<0.001), $\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1}) and

METs (*P*<0.001) increased. All groups increased at least one MET (Table 28 and Figure 9). However, at VT1 and VT2 (mL kg^{-1} min^{-1}) improvements were observed in HV-HIIT for VT1 (*P*=0.003) and both HIIT exercise groups for VT2 (HV-HIIT, *P*<0.001 and LV-HIIT, *P*=0.016). In contrast, no significant changes were seen in the AC and HV-MICT groups for either VT1 or VT2. Following Bonferroni correction, there were no significant between group differences in any hemodynamic variables (*i.e.,* BP and HR) (Table 28). However, AC showed a smaller but significant improvement in $\dot{V}O_{2peak}$ (*P*<0.001) compared with all exercise groups (HV-MICT, mean difference=0.606, 95% CI=-2.193-3.405 mL kg^{-1} min^{-1}; HV-HIIT, mean difference=3.215, 95% CI=0.418-6.012 mL kg^{-1} min^{-1}; and LV-HIIT, mean difference=2.846, 95% CI=0.082-5.610 mL kg^{-1} min^{-1}) and MET (*P*<0.001). Furthermore, both HIIT groups, showed a greater (*P*=0.008) $\dot{V}O_{2peak}$ and MET (*P*=0.018) than HV-MICT. In contrast, there were no significant between group differences in any VT variables.

Anthropometric and body composition (Table 28). Following 16-weeks intervention body mass, BMI, waist and hip circumferences, waist-to-hip ratio (WHR), and fat body mass (FBM) decreased (*P*<0.05) in all groups. In addition, fat-free mass (FFM) and FFM/FBM ratio increased (*P*<0.05). Following Bonferroni correction, there were significant between-group differences in anthropometric and body composition. The AC had a smaller body mass reduction (T0 *vs.* T1 difference%, Δ=-6.6%; *P*=0.029) and change in BMI (Δ=6.7%; *P*=0.030) compared to those in all exercise groups: HV-MICT (Δ=-8.3%), HV-HIIT (Δ=-9.7%) and LV-HIIT (Δ=-6.9%). Further, HV-HIIT had a greater reduction in body mass (*P*=0.011, mean difference=2.436, 95% CI=-4.972-0.099 kg) and BMI (*P*=0.015, mean difference=0.805, 95% CI=-0.066-1.675 $kg \cdot m^{-2}$) compared with LV-HIIT. However, there were no significant between-group differences observed for WHR. With respect to body composition, there were no significant differences in %FFM between AC and all exercise groups (Δ=4.0%; *P*=0.062): HV-MICT (Δ=6.2%), HV-HIIT (Δ=6.8%) and LV-HIIT (Δ=4.6%). However, the %FFM gain in the HV-HIIT was greater than the AC (*P*=0.039) group. Similarly, there were no significant differences in %FBM when exercise groups were compared together with AC (Δ=-8.1%; *P*=0.062): HV-MICT (Δ=-11.3%), HV-HIIT (Δ=-14.1%) and LV-HIIT (Δ=-9.6%). However, HV-HIIT resulted in a greater reduction of %FBM than the AC group (*P*=0.038).

Table 28. Physiological data and body composition for all groups before and after intervention period. Mean±SD

	AC (N=40)	HV-MICT (N=40)	HV-HIIT (N=42)	LV-HIIT (N=41)	*P* AC *vs.* EG	*P* Intergroups	*F-value*	*%Variance*
Rest SBP (mmHg)								
T0	140.0±13.2	132.7±12.7	131.7±10.4	135.6±13.2				
T1	133.0±15.3*	125.4±8.9*	127.1±9.7*	127.1±10.5*	0.897	0.418	1.611	1.9
Rest DBP (mmHg)								
T0	79.9±7.2	75.4±8.0	79.0±6.9	78.2±8.2				
T1	75.1±9.1*	72.0±6.7*	74.1±6.2*	73.9±7.4*	0.544	0.762	0.050	0.8
Rest HR (beats·min^{-1})								
T0	68.9±9.9	73.6±9.2	70.5±11.0	69.2±10.5				
T1	65.2±9.2*	68.1±8.1*	63.7±8.8*	64.4±10.0*	0.747	0.485	0.819	1.7
Rest MBP (mmHg)								
T0	99.9±8.4	94.5±8.5	96.6±7.2	97.3±9.1				
T1	94.4±10.4*	89.8±6.2*	91.8.4±6.9*	91.6±7.6*	0.694	0.808	0.567	0.7
$\dot{V}O_{2peak}$ (L min^{-1})								
T0	2.0±0.6	2.0±0.6	2.0±0.4	2.0±0.5				
T1	2.2±0.7*	2.3±0.7*^{x}	2.5±0.7*$^{x\$}$	2.5±0.6*$^{x\$}$	0.001	0.001	5.329	9.8
$\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1})								
T0	22.6±6.1	21.6±5.2	22.4±4.9	22.3±5.2				
T1	26.3±8.3*	26.7±7.4*^{x}	30.6±8.5*$^{x\$}$	29.1±6.7*$^{x\$}$	0.009	0.003	4.828	8.6
MET								
T0	6.4±1.7	6.1±1.5	6.4±1.4	6.4±1.5				
T1	7.5±2.4*	7.6±2.1*^{x}	8.7±2.4*$^{x\$}$	8.3±1.9*$^{x\$}$	0.011	0.007	4.209	7.6
VT1 (mL kg^{-1} min^{-1})								
T0	13.1±5.8	12.2±3.9	12.7±4.6	12.7±4.4				
T1	13.3±7.2	12.9±5.8	15.7±6.8*	14.2±7.0	0.754	0.238	1.4	2.7
VT2 (mL kg^{-1} min^{-1})								
T0	17.1±6.6	17.7±5.6	17.9±6.5	17.8±6.4				
T1	19.5±10.2	19.7±8.6	24.5±9.6*	21.6±10.3*	0.843	0.057	2.6	4.7

Table 28. Continued

Body mass (kg)								
T0	89.5±14.8	94.0±16.6	90.5±15.7	91.2±14.6				
T1	83.6±14.9*	86.2±15.8 *x	81.7±14.0 *x	84.9±13.6 *x‡	0.029	0.010	3.909	6.9
BMI (kg m^{-2})								
T0	31.2±3.9	32.4±4.4	31.2±3.6	31.6±4.3				
T1	29.1±4.1*	29.7±4.1* x	28.2±3.4*x	29.4±4.1*x ‡	0.030	0.012	3.846	6.7
Waist (cm)								
T0	102.2±11.3	105.1±11.7	102.1±11.1	102.8±10.0				
T1	96.2±11.3*	97.6±10.5 *	93.8±11.4 *	96.2±8.7*	0.146	0.279	1.480	2.4
Hip (cm)								
T0	107.0±8.8	108.8±9.1	106.2±7.7	107.3±8.2				
T1	103.4±8.9*	103.9±9.1 *	102.6±7.2 *	103.4±7.2 *	0.456	0.510	0.440	1.5
Waist/hip ratio								
T0	0.96±0.08	0.97±0.09	0.96±0.08	0.96±0.09				
T1	0.93±0.08*	0.94±0.08 *	0.91±0.08 *	0.93±0.07 *	0.461	0.188	1.388	3.1
FFM (%)								
T0	66.8±7.9	64.6±8.6	67.5±6.4	67.7±7.0				
T1	69.5±8.2*	68.6±8.4*	72.1±7.0*x	70.8±8.1*	0.062	0.035	2.935	5.3
FBM (%)								
T0	33.2±7.9	35.4±8.6	32.5±6.4	32.3±7.7				
T1	30.5±8.2*	31.4±8.3*	27.9±7.0*x	29.2±8.1*	0.062	0.034	2.959	5.4
FFM/FBM								
T0	2.1±0.8	2.0±0.7	2.2±0.6	2.2±0.7				
T1	2.5±1.0*	2.4±0.9*	2.8±0.9*	2.6±1.0*	0.061	0.067	2.439	4.5

SBP, systolic blood pressure; DBP, diastolic blood pressure, HR, heart rate; MBP, mean blood pressure; $\dot{V}O_{2peak}$, peak oxygen uptake; MET, metabolic equivalent; VT, ventilatory threshold; BMI, body mass index; FFM, fat free mass; FBM, fat body mass; AC, attention control group; HV-MICT, high-volume and moderate-intensity continuous training group; HV-HIIT, high-volume and high-intensity training group; LV-HIIT, low-volume and high-intensity training group; EG, exercise groups. BP values show the mean BP calculated by 24 hours ambulatory blood pressure monitoring. *P-$value$<0.05 from T0. ^{x}P-$value$<0.05 from the AC. $^{\$}P$-$value$<0.05 from the HV-MICT. $^{‡}P$-$value$<0.05 from the HV-HIIT.

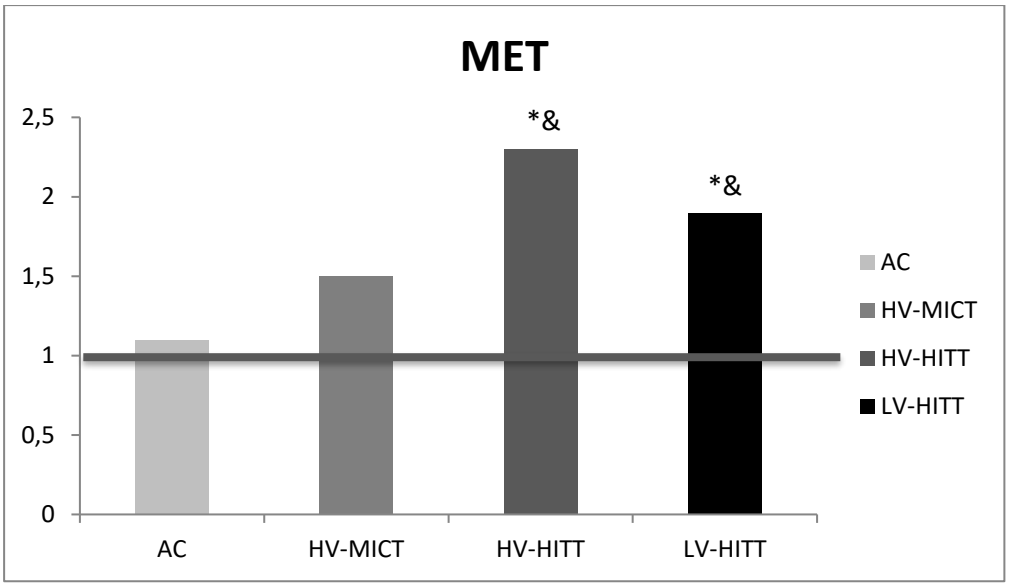

Figure 9. Peak Metabolic Equivalent of Task (MET) differences after the 16-week intervention period for each group.
The horizontal line indicates a minimal of 1 MET increase.* *P-value*<0.05 from the AC. & *P-value*<0.05 from the HV-MICT

Pharmacological therapy. Following the 16-week intervention, medication was reduced from 86.9% to 79.3%. Further, 37.7% of participants, which still took medication, had their dose reduced. The percentage of participants who took one, two, three or more than four medications was also reduced to 35.4%, 29.9%, 8.5%, and 5.4%, respectively. Specifically, 32.3% of participants took ACEI, 39 % ARB, 30.5% diuretics, 15.2% CCB, 6.1% BB, 11.0% statins, 6.7% hypoglucemic, 3.7% antiplatelets, and 1.2% anticoagulants. Chi-square test revealed that there were no significant between-group differences in medication reduction.

6.5. Discussion

To our knowledge, this is the first known study to investigate the impact of exercise programmes, which use different intensities and volumes in conjunction with a dietary intervention in overweight/obese, sedentary adults diagnosed with HTN. The main findings of the study were: 1) all groups significantly improved BP, CRF, body composition following 16-weeks intervention; 2) a substantial decrease of pharmacological treatment was observed; 3) hypocaloric diet and two days of supervised exercise showed improved body mass and CRF compared to a diet only intervention (AC group), but no significant between-group differences were observed in BP; 4) the HV-HIIT exercise

elicited a greater improvement in body mass and body composition than the LV-HIIT exercise, and 5) the exercise-induced improvement in CRF is more dependent on intensity than volume.

In this study, a 16-week lifestyle intervention significantly improved cardiovascular risk factors (*i.e.,* BP, CRF, and adiposity) in all groups and pharmacological therapy was largely reduced or removed completely. Hence, the hypocaloric DASH diet along with both supervised aerobic exercise and no supervised physical activity recommendations could offer an optimal non-pharmacological tool in the management of HTN. As such, this could result in a cost-effective model for cardiovascular disease prevention[141] and healthcare cost reduction. These results corroborate those of previous investigations that suggested overweight/obese people with above-normal BP could improve BP, and body mass, vascular and autonomic function when they combine exercise and DASH diet with calorie restriction.[142,179] Further, we provide evidence that the combined effects of physical activity and hypocaloric diet enhance BP and reduce the need for pharmacological therapy.[212] To this end, contrary to our hypothesis, all supervised exercise groups had a reduced BP similar to the AC group post-intervention (7-9 mmHg in SBP and 3-5 mmHg in DBP). As such, the potential of the DASH diet to elicit significant improvements in SBP and DBP in individuals with HTN who are overweight/obese is confirmed[141], and it appears to be independent of the FITT principle. However, the lack of between-group differences in BP in the current study could in part be explained by 1) the role physical activity plays in augmenting baroreflex dysfunction, which may result in a reduced sympathetic outflow with a lowered BP and HR response,[213,214] 2) the different exercise interventions appear to be medication dependent with similar BP reduction following all exercise intensities (*i.e.,* MICT or HIIT)[207] ; and 3) two days of supervised exercise may not be enough to differentiate between exercise modalities over the 16-week period. Previously, it has been reported that there is a greater antihypertensive effect seen in response to high-intensity exercise when compared to lower exercise intensities.[207] Previous research found that HIIT three times a week elicited greater significant reductions in BP than MICT and a control group following a 12-week intervention.[118] However, it should be noted that participants using the antihypertensive drug in the mentioned study performed a wash-out before inclusion and so a greater effect may have been seen.

To achieve a negative energy balance is to challenge and target specific pathways in order to produce beneficial changes in the pathogenesis of obesity-related HTN.[78] In the present study, despite the antihypertensive medication and the metabolic potential side effects,[9,155] a dual treatment of hypocaloric diet combined with supervised exercise twice a week was the optimal way to reduce body mass compared to AC. More specifically, HV-HIIT significantly enhanced body mass reduction (kg, ↓9.7%), and fat distribution the most (%FFM=↑6.8 and %FBM=↓14.1). Given that, HV-MICT and LV-

HIIT exercise programs were performed with the same frequency but a reduced intensity and volume, respectively, the improvements seen in HV-HIIT compared to the other two exercise programs were likely caused by enhanced energy expenditure. These data suggest that sedentary people with overweight/obesity and HTN can adapt and respond to exercise training during an energy deficit program with a dose-response curve related to volume and intensity. Furthermore, it has been shown that high levels of moderate-to-vigorous-intensity physical activity are associated with long-term body mass loss maintenance,[215] despite the probable adaptive metabolic response caused by the compensatory down-regulation in resting energy expenditure following exercise-induced body mass loss.[216]

Cardiorespiratory fitness is an independent predictor of all-cause and disease-specific mortality in various populations irrespective of BMI.[217] Thereby; the fat-but-fit paradigm has been gven much attention with respect to reducing the risk of illness and death.[217,218] Thus, in the present study (Table 27), while all participants were overweight/obese and considered unfit at baseline with CRF classified as poor (<24.4 mL kg^{-1} min^{-1} in men and <19 mL kg^{-1} min^{-1} in women),[169,211] following the 16-week intervention CRF was improved and classified as "fair-good".[169] Further, all groups improved by at least 1 MET (Figure 9) during the course of the intervention. As such, although participants were still classified as overweight their CRF increased by 16-36%, which is associated with a considerable improvement in cardiovascular risk and reduced all-cause mortality.[219] In addition, the magnitude of change in CRF improvement was significantly different between exercise groups. Specifically, both HIIT programmes elicited significantly greater improvements in CRF than the HV-MICT and AC (Table 28 and Figure 9) groups. Additionally, HIIT groups showed significant improvements in submaximal variables such as VT (Table 28). These enhanced improvements in CRF may be due to stress adaptations, which have been previously shown to cause notable cellular, vascular and metabolic adaptations during HIIT.[220] One remarkable finding of the present study was that HIIT improved CRF irrespective of the training volume (LV *vs.* HV). Our findings reinforce previous studies, which suggest LV-HIIT is a time-efficient and effective protocol in clinical populations answering the question "Can less be more? [221,222] As such, it may be that LV-HIIT is more appealing for individuals who do not have enough time to train for long periods, or for those who have medical conditions which prevent them from performing exercise for prolonged periods of time.[208,220] However, taking into account the urgent need of increasing caloric expenditure and CRF in this population, LV-HIIT could be an option to tailor supervised exercise along with daily recommendations of lower intensities physical activities.[130]

Although the current study has provided clear evidence for the benefits of combining a hypocaloric DASH diet with exercise, there are some limitations which should be considered: 1) though

every effort was made to manage unsupervised time, physical activity performed by participants in AC could not be controlled, and 2) it is difficult to regulate and monitor the adherence of participants to the diet.

6.6. Conclusions

In summary, the present study has shown that the combination of hypocaloric DASH diet with different supervised aerobic exercise programs twice a week offers an optimal non-pharmacological tool in the management of risk factors in sedentary individuals with overweight/obesity and HTN. Benefits include an enhanced control of BP, body mass composition, CRF and pharmacological treatment. A dose-response curve related to volume and intensity in the form of 2-weekly bouts of HV-HIIT provided significantly greater reductions in body mass compared to LV. However, the key to enhancing CRF in this population appears to be linked with exercise intensity irrespective of duration. As such, LV-HIIT may be a time-efficient and effective method of improving health.

Capítulo 7 / Chapter 7

Effects on cardiovascular risk scores and vascular age after aerobic exercise and nutritional intervention in sedentary and overweight/obese adults with primary hypertension: the EXERDIET-HTA randomized trial study

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7.1. Abstract

Aims To evaluate the influence of diet and aerobic exercise program intervention on cardiovascular risk (CVR) factors and predicted CVR and vascular age (VA) profiles in overweight/obese people with primary hypertension (HTN), and to analyze the potential sex differences in the ability to predict VA and CVR via different methods.

Methods The CVR and VA determined (n=167, 53.7±7.8 yr) using the Framingham Risk Score (FRS) and the new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk, before and after the 16-week intervention period (different aerobic exercise programs+hypocaloric diet). The sex-specific risk factors considered were age, high-density lipoprotein cholesterol (HDL-C), total cholesterol, systolic blood pressure (SBP), diabetes mellitus (DM) and smoking status.

Results From baseline to follow-up, participants reduced ($p \leq 0.001$) FRS-CVR score and VA, and SBP. Total cholesterol decreased significantly, but specifically in men ($p \leq 0.001$), and antihypertensive medication (%) in women ($p=0.047$). No significant differences over time were observed for HDL-C, smoking, DM overall for either sex. For ASCVD-CVR there was no overall change or for either sex. After the intervention, women had a lower CVR score than men ($p \leq 0.001$), irrespective of the calculation method.

Conclusions The improvement in CVR factors after 16-week lifestyle changes reduced the risk of suffering a cardiovascular event in overweight/obese adults with HTN through the FRS estimation tool, but not with the ASCVD score. The risk score algorithms could underestimate CVR in women. In contrast, VA could be a useful and easier tool in the management of individuals with CVR factors.

Keywords: Lifestyle intervention; sex; systolic blood pressure

7.2. Introduction

Cardiovascular disease (CVD) is a non-communicable disease, which represents the main cause of disability and death in the world, including Europe.[5,223] Globally, between 2006 and 2016 deaths from CVD increased by 14.5%, although the age-standardized death rate decreased.[86] These data suggest that this condition needs to receive greater priority in prevention policy to reduce avoidable risk factors.[5,86] Prevention is effective, and so, healthy lifestyle behavior promotion in the general population should directly target unhealthy lifestyles, such as poor-quality diet, physical inactivity, and smoking, at the individual level.[5] Cardiovascular risk (CVR) factors assessment is the first step guiding therapeutic strategy for the prevention of CVD,[5] and strategy effectiveness depends on each patient's CVR profile and predictive risk.[224]

There are several risk factor assessment tools for estimating a patient's 10-year risk of developing CVD.[5,224] However, the most well-established risk score algorithm is the Framingham Risk Score (FRS), which was initially validated in 1998 to predict CVR[225,226] and subsequently revised.[49] Recently, the American College of Cardiology and the American Heart Association developed a new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk, the called "Pooled Cohort Risk Equations".[3,50] This new tool was aimed at providing sex- and race-specific estimation of the 10-year risk of ASCVD for African-American and non-Hispanic white men and women aged 40 to 70 years old.[3,50] On the other hand, vascular age (VA, *i.e.,* the age of the vascular system of a person with different CVR factors, calculated as the age a person would be with the same calculated CVR but whose risk factors were all within normal ranges[227]) is an easily understood concept related to CVR and calculated according to the definition of D'Agostino from FRS.[49]

The common prediction factors for CVR models that have a relationship with cardiovascular events and premature death are age, sex, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP, including treated or untreated status), diabetes mellitus (DM), and current smoking status.[3]

Many observational studies have demonstrated graded associations between primary hypertension (HTN) and increased CVD risk[228] Additionally, adults with HTN usually present other modifiable CVR factors such as obesity, hypercholesterolemia, DM, smoking, physical inactivity, and unhealthy diet.[229] Therefore, correcting the dietary habits, lack of exercise and excessive consumption of alcohol through nonpharmacological interventions alone or in combination with pharmacological therapy is fundamental for the management of HTN.[229]

A previous study evaluating CVR using the "Pooled Cohort Equations" (sex-specific risk prediction model) and VA in overweight/obese people with HTN found that CVR was significantly higher in men than in women despite them having the same CVR values, whereas no differences were found between sexes in VA.[230] As such, women could have an underestimated CVR profile based on the misperception that women are "protected" against CVD.[203] Hence, one of the biggest criticisms of the prediction scales of CVR accuracy is their capacity to overestimate or underestimate the risk.[55] Currently, there is no known research that measures the effects of an aerobic exercise program with nutritional intervention on CVR and VA in sedentary and overweight/obese adults with HTN. Considering the importance of CVR assessment, the objectives of this study were: 1) to evaluate the influence of 16-week diet and different aerobic exercise programs intervention on CVR factors and predicted CVR and VA profiles in sedentary and overweight/obese people with HTN, and 2) to analyse the potential sex differences in the ability to predict VA and CVR via different methods resulting from changes in lifestyle.

7.3. Methods

The EXERDIET-HTA study was a multi-arm parallel, a randomized, single-blind controlled experimental trial comparing the effects of 16 weeks of different aerobic exercise programs two days per week, and dietary intervention in a hypertensive, overweight/obese and non-physically active population (www.clinicaltrials.gov, NCT02283047).[143,231] The design, selection criteria, and procedures for the EXERDIET-HTA study have been previously detailed.[143] The study protocol was approved by the Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital (2015-030), and all participants provided written informed consent prior to any data collection. All follow-up examinations were performed in the same laboratory setting and by the same researchers as the baseline measurements. Medical staff was blinded to participant randomization.

One hundred and sixty-seven non-Hispanic white participants (n=108 men and n=59 women) with stage 1 or 2 HTN [≥140 SBP and ≥90 diastolic blood pressure (DBP)] and/or under antihypertensive pharmacological treatment,[9] and classified as overweight (body mass index (BMI) ≥25 kg/m^2 or obese (BMI ≥30 kg/m^2).[34] Participants were recruited from cardiology services and via local media and were enrolled in the study in Vitoria-Gasteiz (Basque Country, Spain).

The measurements for CVR factors used in the present study to determine the CVR and VA of participants were taken before (T0) and after (T1) the 16-week intervention period and were defined as follows:

Ambulatory blood pressure monitoring was conducted over a 24 hour period using an oscillometric ABPM 6100 recorder (Welch Allyn, New York, USA) to evaluate SBP (as used to determine CVR).[3] The device was used in line with the recommendations set by the European Society of Hypertension and the European Society of Cardiology guidelines. As such, BP was measured at 30-minute intervals during awake-time and at 60-minute intervals during the sleep period. Data were only used if at least 75% of the awake-time and sleep periods were successfully recorded.[9]

Fasting venous blood (12.5mL) was collected from each participant following an overnight fast. Diabetes mellitus was defined as fasting glucose of ≥126 mg/dL[163] and/or under pharmacological glycemic control treatment. Additionally, measurements of glucose and lipid profile (total-, and HDL-C) were assayed (ABBOTT, Architect c16000, Orlando, FL, USA). The intra- and inter-assay coefficients of variation were: for glucose 0.65% and 0.84%; for total cholesterol 0.6% and 0.8%; and for HDL-C 1.7% and 1.1%, respectively.

Age and cigarette smoking status were assessed by self-report. All medicines being taken were ascertained from the participant's physician.

Cardiovascular risk and vascular age parameters' assessment have been previously analyzed in the sample at baseline, and the same procedures were applied for the follow-up study.[230] Briefly, the Framingham Heart Study assesses the absolute risk to the individual with a percentage score (*i.e.,* 10% means that there is a 10% chance of having a cardiovascular event within the next 10 years, <6%=low risk; 6-20%=medium risk, and ≥20%=high risk).[49] The Pooled Cohort Risk Equations to estimate the 10-year risk was described as a series of steps.[3] The Framingham method was used to determine the VA of all participants,[49] which indicates the biological age of the individual's vascular system, as the age a person would be with the same calculated CVR, but whose risk factors were all within normal ranges. The sex-specific risk factors considered were age, HDL-C, total cholesterol, SBP, DM, and smoking status. Each variable received a weighted score; the sum of the score for each variable was then translated into the risk of a CV event in 10 years and VA.[49]

After baseline data collection, participants were randomly allocated to one of the four intervention groups stratified by sex, SBP, BMI and age using a time-blocked computerized randomization program by the principal investigator and blind to medical staff. Detailed descriptions of the exercise and diet intervention procedures have been already reported.[143,231] Briefly, the intervention groups were: 1) Attention Control group with physical activity recommendations (*i.e.,* at least 30 min of moderate-intensity aerobic exercise 5-7 days per week and some dynamic resistance exercises); and three supervised aerobic exercise groups training two nonconsecutive days under supervision by

exercise specialists, 2) high-volume moderate-intensity continuous training group, 45 min at moderate intensity; 3) high-volume high-intensity interval training group, 45 min alternating with different protocols moderate-to-high intensity; and 4) low-volume high-intensity interval training group, 20 min alternating with different protocols moderate-to-high intensity. All participants received treatment with a hypocaloric "Dietary Approaches to Stop Hypertension" (DASH) diet. The diet was designed to provide 25% less energy than their daily energy expenditure and to achieve a weekly loss of body mass between 0.5 and 1.0 kg. Approximately 30% of their energy intake came from fat, 15% from protein, and 55% from carbohydrates and was designed in accordance with the DASH diet.[140] This diet is rich in plant foods (*i.e., a* rich source of polyphenols) due to its favourable effect of BP.[232] Every two weeks, participants were weighed and received encouragement and advice alongside nutritional counseling to aid adherence.

Descriptive statistics were calculated for all variables. Data are expressed as means±standard deviations (SD) and the range. ANOVA was used to determine if there were significant pre-intervention differences between sexes for the variables: age, BMI, SBP, total cholesterol, HDL-C, antihypertensive medication, cigarette smoking, DM, CVR, and VA. The comparison of frequencies between sexes was performed using a Chi-Square test. Repeated measures within-between participants ANOVAs were used to determine whether there was a significant difference in the recorded data between pre- and post-intervention for all participants and any time x sex interaction effects, *i.e*. to examine whether the change due to the intervention differed between men and women. A pre- and post-intervention mean difference for each variable was calculated. Statistical significance was set at $P<0.05$. All statistical analyses were performed on an intention-to-treat basis using the SPSS version 22.0. The required sample size was determined for the primary outcome variable (SBP) and previously published.[143,231]

7.4. Results

Baseline characteristics of CVR factors classified by sex are presented in Table 29. The sample was the same as the previous study,[230] but the number of participants is reduced because only those with follow-up values were included. The mean age (±SD) was 53.7±7.8 years old with 64.7% being men, 12.8% of the participants were smokers, and 9.6% of the sample was suffering from DM. The results indicated that there were no significant differences between sexes for all CVR factors at baseline, except for total cholesterol, which was higher in women (mean difference=13.1; 95% CI=25.4-0.85 mg/dL) than in men, with both sexes exceeding cut-off values set by the European Society of Hypertension and the European Society of Cardiology guidelines.[9] The mean HDL-C was similar in men and women with both sexes remaining within the healthy cut-off values suggested by the European Society of Hypertension and the European Society of Cardiology guidelines.[9]

The absolute CVR score was significantly different (p<0.001) between sexes with women having a lower CVR than men, irrespective of calculation method (ASCVD-CVR: mean difference=6.0, 95% CI=4.0-8.0 %, p<0.001; FRS-CVR: mean difference=10.2, 95% CI=7.1-13.4%, p≤0.001, Table 29). Additionally, in accordance with the ASCVD-CVR score, men were considered to be at medium risk (10.5%), whereas women were considered to be at low risk (4.5%). However, using the FRS-CVR score, men were considered to be at high risk (>20%) whereas women were considered to be at medium risk (11.3%). Consequently, significant differences were found between CVR score calculators for CVR prediction (p<0.001, mean difference=9.6, 95% CI=10.6-8.6 %). In contrast, there was no sex difference in VA (mean difference=2.8, 95% CI=-7.5-1.8 yr old, p=0.23), but VA was significantly higher (p<0.001) than chronological age (CA) (mean difference=17.5, 95% CI=19.4-15.7 yr old), irrespective of sex, (p<0.001).

Table 29. Characteristics of risk factors and cardiovascular risk classified by sex. Values are mean±SD or percentage (%)

Dependent variable	All participants (*n*=167)	Men (*n*=108)	Women (*n*=59)	$P_{M\text{-}W}$	*Effect size*
Age (yrs)	53.7±7.8	54.5±7.8	52.4±7.5	0.09	0.135
SBP (mmHg)	135.8±12.1	135.8±11.8	135.7±12.6	0.96	0.004
Total 160olesterol (mg/dL)	205.9±39.8	201.3±40.8	214.4±36.8	0.04	0.166
HDL-C (mg/dL)	50.0±32.9	49.8±39.6	52.1±14.4	0.44	0.038
Antihypertensive medication (%)	92.2	89.8	96.6	0.12	
Cigarette smoking (%)	12.8	13.2	12.1	0.84	
DM (%)	9.6	11.1	6.8	0.36	
ASCVD-CVR (%)	8.3±6.8	10.5±7.3	4.5±3.1	<0.001	0.471
FRS-CVR (%)	17.9±10.9	21.6±11.1	11.3±6.7	<0.001	0.489
Vascular Age	71.3±14.6	70.3±13.5	73.1±16.3	0.2	0.093

SBP, systolic blood pressure; HDL-C *High density lipoprotein* cholesterol; DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; FRS, Framingham Risk Score: CVR, cardiovascular risk.

Table 30 shows CVR factors, CVR scores and VA values at baseline and follow-up. After the intervention, all participants showed decreased SBP, total cholesterol, antihypertensive medication usage (%), CVR score predicted by FRS, and VA (p<0.05). ANOVA showed that SBP decreased in both sexes (T0 *vs.* T1 difference %, men Δ=7.4 %; women, Δ=6.0 %, p≤0.001). Significant time x sex interaction effects revealed that mean total cholesterol significantly reduced in men (Δ=13.6 %, p≤0.001), but not in women (Δ=6.5 %, p=0.12), and antihypertensive medication (%) significantly decreased in women (Δ=10.2 %, p=0.047), but not in men (Δ=4.6 %, p=0.30). No significant differences were observed in HDL-C, smoking habit and suffering from DM after 16-weeks intervention period. When CVR score and VA were analyzed, FRS-CVR and VA decreased overall, and in both sexes (FRS-CVR: men Δ=4.0 %; p≤0.001;

women, Δ=2.0 %; p=0.01) and (VA: men Δ=5.6 %, p≤0.001; women, Δ=6.5 %; p≤0.001, Figure 10). However, no significant changes over time were observed in ASCVD-CVR overall or for either sex (men Δ=0.8 %, p=0.30; women Δ=0.5 %, p=0.08). Finally, the magnitude of change in each CVR variable due to the intervention was not significantly different from each other between sexes, despite some single factor reductions being significant only for men or women, as described above. However, after intervention period, the CVR score remained significantly different (p<0.001) between sexes (at follow-up) with women having a lower CVR than men, irrespective of calculation method (ASCVD-CVR: mean sex difference=5.6, 95% CI=3.0-8.2 %, p<0.001; FRS-CVR: mean sex difference=8.1, 95% CI=5.1-11.2%, p≤0.001, Table 30).

Table 30. Cardiovascular risk factors, cardiovascular risk and vascular age data classified by sex before and after intervention period.

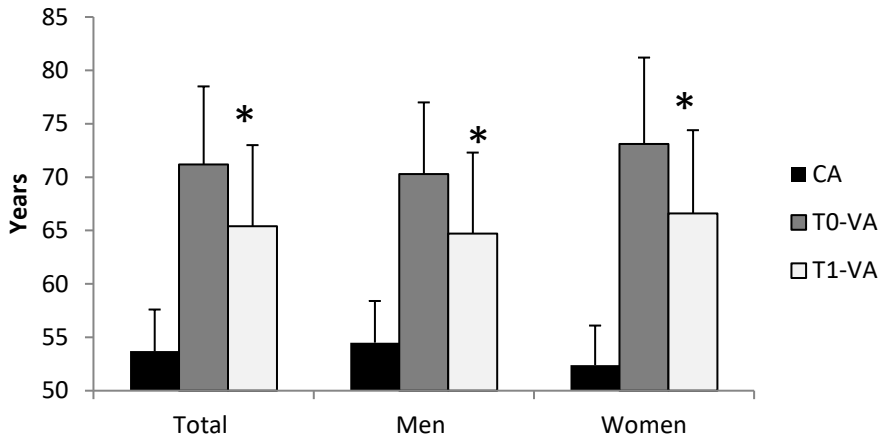
Values are mean±SD or percentage (%) SBP, systolic blood pressure; HDL-C *High density lipoprotein* cholesterol;

Dependent variable	All participants (*n*=167)	*P* T0 *vs.* T1	*Effect Size* η^2	Men (*n*=109)	Women (*n*=58)	*P* M *vs.* W at T1	*Effect size* η^2	*P Time x Sex*	*Effect size* η^2
SBP (mmHg)									
T0	135.8±12.1			135.8±11.8	135.7±12.6				
T1	128.9±11.8*	<0.001	0.277	128.5±11.5*	129.7±12.4*	0.531	0.05	0.54	**0.049**
Total cholesterol (mg/dL)									
T0	205.9±39.8			201.3±40.8	214.4±36.8				
T1	194.8±36.9*	<0.001	0.143	187.7±35.7*	207.9±35.9	0.001	0.271	0.21	**0.454**
HDL-C (mg/dL)									
T0	50.0±32.9			49.8±39.6	52.1±14.4				
T1	47.7±11.6	0.35	0.046	45.8±11.1	51.0±11.8	0.006	0.221	0.71	**0.033**
Antihypertensive medication (%)									
T0	92.2			89.8	96.6				
T1	85.6*	0.05		85.2	86.4*	0.826		0.15	
Cigarette smoking (%)									
T0	13.8			13.9	13.6				
T1	13.8	1.00		13.9	13.6	0.860		1.00	
DM (%)									
T0	9.0			11.1	6.8				
T1	9.0	1.00		11.1	6.8	0.268		1.00	
ASCVD-CVR %									
T0	8.3±6.8			10.5±7.3	4.5±3.1				
T1	7.6±8.6	0.18	0.045	9.6±9.4	4.0±3.1	<0.001	0.371	0.21	**0.041**
FRS-CVR %									
T0	17.9±10.9			21.6±11.1	11.3±6.7				
T1	14.7±10.2*	<0.001	0.149	17.6±10.9*	9.4±5.9*	<0.001	0.423	0.13	**0.126**
Vascular Age									
T0	71.3±14.6			70.3±13.5	73.1±16.3				
T1	**65.4±15.2***	**<0.001**	**0.194**	**64.7±15.1***	**66.6±15.7***	**0.448**	**0.061**	**0.62**	**0.40**

DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; FRS, Framingham Risk Score, CVR, cardiovascular risk.

* *P*-value<0.05 from T0.

Figure 10. Vascular age (VA) values at baseline (T0) and follow-up (T1) periods compared to chronological age (CA).



* *P*-value<0.05 from T0.

7.5. Discussion

To our knowledge, this is the first study investigating the impact of a 16-week intervention (hypocaloric DASH diet plus aerobic exercise) on CVR factors, CVR score calculators and VA in sedentary overweight/obese and hypertensive adults. The main findings of the study were that after aerobic exercise and hypocaloric DASH diet intervention: 1) participants significantly improved SBP, total cholesterol and decreased antihypertensive medication usage; 2) CVR and VA using the FRS model was significantly reduced in both sexes but not CVR estimated by ASCVD Pooled Cohort Equations; 3) regardless of the CVR assessment tool, men showed significantly higher values than women post-intervention albeit no differences in percentage change resulting from the intervention, and 4) VA could better identify the effect of a non-pharmacological intervention in both sexes than other CVR tools.

Based on a rigorous approach to the validation of equations, the American College of Cardiology and the American Heart Association guideline strongly recommends the use of Pooled Cohort Equations in non-Hispanic African Americans and non-Hispanic whites (40 to 79 years old) for the assessment of the 10-year risk of a first hard ASCVD event.[3] However, although the ASCVD-CVR equations have been developed from the FRS,[3,49] and the role of the major variables in the development of CVR was similar in both score calculators, in the present study, after the exercise and diet intervention, CVR was still 7.1% lower with ASCVD-CVR than with FRS-CVR (*P*<0.001) in all participants (Table 30). Thus, the observed and predicted risks for participants in this study at follow-up were 9.6% and 17.6% (medium risk) in men and 4.0% (low risk) and 9.4% (medium risk) in women for the ASCVD-CVR and FRS-CVR,

respectively. Hence, it could be considered that the ASCVD-CVR score calculator by the American College of Cardiology and the American Heart Association would identify the least number of participants with CVR (*i.e.,* underestimation), or the FRS-CVR would stratify a maximum number of individuals with high CVR (*i.e.,* overestimation).[226] This difference could likely be caused by the objective of each score; the FRS estimates CVR for a large combination of CVD outcomes and the ASCVD tool estimates risk mainly for myocardial infarction (fatal and nonfatal) and stroke only [233] and does not consider family history, which influences mortality.[233]

An appropriate lifestyle change, including diet and exercise, has been shown to effectively improve markers of CV health[9] and CVD prevention.[5] Likewise, previous studies have proven that a dose-response curve for physical activity and HTN has a clinically meaningful role in primary prevention of HTN,[234] along with a diet rich in polyphenols.[232] Related to that, in the current study, the decreases ($p<0.05$, before-after intervention) in SBP (Δ=7.3 mmHg in men and Δ=6 mmHg in women), total cholesterol in men (Δ=13.6 mg/dL) and antihypertensive medication use in women (Δ=10.5%) could rightfully be considered the reason underlying the reduction in the FRS-CVR score and VA. However, given that drug therapy for primary prevention of CVD is nowadays based on absolute CVD risk, where the BP-lowering drug treatment is determined by BP level along with other CVR factors (*i.e.,* sex, age, total cholesterol, HDL-C, DM, and smoking status),[235] and that a reduction of 5 mmHg in SBP was associated with a lower risk of CVD mortality,[236] it seems that the ASCVD-CVR estimation tool does not have enough sensitivity to show the benefits of a lifestyle intervention. Hence, the lack of significant changes in ASCVD-CVR estimation, in the presence of other CVR factor improvements, could have a negative effect on the advice to treat individuals with an ASCVD-CVR >7.5% with statins.[55] It is important, therefore, to note that treatment decisions should be individualized (*i.e.,* after a clinician-patient risk/benefit discussion addressing optimal lifestyle), as suggested by the latest cholesterol guidelines,[87] and not just absolute CVR estimation.

On the other hand, the present study showed that after 16-week of intervention with diet and aerobic exercise, absolute CVR remained higher in men than in women for both CVR scores (ASCVD, 5.6%; FRS, 8.2%). As such, the straightforward discussion would claim that men have a higher risk of suffering a CV event in the following 10 years, underlining the sex differences in life expectancy and quality of life, due, in part, to unhealthy behaviors.[237] However, a deeper analysis of data and literature revealed that in the current study after lifestyle intervention: 1) there were no differences in the percentage change after intervention between men and women (ASCVD, p=0.73; FRS, p=0.09); 2) post-intervention women showed higher total cholesterol values with hyperlipidemia >190mg/dL, with no differences in HDL-C (normal values >40 mg/dL), antihypertensive medication use, smoking habit or DM

compared to men; 3) the new cholesterol guidelines have no sex-specific differences in recommendations,[238] and 4) menopausal status in women is not taken into account when CVR is estimated irrespective of tool (in this study 50% were post-menopausal women). Given this, and that deaths from CVD have been greater in women compared with men over the past 30 years, with CVR increases during the menopausal transition and after menopause mainly marked by progressive endothelial dysfunction,[239] would be logical to conclude that CVR is underestimated in women.

Noting the imprecise previous tools for calculating the CVR, mainly due to the various underlying mathematical models used to calculate the scores, VA could be a useful tool in the management of individuals with CVR factors, and easier to use and understand the effect of an intervention in terms of life years.[227] Thus, in the present study after 16-week lifestyle intervention, VA decreased in all participants (Table 30, Figure 10) with no differences between sexes. These results could identify biologically plausible mechanisms underlying exercise and diet-induced effects on CVD risk reduction irrespective of sex. Overall, the CVR factors-associated arterial wall thickening, which contributes to vascular stiffening, are sensitive to a non-pharmacological lifestyle intervention.[206]

Although the present study has highlighted the importance of determining CVR factors in a hypertensive population after a lifestyle intervention, several limitations should be acknowledged. Firstly, although the sample size was sufficient as an initial investigation into CVR and HTN; it would not be comparable to that of larger epidemiological studies, and future studies should consider large-scale investigations. Secondly, the current study only had 35.3% of women which does not represent an equal gender split. As this poses statistical issues, future studies should look to recruit equal numbers, or even to study effects only in women.

7.6. Conclusions

The improvements in CVR factors after a 16-week lifestyle change intervention reduced the risk of suffering a CV event in the following 10 years in overweight/obese adults with HTN assessed with the FRS estimation tool. However, the ASCVD-CVR score calculator was not sensitive enough to show the benefits of diet and exercise. The risk score algorithms (FRS and ASCVD) might underestimate the CVR in women as they always consider men to be higher risk irrespective of age. Therefore, VA could be a useful tool in the management of individuals with CVR factors, and easier to apply and understand the effect of an intervention in terms of life expectancy.

Capítulo 8 / Chapter 8

Light at the end of the tunnel

8. Light at the end of the tunnel

8.1. Conclusiones

- En una población hipertensa, obesa y sedentaria, existen patrones clínicos, físicos, fisiológicos y dietéticos específicos que sugieren tratar comportamientos clave tales como mejorar la calidad nutricional y la CCR a través de la AF regular para obtener una "población sana" con efectos beneficiosos sobre los FRCV.

- Una población hipertensa, obesa y sedentaria presenta un alto perfil de RCV que muestra la siguiente caracterización: obesidad metabólicamente anormal con un nivel bajo de CCR, HTA inducida por el ejercicio y un patrón alimentario no saludable. Específicamente, las mujeres muestran un mejor perfil bioquímico y patrón dietético que los hombres, pero una peor composición corporal y CCR. Sin embargo, el RCV en mujeres podría estar subestimado, ya que cuando ambos sexos presentan los mismos valores de factores de RCV y edad, los hombres tienen un mayor riesgo de sufrir un evento CV en los siguientes 10 años según la ecuación más utilizada para predecir el RCV, the Pooled Cohort Equations. La EV en estas personas es superior a la edad cronológica, independientemente del sexo, lo que acentúa la necesidad de adopción de un estilo de vida más saludable

- Las predicciones de la estimación de CVR y VA pueden representar una herramienta clínica útil para detectar individuos en riesgo de un evento cardíaco, pero las ecuaciones de estimación deberían centrarse más en las diferencias de sexo

- Un tratamiento dietético combinado con diferentes programas EF aeróbico supervisado tanto de forma moderada, como intercalando intensidades altas y moderadas, dos veces a la semana, ofrece una optima herramienta no farmacológica para el control de los FR en personas con sobrepeso/obesidad y HTA. Los beneficios incluyen una mejora del control de la PA, composición corporal, CCR y el tratamiento farmacológico.

- A priori, no hay evidencia científica de que el EF aerobico HIIT tenga mayor o menor reducción de la masa corporal o mejora de la composición corporal. Sin embargo, un volumen mayor de HIIT proporciona reducciones significativamente mayores en la masa corporal en comparación con un bajo volumen.

- HIIT es el programa de EF clave que mayores mejoras genera en la capacidad aeróbica, siendo el entrenamiento de alta intensidad y bajo volumen el programa de EF más efectivo.

- Las mejoras en los FRCV después de una intervención de cambio de estilo de vida de 16 semanas reduce el riesgo de sufrir un evento CV en los siguientes 10 años en personas con HTA primaria y sobrepeso u obesidad evaluados con la herramienta de estimación FRS.

- Los algoritmos de puntaje de riesgo (Framingham y New Pooled Cohort Equations) podrían subestimar el RCV en las mujeres, ya que siempre consideran que los hombres tienen un mayor riesgo independientemente de la edad.

- La estimacion de la EV podría ser una herraimenta útil en el manejo de individuos con FRCV, y más fácil de aplicar y comprender el efecto de una intervención en términos de "esperanza de vida".

8.2. Limitaciones del trabajo y propuestas de futuro.

Una de las limitaciones ha sido el tamaño de muestra en este estudio. Aunque nuestro tamaño de muestra cumple con la potencia estadística para un estudio aleatorizado experimental del estudio EXERDIET-HTA, los estudios transversales que se han realizado con los datos pre-intervención de la investigación no son comparables con los estudios epidemiológicos más amplios. Ademas, debido al reducido número de mujeres (31,4% mujeres y 68,6% hombres) que han participado en el estudio, no resulta representada de igual manera la muestra en relación con el sexo, tanto a la hora de analizar los datos, como para estimar los efectos de cada tipo de EF dependiendo del sexo. De cara a futuras investigaciones habria que encontrar una muestra igualitaria en relación al sexo de los participantes o solo estudiar los efectos en las mujeres. Poder colaborar con otras universidades, donde pueden llevar a acabo el mismo proyecto, con la misma metodolgía, podría ser otra forma para poder conseguir un tamaño de muestra mas amplio y asi resultados con mas potencia estadistica.

Otra de las limitaciones ha sido el no poder controlar el tiempo no supervisado de los participantes del estudio. Por un lado, no se ha podido regular y controlar con exactitud la adherencia de los participantes a la dieta y por otro lado la AF realizada por los participantes del grupo de AC no ha sido controlada. Teniendo en cuenta que se dieron recomendaciones de AF, sería interesante conocer si el mero hecho de hacer, a las personas participantes conocedoras de tales recomendaciones, puede influir de forma significativa en sus costumbres y consecuentemente en su salud. Teniendo lo anterior en consideración, sería preferible para el interés investigador poder controlar la ingesta alimentaria de cada participante y portar acelerómetros que regulen la actividad diaria de modo objetivo de cada persona. Por otro lado, y desde un punto de vista ético, siempre conviene mejorar los hábitos y estilos de vida, hacia los más saludables para cada persona por lo que resultaría éticamente incorrecto no dar a conocer las recomendaciones sobre estilos de vida saludables.

Para finalizar, se necesita más investigación que permita llegar a conclusiones generalizables en cuanto a los componentes de la carga de entrenamiento definidos con el principio FITT, así como por ejemplo examinar el efecto del entrenamiento de fuerza y sus efectos en la salud de personas con HTA primaria y sobrepeso u obesidad, para diseñar programas de EF combinándolos adecuadamente.

8.3. ¿Y AHORA QUÉ?

Me da vértigo y miedo lo rápido que pasa el tiempo. A veces siento que estoy perdiendo el tiempo, me agobio, me pongo a hacer muchos planes, a vivir muchas experiencias y siento entonces que no las estoy disfrutando como debería. ¿Dónde está el término medio? No lo sé. ¿Existe equilibrio al sentir que estas aprovechando tu vida y a la vez disfrutándola? Miro atrás. Me han pasado muchas cosas estos cuatro años. He cometido errores. He aprendido de ellos, he intentado no volver a cometer. He aprendido, he cambiado, he crecido mucho. He añorado. He amado. ¿Los habré aprovechado? Todo aquello que vivimos nos convierte en quien somos. La escuela de la vida, no se si soy alumna aventajada, ni tampoco quien seré dentro de unos años, pero espero seguir siendo la misma disfrutona que soy de tal forma que lo único que me quede por recuperar sea más vida, más experiencias, más aprendizajes y con vosotros.

VIVIMOS RÁPIDO

Vivimos esperando
a que la vida nos espere
La vida es lenta, muy lenta
y nosotros vamos rápido, muy rápido,
comemos rápido, hablamos rápido y dormimos rápido,
la vida es eso que pasa
mientras nosotros corremos

Vivimos esperando el momento perfecto,
sin utilizar el momento y hacerlo perfecto.

Vivimos esperando
que la jornada termine para llegar a casa,
vivimos esperando que sea viernes
(olvidando que el que no es feliz un miercoles
tampoco lo sera el fin de semana)
Vivimos esperando que lleguen los puentes,
las vacaciones , el verano.

Vivimos esperando que pase algo,
y lo unico que pasa,
es la vida.

Capítulo 9 / Chapter 9

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Capítulo 10 / Chapter 10

Anexos y publicaciones

10. ANEXOS Y PUBLICACIONES/ Annexes and publications

10.1. Anexo 1. Indicadores de calidad

Los indicadores de calidad de los artículos publicados, según *Journal Citation Reports* (JCR) y el *Cite Score* de Scopus en el año 2016 son los siguientes:

Revista	ISSN	País	Categoría	JCR		Scopus	
				JCR	Cuartil	Cite score	Cuartil
CLINICAL AND EXPERIMENTAL HYPERTENSION	1064-1963	EEUU	PERIPHERAL VASCULAR DISEASE	1.162	4	1.394	2
BLOOD PRESSURE MONITORING	1359-5237	EEUU	PERIPHERAL VASCULAR DISEASE	1.415	4	1.109	1
EUROPEAN JOURNAL OF PREVENTIVE CARDIOLOGY	2047-4873	UK	CARDIAC & CARDIOVASCULAR SYSTEMS	3.606	1	4.628	1
HIGH BLOOD PRESSURE & CARDIOVASCULAR PREVENTION	1120-9879	UK	CARDIOLOGY AND CARDIOVASCULAR MEDICINE	1.09		1.433	2

EEUU, Estados Unidos de América; ISSN, international standard serial number; JCR, Journal Citation Reports; UK, United Kingdom

10.2. Anexo 2. Publicaciones en formato original

Clinical, physical, physiological, and dietary patterns of obese and sedentary adults with primary hypertension characterized by sex and cardiorespiratory fitness: EXERDIET-HTA study. (*p*. 206).

Assessment of cardiovascular risk and vascular age in overweight/obese adults with primary hypertension: EXERDIET-HTA study. (*p*. 215).

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Clinical, physical, physiological, and dietary patterns of obese and sedentary adults with primary hypertension characterized by sex and cardiorespiratory fitness: EXERDIET-HTA study

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ABSTRACT

The main purpose of this study was to determine some key physical, physiological, clinical, and nutritional markers of health status in obese and sedentary adults (54.0 ± 8.1 years, 141 men and 68 women) with primary hypertension (HTN) characterized by sex and cardiorespiratory fitness (CRF) level. The studied population showed a high cardiovascular risk (CVR) profile including metabolically abnormal obese, with poor CRF level (22.5 ± 5.6 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$), exercise-induced HTN (Systolic Blood Pressure>210 mmHg in men and >190 mmHg in women at the end of the exercise test) and with non-healthy adherence to dietary pattern (Dietary Approaches to Stop Hypertension, 46.3%; Mediterranean Diet, 41.1%; and Healthy Diet Indicator, 37.1%). Women showed a better biochemical and dietary pattern profile than men (lower values, $P < 0.05$, in triglycerides, mean difference = 26.3; 95% CI = 0.9–51.7 mg/dL, aspartate transaminase, mean difference = 4.2; 95% CI = 0.3–8.0 U/L; alanine transaminase, mean difference = 8.2; 95% CI = 1.6–14.8 U/L; gamma-glutamyl transpeptidase, mean difference = 11.0; 95% CI = -1.1–23.2 U/L and higher values, $P = 0.002$, in high-density lipoprotein cholesterol, mean difference = 5.0, 95% CI = -13.3–3.3 mg/dL), but physical and peak exercise physiological characteristics were poorer. A higher CRF level might contribute to the attenuation of some CVR factors, such as high body mass index, non-dipping profile, and high hepatic fat. The results strongly suggest that targeting key behaviors such as improving nutritional quality and CRF via regular physical activity will contribute to improving the health with independent beneficial effects on CVR factors.

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Introduction

The 2013 guidelines on hypertension (HTN) of the European Society of Hypertension and the European Society of Cardiology (1) and the guidelines of the American College of Cardiology and the American Heart Association for the management of overweight and obesity in adults (2) presented new evidence on several diagnostic and therapeutic aspects of HTN and overweight/obesity, including lifestyle modification to reduce cardiovascular risk (CVR). Obesity and HTN frequently coexist in the same individual, and they have been recognized as a pre-eminent cause of CVR (3,4). It is well known that blood pressure (BP) and cardiovascular (CV) damage are related and how CV mortality is modified by the concomitance of other CVR factors (5). Prevalence of HTN, defined as values ≥140 mmHg systolic BP (SBP) and/or ≥90 mmHg diastolic BP (DBP) and/or prescription of antihypertensive drug therapy, appears to be around 30–45% of the general population (1).

Specifically, in the Spanish population, HTN was found in 42.6% aged ≥18 years, and it was more common among men (49.9%) than women (31.5%) (6). In addition, current estimates suggest that 69% of adults are either overweight or obese, with approximately 35% obese (2). Hence, for the management of HTN and the prevention of coronary heart disease, it is mandatory to quantify the total CVR, since only a small fraction of the hypertensive population has an elevation of BP alone, with the main portion exhibiting additional CVR factors, thereby increasing the total CVR (1). Accordingly, BP measurements (*i.e.*, daytime, night-time, and 24-h BP), medical history (*i.e.*, first diagnosis of HTN, biochemical profile, medications, concomitant diseases, smoking habit, family history), physical examination (*i.e.*, electrocardiography and body composition), laboratory investigation with BP during

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exercise and lifestyle assessment (*i.e.*, physical activity and dietary pattern) should be implemented (1,2).

Experimental studies indicate that sex affects the developmental programming of BP and CVR. Thus, testosterone appears to serve as a pro-hypertensive factor, whereas estrogen is suggested to contribute an anti-hypertensive influence and sensitivity to vasoactive factors (7). However, whether gender differences in prognosis represent a true result from differences in patient management and diagnostic approach is not yet clarified (8).

On the other hand, cardiorespiratory fitness (CRF) is considered a vital sign, and its strong association with CVR is well known (*i.e.*, poor CRF level corresponds with a substantially increased mortality risk) (9). A previous meta-analysis also indicated that the risk of death was dependent upon CRF level and not body mass index (BMI); thus, it was asserted that fit individuals who were overweight/obese were not automatically at a higher risk for all-cause mortality (10). Therefore, it should be of interest to assess the characteristics of overweight/obese individuals with HTN diagnosis taking into account different CRF levels.

An unhealthy dietary pattern is also considered a CVR factor (11). Hence, nutrition research is focusing more on the impact of dietary pattern on disease risk rather than on individual food groups or nutrients (12). The Healthy Diet Indicator (HDI), Mediterranean Diet (Med), and The Dietary Approaches to Stop Hypertension (DASH) are the most well-known dietary guidelines that specifically target lowering CV disease risk. However, to the best of our knowledge, no reports are available on the adherence to dietary guidelines by overweight/obese individuals with HTN.

The main purpose of this study was to determine some key physical, physiological, clinical, and nutritional markers of health status in obese and sedentary adults with primary HTN characterized by sex and CRF before starting a non-pharmacological therapeutic strategy.

Methods

Study participants

The EXERDIET-HTA study was conducted between September 2012 and June 2016 in Vitoria-Gasteiz (Basque Country, Spain). The current baseline study comprised a total of 209 participants aged between 24 and 70 years (mean 54.0 ± 8.1 years), 141 men (67.5%) and 68 women (32.5%). All participants were overweight/obese, sedentary, and had been diagnosed of HTN. Participants were considered to have HTN if they had a mean SBP≥140 mmHg and/or DBP≥90 mmHg or used antihypertensive medications. All other inclusion and exclusion criteria have been specified in the protocol of the study (13). The Ethics Committee of the University of the Basque Country (UPV/EHU, CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital (2015-030) approved the study design, study protocols, and informed consent procedure (Clinical Trials.gov identifier, NCT02283047).

Measures

Stature and body mass were measured, and BMI was calculated as total body mass divided by height squared (kg/m^2). Waist and hip circumferences were taken, and waist to hip ratio (WHR) was defined as waist circumference divided by hip circumference both in centimeters. Moreover, the estimation of fat-free mass (FFM), total body water (TBW), and fat mass (FM) was made by bioelectrical impedance (Tanita, BF 350, Arlington Heights, IL, USA).

Blood pressure measures were obtained by wearing an ambulatory BP monitoring (ABPM) 6100 recorder (Welch Allyn, New York City, NY, USA). The device measured BP an entire day, at 30-min intervals during the daytime, and at 60-min intervals during night time. The variables taken into account from the ABPM measures were mean values of SBP and DBP, mean BP (MBP), pulse pressure (PP), and heart rate (HR). Blood pressure mean dipping pattern was the percent of the nocturnal reduction in SBP in relation to diurnal mean SBP, and it was calculated as ([daytime SBP-nighttime SBP]/daytime SBP×100) (14). Based on the percentage decline in nocturnal BP, participants were grouped as dippers ≥10% or non-dippers ≤ 10% (1).

All medications prescribed to participants were recorded and classified in their group: angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), diuretics, calcium channel blockers (CCB,) beta blockers (BB), statins, hypoglycemic agents, antiplatelets, and anticoagulants.

Physical fitness measures included the Modified Shuttle Walking Test (MSWT) (15) and a peak, symptom-limited cardiopulmonary exercise test (CPET). Walked distance (m) was recorded at the completion of each MSWT. The CPET was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, Netherlands) starting at 40W with a gradual increment of 10W each minute in ramp protocol. Expired gas was analyzed with a system (Ergo CardMedi-soft S.S, Belgium Ref. USM001 V1.0) that was calibrated before each test for the determination of peak oxygen consumption ($\dot{V}O_{2peak}$) (13).

The distributions of $\dot{V}O_{2peak}$ were divided into tertiles (low, moderate, and high CRF) in each sex. The details regarding the range in each group were as follows: the lowest tertile (Low-CRF group): $\dot{V}O_{2peak} \leq 21$ mL·kg^{-1}·min^{-1} in men and $\dot{V}O_{2peak} \leq 16$ mL·kg^{-1}·min^{-1} in women; the medium tertile (Moderate-CRF group): $21 < \dot{V}O_{2peak} \leq 26$ mL·kg^{-1}·min^{-1} in men and $16 < \dot{V}O_{2peak} \leq 21$ mL·kg^{-1}·min^{-1} in women; the highest tertile (High-CRF group): $\dot{V}O_{2peak} > 26$ in men and $\dot{V}O_{2peak} > 21$ mL·kg^{-1}·min^{-1} in women.

A blood sample (12.5mL) was collected from each participant in the Clinical Trials Unit of Tecnalia (HUA, Vitoria-Gasteiz) after an overnight fast to determine the biochemical profile including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose, insulin, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), and C-Reactive Protein (CRP) (13). Type 2 Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL (16). HOMA-IR was used to evaluate insulin resistance

[fasting serum insulin (μU/mL) × fasting plasma glucose (mg/dL)/405] (17).

For the dietary assessment, two face-to-face non-consecutive 24-h recalls were used to examine dietary habits by trained dieticians, allowing for important correction for within-subject variability in nutrient intake (18). This is considered the most cost-effective method to implement within a pan-European dietary survey (19). Moreover, statistical methods suggest that to achieve detailed dietary data, at least two measurements are required and also to get an equal distribution of the different days of the week (20). Fixed instructions to the interviewers were done to minimize the time between registrations days and emphasizing that participants were not allowed to choose the most convenient days for them (19). All dietary data were calibrated in Easy Diet computer program, and dietary nutritional composition was obtained. Adherence to the Med was obtained based on the score proposed by previous studies (21). Nevertheless, instead of median cut-offs, mean cut-offs were used because of the low consumption in some food groups. A sum of nine food groups and nutrients were included in calculating the Med score. Intakes of vegetables, legumes, fruits and nuts, cereals, fish and seafood, and monounsaturated to saturated fats ratio were considered as positive dietary components, whereas dairy, meat products, and alcohol were considered as negative. Sex-specific mean intakes were calculated as a cut-off in each food group to recode the components. A value of 1 was given when the positive dietary components were above the mean and when the negative ones were below the mean. In contrast, a value of 0 was given either when food groups considered as positive were below the mean or when the negative components were above the mean. However, when alcohol consumption among men and women was ≤2 drinks per day and ≤1 per day, respectively, a value of 1 was given, whereas a value of 0 was given with higher intakes of alcohol. Therefore, with the sum of all the recoded dietary elements, the adherence to the Med score was ranged from 0 (minimal adherence) to 9 points (maximal adherence). The adherence to the DASH dietary pattern was calculated with the sum of eight dietary elements, considering the consumption of fruits, vegetables, nuts and legumes, whole grains, and low-fat dairy products as positive components and intakes of sodium, red and processed meat, and sweetened beverages as negative (12). As above, values of 0 or 1 were given when the intakes were above or below the sex-specific means. Thereby, the adherence to the DASH dietary pattern was ranged between 0 and 8 (from lowest to highest adherence). The adherence to HDI proposed by the World Health Organization was calculated following healthy diet recommendations for the general population (12). This score is composed of seven dietary nutrients and food groups, and values of 1 or 0 were also given depending on the meeting established criteria. The components of this dietary pattern were the following: saturated fatty acid (≥10% of total energy intake = 0, <10% of total energy = 1), polyunsaturated fatty acids (<6% or >10% of total energy = 0, 6–10% = 1), cholesterol (≥ 300 mg = 0, ≤300 mg = 1), protein (<10% or >15% of total energy = 0, 10–15% of total energy = 1), fiber (<25g = 0, ≥25g = 1), fruits and vegetables (<400 g = 0, ≥400 g = 1), and free sugars (≥10% of total energy = 0, <10% of total energy = 1).

Statistical analyses

Descriptive statistics were calculated for all variables. Data are expressed as mean±standard deviation (SD). All variables were deemed normally distributed using a Kolmogorov-Smirnov apart from age, BMI, waist circumference, WHR, FM, TBW, FFM, DBP means, %BP dipping, $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$ and $mL \cdot kg^{-1} \cdot min^{-1}$), metabolic equivalent of task (MET), TC, HDL, TG, glucose, AST, ALT, and GGT that had a skewed distribution and were therefore log transformed prior to any analysis. The Chi-square test was used to test differences in categorical variables between sexes. An independent samples *t*-test was used to determine whether there was a significant sex difference for all parametric variables. Analysis of covariance (ANCOVA) was used to examine dependent variables of the participants classified by CRF level (low, medium, and high), adjusting the analysis for age, sex, and body mass. A Bonferroni post-hoc test was used to determine the level of significance when a significant main effect was found. Cohen's d was calculated to describe the standardized mean difference between sex effect sizes. Omega squared (ω^2) was calculated to describe the standardized mean difference of an effect between CRF groups. The effect sizes were interpreted as small (d = 0.2), medium (d = 0.5), and large (d = 0.8) based on benchmarks suggested by Cohen (22). Statistical significance was set at $P < 0.05$. The statistical analyses were performed with the SPSS version 22.0 software package.

Results

Characteristics of the study population are shown in Table 1. Although one of the inclusion criteria was to be overweight/obese, after statistical analysis, the mean BMI>30 kg/m^2, which is considered obesity, and the mean WHR was 0.96 ±0.11, which is considered a CVR factor in accordance with guidelines for the management of overweight and obesity in adults (2). Significant differences were observed between men and women in body mass, WHR, and body composition variables ($P < 0.001$). Men showed a higher proportion of FFM ($P < 0.001$, $\Delta = 16.1\%$) and TBW ($P = <0.001$, $\Delta = 17.7\%$) compared to women, whereas women had a higher proportion of FBM ($P = <0.001$, $\Delta = 32.2\%$) compared to men.

No differences were found in mean SBP between sexes. However, mean DPB values were significantly higher in men ($P = 0.001$, $\Delta = 5.0\%$) compared to women. Consequently, MBP was significantly lower in women ($P = 0.027$, $\Delta = -3.14\%$) compared to men. Mean HR was lower ($P = 0.005$, $\Delta = -5.6\%$) in men compared to women, showing 4.1 beats less per minute. Taking into account the mean of sleep–time–relative SBP decline (*i.e.*, ≥%10), all individuals were broadly classified as BP dippers in accordance with ESH/ESC Guidelines for the management of arterial HTN (1).

Table 1. Characteristics of the study population and medication-pharmacological therapy.

Variables	AP (n = 209)	Men (n = 141)	Women (n = 68)	$P_{M\text{-}W}$	d Cohen
Age (yrs)	54.0 ± 8.1	54.3 ± 7.9	53.4 ± 8.6	0.4	0.1
Body mass (kg)	90.1 ± 15.5	95.0 ± 14.07	80.0 ± 13.5	<0.001***	1.1
BMI (kg/m^2)	31.3 ± 4.6	31.3 ± 4.3	31.5 ± 5.2	0.9	0.04
WHR (cm)	0.96 ± 0.11	1.0 ± 0.08	0.9 ± 0.13	<0.001***	1
FFM (%)	66.7 ± 8.7	69.9 ± 8.0	60.2 ± 5.9	<0.001***	1.4
TBW (%)	48.7 ± 6.6	51.2 ± 5.5	43.5 ± 5.5	<0.001***	1.4
FBM (%)	33.3 ± 8.7	30.1 ± 8.0	39.8 ± 5.9	<0.001***	1.4
SBP (mmHg)	135.9 ± 14.1	136.4 ± 12.9	134.8 ± 16.3	0.4	0.1
DBP (mmHg)	78.9 ± 8.6	80.1 ± 7.8	76.3 ± 9.6	<0.001***	0.5
Mean HR (beats·min^{-1})	71.0 ± 10.0	69.8 ± 9.9	73.9 ± 9.7	0.005**	0.4
MBP (mmHg)	97.9 ± 9.5	98.9 ± 8.7	95.8 ± 10.9	0.027*	0.3
PP (mmHg)	57.0 ± 10.4	56.3 ± 9.5	58.5 ± 11.9	0.2	0.2
BP dipping (%)	11.4 ± 7.0	11.6 ± 7.0	11.0 ± 7.0	0.6	0.1
Cigarette smoking (%)	11.4	10.6	13.2	0.6	
DM (%)	4.5	5	3	0.5	
ACEI (%)	36.8	34.8	41.2	0.4	
ARB (%)	43.6	45.4	39.7	0.4	
DIURETICS (%)	32.1	31.2	33.8	0.7	
CCB (%)	17.7	21.3	10.3	0.05	
BB (%)	9.6	8.5	11.8	0.4	
STATINS (%)	12.9	12.8	13.2	0.9	
HYPOGLYCEMIC AGENTS (%)	5.3	6.4	2.9	0.3	
ANTIPLATELETS (%)	3.9	4.3	2.9	0.6	
ANTICOAGULANTS (%)	1	0.7	1.5	0.6	

AP, all participants; BMI, body mass index; WHR, waist to hip ratio; FFM, fat-free mass; TBW, total body water; FBM, fat body mass; SBP, systolic blood pressure; DBP diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; PP, pulse pressure; BP, blood pressure; DM, diabetes mellitus. ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin ii receptor blockers; CCB, calcium channel blockers; BB, beta blockers. P < 0.05: Significant difference between men (M) and women (W)

*P < 0.05, ** P < 0.01, *** P < 0.001.

Related to **medication-pharmacological therapy**, 87.1% of participants received antihypertensive and/or other medications, while 12.9% did not. The percentage of participants who took one, two, three, or four or more medications was 40.2%, 27.3%, 12.9%, and 6.7%, respectively. Referring to the antihypertensive drugs, 36.8% of participants took ACEI, 43.5% ARB, 32.1% diuretics, 17.7% CCB, and 9.57% BB. Chi-square test analysis revealed no significant differences between sexes (Table 1).

When **exercise capacity** was objectively analyzed (*i.e.*, through CEPT), all participants made an exhaustive exercise effort (RER = 1.1±0.1). According to the American College of Sport Medicine, participants of the present study were classified as "very poor" CRF level (23) taking into account $\dot{V}O_{2peak}$ values (22.5 ± 5.6 and mL·kg^{-1}·min^{-1}) and presented "exercise HTN" with SBP values higher than 210 mmHg in men and >190 mmHg in women at the end of the exercise test (24). Higher values in men compared to women were observed in peak workload (W, P < 0.001, Δ = 47.3%), $\dot{V}O_{2peak}$ (L·min^{-1}, P < 0.001, Δ = 53.3% and mL·kg^{-1}·min^{-1}, P < 0.001, Δ = 24.2%), $\dot{V}CO_{2peak}$ (L·min^{-1}, P < 0.001, Δ = 38.9%), RER, and MET. However, no differences (P = 0.3) were found for MSWT distance between sexes (Table 2).

Regarding participants' **biochemical profile** characteristics and according to the Adult Treatment Panel III (25), LDL-C values were upper to optimal values (<100 mg/dL), TC showed higher values than desirable (<200 mg/dL), and also "cholesterol ratio" (*i.e.*, TC/HDL-C) presented values above the ideal (<3.5). On the other hand, there were normal triglycerides (<200 mg/dL) and HDL-C (>40 mg/dL) values. Furthermore, according to the new International Diabetes Federation definition (26), participants showed slightly raised fasting glucose (>100mg/dL). The 90th percentile for the HOMA-IR was lower than 3.8, which is not considered diagnostic of IR (27). Although evidence has shown that CRP concentrations, a proinflammatory biomarker, could be

Table 2. Participants' peak exercise function.

Variables	AP (n = 209)	Men (n = 141)	Women (n = 68)	$P_{M\text{-}W}$	d Cohen
Workload (W)	131.1 ± 39.6	146.4 ± 36.1	99.4 ± 25.0	<0.001***	1.5
SBP (mmHg)	211.6 ± 29.9	210.7 ± 31.6	213.6 ± 26.1	0.7	0.1
DBP (mmHg)	101.00 ± 18.5	99.9 ± 16.9	105.7 ± 21.1	0.05	0.3
HR (beats·min^{-1})	151 ± 19.2	150.3 ± 20.0	154.8 ± 17.3	0.2	0.2
$\dot{V}O_{2peak}$ (L·min^{-1})	2.0 ± 0.5	2.3 ± 0.4	1.5 ± 0.3	<0.001***	2.3
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	22.5 ± 5.6	24.1 ± 5.4	19.4 ± 4.6	<0.001***	0.9
$\dot{V}CO_{2peak}$ (L·min^{-1})	2.23 ± 0.6	2.5 ± 0.5	1.8 ± 0.4	<0.001***	1.6
RER	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	<0.001***	1
MET	6.4 ± 1.7	6.8 ± 1.6	5.5 ± 1.3	<0.001***	0.9
MSWT (m)	834.1 ± 265.0	848.3 ± 264.8	804.7 ± 265.0	0.3	0.2

AP, all participants; SBP, systolic blood pressure; DBP diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; PP, pulse pressure; $\dot{V}O_{2peak}$, peak oxygen uptake; $\dot{V}CO_{2peak}$, peak carbon dioxide production; RER, respiratory exchange ratio; MET, metabolic equivalent of task; MSWT, modified shuttle walk test distance. P g< 0.05: Significant difference between men (M) and women (W)

*** P < 0.001.

modulated by dietary fatty acid intake (28), levels of CRP>3mg/L were considered cardiometabolic abnormal (29). Therefore, taking into account Wildman Modified criteria, participants of the present study were classified as metabolically abnormal obese (*i.e.*, BMI≥30kg/m^2 and ≥2 cardiometabolic abnormalities) (30). Furthermore, among the three hepatic enzymes, which are indices for the diagnosis of non-alcoholic fatty liver disease (*i.e.*, AST, ALT, and GGT), only ALT showed abnormal criteria (>30 U/L) (31) (Table 3). Triglycerides (mean difference = 26.3; 95% CI = 0.9–51.7 mg/dL), AST (mean difference = 4.2; 95% CI = 0.3–8.0 U/L), ALT (mean difference = 8.2; 95% CI = 1.6–14.8 U/L), GGT (mean difference = 11.0; 95% CI = -1.1–23.2 U/L), and AST/ALT (mean difference = -0.1; 95% CI = -0.2–0.0) were significantly lower in women than men. Moreover, HDL-C was higher (P = 0.002) in women than in men (mean difference = 5.0, 95% CI = -13.3–3.3 mg/dL) (Table 3), but both sexes presented healthy values.

The adherence to different healthy **dietary patterns** was calculated to examine the diet quality of the participants (Table 4). The highest adherence was observed in DASH dietary pattern (46.3%), followed by Med (41.1%) and HDI (37.1%) dietary pattern. A higher adherence to Med (P = 0.022) was shown in women compared to men, with no significant differences between sexes concerning DASH (P = 0.464) and HDI dietary (P = 0.406) pattern.

Characteristics of all participants divided by **CRF levels** are indicated in Table 5. Significant differences were found in age between high and low CRF level participants (P < 0.05, Δ = -9.7%). High CRF level participants had lower BMI than those with medium or low CRF level (P < 0.001, Δ = -8.7% and P < 0.01, Δ = -16.2%, respectively). Although no significant differences were found in mean SBP and DBP, there were differences in percentage of BP dipping (P = 0.048). Those with low CRF level were broadly designated as non-dippers, whereas those in medium and high CRF level were designated as dippers in accordance with ESH/ESC Guidelines for the management of arterial HTN (1). According to biochemical profile, significant differences were found in ALT, GGT, and AST/ALT ratio. Thus, participants with low CRF level showed elevated ALT and GGT and lower AST/ALT ratio (P = 0.001, P = 0.030, and P = 0.018, respectively) compared to medium (ALT: P < 0.05, Δ = 50.8%, and GGT: P = 0.085, Δ = 41.2%) and high (ALT: P < 0.001, Δ = 118.8%, GGT: P = 0.035, Δ = 76.4% and AST/ALT ratio: P = 0.014, Δ = 27.3%) CRF level. No significant differences were observed in the rest of biochemical parameters among CRF levels.

Table 4. Adherence to the Mediterranean (Med), Dietary Approaches to Stop Hypertension (DASH), and Healthy Diet Indicator (HDI) dietary patterns among participants of the study.

Variables	AP (n = 165)	Men (n = 114)	Women (n = 51)	$P_{M\text{-}W}$	d Cohen
Med-score (0-9)	3.7 ± 1.7	3.5 ± 1.5	4.2 ± 1.8	0.022*	0.4
Adherence (%)	41.1	38.9	46.7		
DASH score (0–8)	3.7 ± 1.7	3.6 ± 1.6	3.8 ± 1.7	0.5	0.1
Adherence (%)	46.3	45	47.5		
HDI score (0–7)	2.6 ± 1.3	2.6 ± 1.3	2.4 ± 1.4	0.4	0.2
Adherence (%)	37.1	37.1	34.3		

*P < 0.05.

Discussion

This was the first study showing the clinical, physical, physiological, and dietary patterns of overweight/obese and sedentary adults diagnosed with primary HTN characterized by sex and CRF level. The data collected provide a thorough understanding of the physiopathology of the studied population and emphasize the importance of CVR screening for CV disease prevention in clinical practice. Overall, the assessed individuals suffered from resting HTN, were metabolically abnormal obese with poor CRF level, exercise-induced HTN, and the majority of them lacked a healthy dietary pattern, which confirms a high CVR profile. Specifically, women showed a better biochemical and dietary pattern profile than men, but physical and exercise physiological characteristic were poorer, and hence, calling into attention the sex differences in physiology between women and men. Finally, a favorable CRF level seems to contribute to the attenuation

Table 3. Biochemical profile characteristics of the study's participants.

Variables	AP (n = 209)	Men (n = 141)	Women (n = 68)	$P_{M\text{-}W}$	d Cohen
TC (mg/dL)	213.0 ± 134.1	214.1 ± 162.8	210.8 ± 34.0	0.2	0.03
HDL-C (mg/dL)	50.7 ± 33.2	49.1 ± 39.2	54.1 ± 13.9	0.002**	0.2
LDL-C (mg/dL)	127.7 ± 32.2	124.8 ± 33.6	133.5 ± 28.8	0.1	0.3
Triglycerides (mg/dL)	133.9 ± 78.4	142.5 ± 85.4	116.1 ± 57.9	0.03*	0.4
TC/HDL-C ratio	4.7 ± 4.1	5.0 ± 5.3	4.1 ± 1.1	0.1	0.2
Glucose (mg/dL)	106.4 ± 82.4	108.7 ± 100.0	102.1 ± 20.6	0.9	0.1
Insulin (μU/mL)	9.8 ± 5.4	9.4 ± 5.3	11.0 ± 6.0	0.2	0.3
HOMA-IR	2.5 ± 1.6	2.2 ± 1.1	3.0 ± 2.3	0.3	0.4
CRP (mg/L)	4.5 ± 4.5	4.1 ± 4.3	5.4 ± 4.9	0.4	0.3
AST (U/L)	25.3 ± 12.0	26.6 ± 13.0	22.5 ± 9.4	0.01*	0.4
ALT (U/L)	31.9 ± 20.7	34.6 ± 21.2	26.4 ± 18.7	0.01*	0.4
GGT (U/L)	37.3 ± 38.5	40.6 ± 42.8	29.5 ± 25.2	0.006**	0.3
AST/ALT (U/L)	0.9 ± 0.5	0.9 ± 0.5	1.0 ± 0.3	0.029*	0.2

AP, all participants; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; CRP, C-Reactive Protein; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase. P < 0.05: Significant difference between men (M) and women (W)
*P < 0.05, ** P < 0.01, *** P < 0.001.

Table 5. Characteristics of the study population classified by cardiorespiratory fitness level (low, medium, high).

	Cardiorespiratory fitness groups				
Variables	Low (M = 48,W = 24)	Medium (M = 51,W = 23)	High (M = 42,W = 21)	*P*-value	*ω-squared*
Age (yrs)	56.7 ± 1.0	53.8 ± 0.9	51.2 ± 1.1	0.003**	0.00995
BMI (kg/m^2)	34.0 ± 0.5	31.2 ± 0.5	28.5 ± 0.5	<0.001***	0.206
WHR (cm)	0.97 ± 0.1	0.98 ± 0.13	0.95 ± 0.08	0.8	−0.0807
SBP (mmHg)	136.6 ± 1.8	135.8 ± 1.6	135.2 ± 1.9	0.9	−0.005
DBP (mmHg)	78.4 ± 1.0	78.6 ± 0.9	79.7 ± 1.1	0.7	0.0006
BP DIPPING (%)	9.7 ± 7.3	12.5 ± 6.8	12.1 ± 6.6	0.048*	0.0228
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	17.8 ± 0.5	22.6 ± 0.5	27.7 ± 0.6	<0.001***	0.6739
MET$_{peak}$	5.0 ± 0.2	6.5 ± 0.2	7.5 ± 0.2	<0.001***	0.59183
TC (mg/dL)	202.4 ± 19.2	233.5 ± 20.2	206.0 ± 22.1	0.7	−0.0024
HDL-C (mg/dL)	48.9 ± 4.6	46.8 ± 4.6	57.2 ± 5.2	0.4	−0.08124
LDL-C (mg/dL)	127.6 ± 4.5	120.8 ± 4.7	134.9 ± 5.1	0.1	0.01376
Triglycerides (mg/dL)	134.0 ± 10.6	144.2 ± 10.6	122.7 ± 12.0	0.3	0.00191
TC/HDL-C	4.4 ± 1.2	5.6 ± 7.8	4.1 ± 1.4	0.3	0.012357
Glucose (mg/dL)	117.6 ± 11.5	101.0 ± 11.1	99.1 ± 12.7	0.7	0.00255
Insulin (μU/mL)	7.9 ± 1.3	11.8 ± 1.2	9.4 ± 1.5	0.2	0.97905
HOMA-IR	1.9 ± 0.4	3.1 ± 0.4	2.3 ± 0.4	0.1	0.000739
CRP (mg/L)	5.9 ± 5.3	4.2 ± 4.3	2.5 ± 1.6	0.5	0.0565
AST (U/L)	28.4 ± 2.2	25.3 ± 2.3	25.5 ± 2.8	0.5	-0.0032
ALT (U/L)	46.6 ± 4.4	30.9 ± 4.5	21.3 ± 5.1	0.001**	0.06250
GGT (U/L)	49.4 ± 59.02	33.1 ± 21.0	28.0 ± 14.4	0.030*	0.04139
AST/ALT ratio	0.8 ± 0.3	0.9 ± 0.2	1.1 ± 0.8	0.018*	0.04567

BMI, body mass index; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP diastolic blood pressure; MBP, mean blood pressure.; VO_{2peak}, peak oxygen uptake; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; CRP, C-Reactive Protein; AST, aspartate transaminase; ALT, alanine transaminase. P < 0.05: Significant difference between men (M) and women (W)
*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

of some CVR factors, such as high BMI, non-dipping profile, and high hepatic fat.

All population

In addition to HTN and obesity, the results of the present study clearly showed additional CVR factors, which may potentiate each other, leading to a total CVR that may be greater than the sum of its individual components (1). Potentially, some of the modifiable risk factors were very much present in the studied population (*i.e.*, HTN, obesity, physical inactivity, atherogenic diet) along with non-modifiable risk factors related to age (men ≥45 years, women ≥55years) (25). As a result, although the population of this study presented favorable metabolic features such as low levels of HOMA-IR and fasting triglycerides as well as normal HDL-C, a clustering of cardiometabolic risk factors is shown (*i.e.*, BMI ≥30 kg/m^2 and ≥2 cardiometabolic abnormalities: HTN, elevated glucose level, and systemic inflammation) along with non-healthy levels of TC, ALT, and TC/HDL-C ratio. These results lead to categorizing the individuals as metabolically abnormal obese according to Wildman Modified criteria (30). Indeed, both inflammation (exemplified by high C-reactive protein levels, 4.5 ± 4.5 mg/dL) and TC/HDL-C ratio (4.7 ± 4.1) are factors associated with the development of atherosclerosis and the pathogenesis of CV disease in the general population (32). Furthermore, previous studies have also shown that high ALT values (31.9 ± 20.7 U/L, in the present study) were related to higher levels of hepatic fat, abdominal fat, and insulin resistance (31), and it was also independent predictor of Diabetes Type II (33). Adding to that, knowing that the risk of CV disease and death is often more related to fitness level than BMI (34), the very poor CRF level in this population could be another important, yet not recognized, clinically risk marker (32). On the other hand, even though there is currently no consensus on the normal BP response during dynamic exercise testing, participants of the present study showed "exercise-induced HTN" (*i.e.*, SBP peak values >210 mmHg for men and >190mmHg for women) (24). Related to that, proposed pathophysiologic factors include excessively high sympathetic tone during exercise, decreased aortic distensibility, increased left ventricular mass, and endothelial dysfunction (24,35). These results may identify those individuals that are not well controlled in resting HTN in clinical practice and could present a cardiac "end-organ" manifestation of HTN in the future. Thus, some authors have even proposed exercise SBP as being an effective and more convenient technique than ABPM for identifying the prehypertensive state and to predict future risk for adverse CV events (24).

There is increasing evidence that **sex differences** are important in pathophysiology treatment, and more relevant for noncommunicable diseases as HTN. With regard to body composition, the heterogeneity by sex in the relationship between hormones and body composition is well known. Thus, women present increased subcutaneous fat accumulation promoted by estrogen, and men feature a greater trunk and visceral and liver fat (36). The aforementioned was corroborated by the results of the present study in relation to a "better" body composition in men (*i.e*, higher FFM and lower FBM, Table 1) compared to women, but women showed a better metabolic profile (higher values in HDL-C and lower triglycerides and hepatic enzymes, Table 3) than men. However, taking into account the percentage of FBM, both sexes were obese according to cut off points for body fat percentage (*i.e.*, ≥25.0% for men and ≥35.0% for women) (37). Hence, men could present a higher CV or metabolic risk profile mainly due to the higher liver enzyme activities

(*i.e.*, ALT, ALT, GGT, and AST/ALT ratio), and specifically with ALT values upper to healthy cutoff (<30 U/L), which is closely associated with non-alcoholic fatty liver disease (38). Furthermore, even though both sexes presented HDL-C and triglycerides values within the normal healthy range, the indirect vascular effect of estrogen in women may have had an influence on serum lipid concentrations with better values compared to men (Table 3), leading to a cardioprotective effect (39). Likewise, circulating estrogen in women may potentiate the vasodilatory effect of β-adrenergic activation by a nitric oxide mechanism causing vasodilation and favoring a lower resting DBP (P = 0.001) compared to men (Table 1) (40).

Regarding the **exercise function**, this study showed that there are natural physiological differences between men and women when objective variables are considered (*i.e.*, $\dot{V}O_{2peak}$), but not when the physical capacity is evaluated through a field test (*i.e.*, MSWT) (Table 2). These results may question the validity of using this or similar field tests to evaluate CRF in this population. Thus, sex differences in body fat, hemoglobin, dimensions of the oxygen transport system and musculature could account for the different CRF level (41). However, according to ACSM´s Guidelines for Exercise Testing and Prescription (23), both sexes presented "very poor" CRF level (Table 2), which is associated with a high risk of CV disease and all-cause mortality (42).

The **adherence to healthy dietary patterns** in relation to CV disease has been previously examined. In this way, the Med pattern, which shares many of the characteristics of the DASH diet, was inversely associated with arterial BP (43), knowing that a higher adherence leads to 70% less prevalence of HTN (44). However, in a representative Spanish population, only 17.3% of those diagnosed with HTN had a DASH-accordant diet and 17.2% Med-accordant diet (45). These results are in keeping with other population studies showing that a lower adherence to HDI and DASH diet was associated with the prevalence of HTN (46,47). A similar adherence to the Med compared to the present study (41.1%, Table 4) was observed in a Balearic adult population (43.1±5.8%) (48), thus confirming the association between adherence to a healthy diet and HTN and the higher adherence to Med diet in women with better metabolic profile than men.

It has been proposed that **CRF** should be incorporated as a vital sign in CV disease risk factor evaluation and management (9) and that the addition of CRF to traditional risk factors would significantly improve the classification of risk for adverse outcomes (42). Previous studies have suggested that low CRF appeared to have an indirect effect on the risk for subsequent CV events moderated through higher metabolic risk (49). In the current study, similarly, it was found that CRF could significantly moderate some CVR factors. Thus, the low CRF group was older (P = 0.003), had higher BMI (P < 0.001), no-dipping profile (P = 0.048), and higher hepatic fat (ALT, P = 0.001; GGT P = 0.030; AST/ALT ratio P = 0.018) compared to moderate and high CRF level (Table 5). Taking into account that other studies have also demonstrated that the least fit individuals (<6 METS for those without CV disease) had >4-fold increased risk of all-cause mortality compared with the fittest (50), it could be stated that the addition of CRF to established risk scores would further improve risk prediction (42). Results of the present study reinforce previous investigations showing that worse CRF was associated with increasing non-alcoholic fatty liver disease represented by non-healthy values of ALT, GGT, and AST/ALT ratio (31). Furthermore, previous studies also showed that an absent normal dipping BP pattern (*i.e.*, <10% fall in nocturnal BP relative to diurnal BP) was independently predicted by increasing age, BMI, and treated HTN (among other factors). These results confirm that non-dipping BP pattern 1) is associated with increased CV mortality risks (51) and 2) is determined mainly by non-genetic factors (52).

This study has limitations. Firstly, although our sample size was sufficient as an initial investigation for the EXERDIET-HTA study, it would not be comparable with that of larger epidemiological studies. Secondly, the current study only had 32.5% of women, which does not represent an equal gender split of the sample. However, even though female is usually lower than male enrollment in clinical trials, we have got significant differences, which adds knowledge in the gap for BP management to improve women's health.

In summary, the studied population diagnosed with primary HTN presented a high CVR profile showing the following characterization: obesity metabolically abnormal with poor CRF level, exercise-induced HTN, and non-healthy dietary pattern. Specifically, women showed a better biochemical and dietary pattern profile than men, but physical and exercise physiological characteristics were poorer. Furthermore, a favorable CRF level seemed to contribute to the attenuation of some CVR factors, such as high BMI, non-dipping profile, and high hepatic fat.

In closing, by analyzing a hypertensive, obese, and sedentary population, we have identified specific clinical, physical, physiological, and dietary patterns that strongly suggest that targeting key behaviors such as improving nutritional quality and CRF through regular physical activity will contribute to getting a "healthy population" with independent beneficial effects on CVR factors.

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Declaration of interest

The authors have nothing to disclose.

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Assessment of cardiovascular risk and vascular age in overweight/obese adults with primary hypertension: the EXERDIET-HTA study

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Objective **Hypertension (HTN), obesity and low cardiorespiratory fitness (CRF) are associated with an increased risk for a cardiovascular event. Enrolling overweight/obese individuals with HTN, the current study aimed to estimate cardiovascular risk (CVR) and vascular age (VA) profiles analyzing potential sex differences, determine whether VA is higher than chronological age, and whether CVR is associated with a low level of CRF.**

Methods **Overweight/obese non-Hispanic White participants ($n = 209$; 141 men and 68 women) with primary HTN had their CVR and VA determined using the New Pooled Cohort Risk Equations and The Framingham method, respectively. Considering values of peak oxygen uptake, participants were divided into tertiles for each sex.**

Results **The CVR, but not VA ($P = 0.339$), was higher ($P < 0.001$) in men compared with women irrespective of age. Irrespective of sex, VA was higher than chronological age ($P < 0.001$). Age and BMI were higher ($P < 0.05$) in the low CRF group compared with that in other groups. There were no differences in CVR ($P = 0.907$) and VA ($P = 1.643$) when values were separated into CRF groups.**

Conclusion **Pooled Cohort Equations could underestimate the risk of suffering a cardiovascular event in the following 10 years in overweight/obese non-Hispanic White women with HTN compared with men. The VA appears to be a useful tool in communicating CVR in this population irrespective of sex. The CRF alone may not be enough to moderate the CVR.** ***Blood Press Monit*** **22:154–160**

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Keywords: cardiorespiratory fitness, cardiovascular disease, chronological age

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Introduction

Cardiovascular disease (CVD) is the leading cause of early morbidity and hospitalization in the world [1]. According to the WHO 17.5 million people died from CVD in 2012, representing 31% of all deaths, of which 7.4 and 6.7 million were due to coronary heart disease and cardiovascular (CV) events, respectively [2]. Furthermore, a large number of individuals have a heightened risk for CVD because they have two or more associated risk factors [1,3,4].

Several attempts have been made to determine cardiovascular risk (CVR) factors associated with a cardiac event. Guidelines indicate that age, sex, diabetes, smoking, cholesterol and hypertension (HTN) have a causal relationship with CV events and premature death [1,3,5]. High blood pressure (BP), often referred to as HTN, is the most common CVR factor that leads to heart failure, stroke, angina and premature death if not detected early and treated adequately [6]. Additionally, population-based research suggests that obesity is directly related to HTN [7]. An appreciation of the clinical significance of obesity-related HTN has since grown substantially over time. As such, obesity is now recognized as a major cause of HTN (≥75% of all cases), and the combination of both is well known to increase CVR [7]. Additionally, CVR factors, associated with the development of CVD, are similar in both sexes [8]. However, with the same risk factors, CVR is 2–5 times more common in men than in women; that is, women have a lower predicted 10-year risk [9]. It has previously been suggested that this discrepancy may be due to the protective action of estrogens [8] or because substantial disparities exist in the prevention, recognition, management and clinical outcomes of CVD in women [10]. A CVR score can be used to determine CVD using the Pooled Cohort Equations and the Framingham Heart Study, which are tools commonly used to define the

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10-year risk for developing CVD [9]. An additional tool for evaluating the overall CVR is vascular age (VA). This is a quite novel concept derived from Framingham CVR tables, which indicates the biological age of an individual's arteries (i.e. the age of the vascular system of a person with different CVR factors) [1,11]. This process is accelerated with the presence of additional CVR factors and is associated with changes in the mechanical and structural properties of the vascular wall, which leads to poor endothelial health and loss of arterial elasticity [1,7].

The relationship between poor lifestyle and increased CVR is well documented. As such, there is a persistent need to discuss cardiometabolic lifestyle factors with all patients, in order to reduce CVD and control the CVR factors. CVR factors can be classified as modifiable and nonmodifiable. Nonmodifiable risk factors are (but not limited to) age, sex and family history. Modifiable CVR factors are cardiometabolic lifestyle factors and can be altered during the cause of one's life; these include but are not limited to smoking, alcohol, diet and importantly physical activity [12]. Higher levels of physical activity can improve the CVR in diseased or at-risk patients. Cardiorespiratory fitness (CRF) can be used to quantify these positive effects as it is negatively associated with a reduction in CV morbidity and mortality [12].

Currently, there is no known research that measures CVR and VA and its association with CRF in primary hypertensive and overweight/obese adults. Considering the importance of CVR factors and the limited scientific literature, the aims of the study were (a) to estimate CVR and VA profiles of overweight/obese patients with HTN, analyzing potential sex differences, (b) to determine whether VA is higher than chronological age (CA) and (c) to determine whether CVR is associated with a low level of CRF.

Methods

Study design

Baseline data from the EXERDIET-HTA randomized controlled experimental trial were taken for the purpose of this study [13]. The design, selection criteria and procedures for the EXERDIET-HTA study have been previously detailed [13]. The study protocol was approved by the Ethics Committee of the University of the Basque Country (UPV/EHU, CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital (2015-030), and all participants provided written informed consent before any data collection.

Participants

Non-Hispanic White participants ($n = 209$) with primary HTN [≥ 140 systolic blood pressure (SBP) and ≥ 90 diastolic BP] [4], who were classified as being overweight (BMI ≥ 25) or obese (BMI ≥ 30) [14] were recruited from the cardiology services and local media.

Cardiorespiratory fitness

Cardiorespiratory fitness was determined using a cardiopulmonary exercise test to assess VO_{2peak}. Briefly, the test was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). The testing protocol was started at 40 W (70 rpm) with gradual increments of 10 W every minute until exhaustion with continuous ECG monitoring. Expired gas analysis was determined using a commercially available metabolic cart (Ergo CardMedi-soft S.S, Sorinnes, Belgium; Ref. USM001 V1.0), which was calibrated before each test with a standard gas of known concentration and volume. Breath-by-breath data were measured continuously during exercise before being averaged over each 60 s period. Blood pressure was measured every 2 min throughout the test. At the end of each stage the rate of perceived exertion (6–20) was recorded (Borg Scale). Peak oxygen uptake was defined as the highest oxygen uptake value attained toward the end of the test. Achievement of VO_{2peak} was assumed with the presence of two or more of the following criteria: (a) volitional fatigue (>18 on Borg Scale); (b) peak respiratory exchange ratio (VCO_2/VO_2) of at least 1.1; (c) achieving more than 85% of age predicted maximum heart rate; and (d) failure of VO_2 and/or heart rate to increase with further increases in work rate [13].

The distributions of VO_{2peak} were divided into tertiles for each sex: the lowest tertile (low-CRF group), $VO_{2peak} \leq 21$ in men and $VO_{2peak} \leq 16$ in women; the intermediate tertile (medium-CRF group); $21.1 < VO_{2peak} \leq 26$ in men and $16.1 < VO_{2peak} \leq 21$ in women; and the highest tertile (high-CRF group), VO_{2peak} more than 26 in men and VO_{2peak} more than 21 ml·kg/min in women.

Measurement of cardiovascular disease risk factors

Established CVR factors used in the present study to determine the CVR and VA of participants were defined as follows:

Blood pressure

Ambulatory BP monitoring was conducted over a 24 h period using an oscillometric ambulatory BP monitoring 6100 recorder (Welch Allyn, New York, New York, USA) to evaluate SBP (as used to determine CVR) [9]. The device was used in line with the recommendations set by the ESH/ESC guidelines. As such, BP was measured at 30-min intervals during the awake time and at 60-min intervals during periods of sleep. Data were only used if at least 75% of the awake time and sleep periods were successfully recorded [13].

Blood sampling

Fasting venous blood (12.5 ml) was obtained from each participant. Diabetes mellitus (DM) was defined as a fasting glucose of at least 126 mg/dl. Additionally, measurements of glucose and lipid profile [total cholesterol,

high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)] were assayed.

Self-report

Age and cigarette smoking status were assessed by self-report. All medicines were ascertained from the participant's physician.

Cardiovascular risk

The Framingham Heart Study is a quantitative method used in primary care for assessment of general CVR profile. The absolute risk applies to the individual; a score of 10% means that there is a 10% chance of having a CV event within the next 10 years [9,11], under 6% is considered low risk, between 6 and 20% is considered medium risk, and a score of at least 20% is considered high risk [11]. Recently, New Pooled Cohort Risk Equations have been developed from the Framingham Heart Study [9,11]. The equation to estimate the 10-year risk of developing a first atherosclerotic CVD event was developed from sex-specific and race-specific proportional-hazard models that included the covariates of age, treated or untreated high SBP level, total cholesterol and HDL-C concentrations, current smoking status, and history of DM. For the equation, the values for age, lipids, and SBP were log transformed. Interactions between age and lipids or age and SBP used the natural log of each variable. Calculation of the 10-year risk estimate for hard atherosclerotic CVD is described as a series of steps [9].

Vascular age

The Framingham method was used to determine the VA of all participants [11]. The VA indicates the biological age of the individual's vascular system, as the age a person would be with the same calculated CVR but whose risk factors were all within normal ranges. The sex-specific risk factors considered were age, HDL-C, total cholesterol, SBP, DM and smoking status. Each variable received a weighted score; the sum of the score for each variable was then translated to the risk for a CV event in 10 years and the VA [11].

Statistical analysis

Descriptive statistics were calculated for all variables. Data are expressed as mean ± SD. All variables were deemed normally distributed using a Kolmogorov–Smirnov test, apart from age, total cholesterol, HDL-C, CVR, and VA, which had a skewed distribution and were therefore log transformed before any analysis.

A two sample *t*-test was used to determine whether there was a significant sex difference for the variables: age, BMI, SBP, total cholesterol, HDL-C, antihypertensive medication, cigarette smoking, and DM. Analysis of covariance was used to examine the dependant variables (age, BMI, SBP, total cholesterol, HDL-C, antihypertensive medication, cigarette smoking, DM, CVR, and VA) of the participants classified by CRF level (low, medium, and high). A Bonferroni test was used to determine the level of significance when a significant main effect was found. Statistical significance was set at P value less than 0.05. The statistical analyses were performed with SPSS, version 22.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, New York).

Results

The characteristics of CVR factors classified by sex are presented in Table 1. The mean ± SD age of participants was 54.0 ± 8.1 years with 67.5 and 32.5% being men and women, respectively. All participants were classified as obese (BMI > 30 kg/m^2) in accordance with AHA/ACC/TOS guidelines for the Management of Overweight and Obesity in Adults [14]. Although 87.1% of all participants were taking antihypertensive medication, the mean SBP suggested that all participants irrespective of sex were prehypertensive. However, there was a trend to suggest that women had a lower SBP compared with men [mean difference = 1.6; 95% confidence interval (CI) = − 2.5–5.7 mmHg]. The mean total cholesterol was similar in men and women, with both sexes exceeding cutoff values set by the ESH/ESC guidelines [4], but there was also a trend to suggest that women had lower total cholesterol than did men (mean difference = 3.3; 95% CI = − 30.6–37.3 mmHg). Moreover, HDL-C was significantly higher (P = 0.002) in women than in men (mean difference = 5.0, 95% CI = − 13.3–3.3 mg/dl), but both were inside the healthy cutoff values suggested by the ESH/ESC guidelines [4]. Smoking was present in 11.4% of the participants, and 4.5% of the sample was suffering from DM.

The absolute CVR was significantly different (P < 0.001) between sexes, with women having a lower CVR than did men (mean difference 5.8, 95% CI = − 3.8–7.7%, Table 1). Additionally, in accordance with the Framingham study and ACC/AHA Guidelines on the assessment of CVR [9,11], men were considered to be at medium risk, whereas women were considered low risk. As shown in Table 2, there were no sex differences in VA (mean difference = 1.4, 95% CI = − 2.4–5.1 years). However, VA was significantly higher (P = 0.001) than CA (mean difference = 8.8, 95% CI = 7.2–10.3 years).

Characteristics of the participants separated into CRF groups are presented in Table 3. Bonferroni analysis revealed that age was higher (P < 0.05, Δ = − 9.7%) in the low CRF group compared with that in the high CRF group. Moreover, BMI was higher in the low CRF group compared with that in the medium CRF group (34.0 ± 0.5 vs. 31.2 ± 0.5 kg/m^2; mean difference = 2.8, 95% CI = 1.1–4.4 kg/m^2) and the high CRF group (34.0 ± 0.5 vs. 28.5 ± 0.5 kg/m^2; mean difference = 5.5, 95% CI = 3.8–7.2 kg/m^2). No significant differences were observed among CRF groups in terms of SBP, total

Table 1 Characteristics of risk factors and cardiovascular risk classified by sex

Dependant variables	All participants ($n=209$)	Men ($n=141$)	Women ($n=68$)	P
Age (years)	54.0±8.1	54.3±7.9	53.4±8.5	0.426
BMI (kg/m^2)	31.3±4.6	31.3±4.3	31.5±5.2	0.873
SBP (mmHg)	135.9±14.1	136.4±12.9	134.8±16.3	0.433
Total cholesterol (mg/dl)	213.0±126.1	214.1±162.8	210.8±34.0	0.245
HDL-C (mg/dl)	50.7±33.1	49.1±39.2	54.1±13.8	0.002*
Antihypertensive medication	87.1	85.1	91.2	0.220
Cigarette smoking	11.4	10.6	13.2	0.581
DM	4.5	5	3	0.500
Cardiovascular risk	8.1±6.3	10.0±6.5	4.3±3.6	<0.001*

Values are mean±SD or percentage.
DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure.
*Significant difference ($P<0.05$) between men and women.

Table 2 Results of vascular and chronological age

Dependant variables	VA (years)	CA (years)	P
Total ($n=209$)	61.7±9.5	54.0±8.1	<0.001*
Men ($n=141$)	62.1±8.5	54.3±7.9	<0.001*
Women ($n=68$)	60.8±11.1	53.4±8.5	<0.001*
P	0.339	0.426	

Values are mean±SD.
CA, chronological age; VA, vascular age.
*Significant difference ($P<0.05$) between vascular and chronological age.

cholesterol, antihypertensive medication, smoking, DM or HDL-C ($P>0.05$).

Bonferroni analysis revealed that no significant differences were observed in CVR ($P=0.907$) and VA ($P=1.643$), when values were separated into CRF groups (Table 3). However, the low CRF group showed an upward trend in VA with higher values compared with those with medium CRF (mean difference = 0.5, 95% CI = −4.1–5.0 years) or higher CRF (mean difference = 3.4, 95% CI = −1.5–8.4 years).

Discussion

To our knowledge this is the first known study to estimate the CVR and VA in overweight/obese people with HTN and its association with CRF level using the recently developed Pooled Cohort Equations [9] and the original 2008 Framingham model. The main findings of this study were as follows: (a) CVR is significantly higher in men than in women despite them having the same CVR values and this is not affected by age; (b) predicted VA is significantly higher than CA in overweight/obese people with primary HTN with no sex-related differences; and (c) CRF alone did not appear to significantly moderate CVD. These findings highlight the importance of being able to determine the CVR and VA of overweight/obese people with primary HTN. Considering the known increase in CVD in hypertensive patients and the relative ease of predicting 10-year CVR; defining CVR and VA in a hypertensive population would likely be a useful tool for clinicians.

Although the role of major CVR factors in the development of CVD and VA was similar in both sexes, Table 1 shows that CVR is 57% higher in men than in women ($P=0.001$), with an estimated 10-year risk for hard atherosclerotic CVD event of 10% in men and 4.3% in women, which represents medium and low risk, respectively. As such, it is likely that men have a higher risk of suffering a CV event in the following 10 years. The difference in the HDL-C level could be one of the determinants of the sex-related difference in CVR profile in

Table 3 Cardiovascular risk factors, cardiovascular risk and vascular age classified by fitness level

	Cardiorespiratory fitness groups			One-way ANOVA		
Dependant variables	Low (men = 48, women = 24)	Moderate (men = 51, women = 23)	High (men = 42, women = 21)	P-value	F-value	%Variance
Age (years)	56.7±1.0	53.8±0.9	51.2±1.1	0.003*	6.5	6.0
SBP (mmHg)	136.6±1.8	135.8±1.6	135.2±1.9	0.882	0.126	0.1
BMI (kg/m^2)	34.0±0.5	31.2±0.5	28.5±0.5	<0.001*	29.631	22.5
Total cholesterol (mg/dl)	202.4±19.2	233.5±20.2	206.0±22.1	0.744	0.272	1.0
HDL-C (mg/dl)	48.9±4.6	46.8±4.6	57.2±5.2	0.363	1.185	1.5
Antihypertensive medication	88.9	86.5	85.7	0.845		
Cigarette smoking	15.3	10.8	8	0.400		
DM	1.4	6.7	4.8	0.273		
Cardiovascular risk	8.1±0.6	8.4±0.6	7.9±0.7	0.907	0.253	0.4
Vascular age (years)	62.9±1.3	62.5±1.3	59.4±1.4	1.643	1.710	2.9

Values are mean±SD or percentage.
%Variance is the estimated variance explained by the mean effects within each group for the named variable.
ANOVA, analysis of variance; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure.
*Shows the significantly different ($P<0.05$) among groups.

the present study, with women showing higher concentrations compared with men. It is well known that high concentrations of HDL-C prevent the development of atherosclerosis and CVD. In particular, the transport of reserve cholesterol and the inhibition of oxidized LDL-induced monocyte infiltration can avoid this development [15]. In addition, the Framingham Heart Study showed that HDL-C was the most powerful lipid predictor of CHD risk in both sexes older than 49 years. For every 1 mg/dl increment in HDL-C, there was an associated 2% decrease in the risk for CHD in men, and a 3% decrease in women [16]. Previous studies have shown that the increased CVR in men was hidden behind an almost-normal classic lipid profile, with total cholesterol, LDL-C, and TG being higher, and HDL-C concentrations significantly lower than those in women (premenopausal or postmenopausal status), with all values within the normal range [17]. In our study, both sexes presented hyperlipidemia values (total cholesterol > 190 mg/dl) and prehypertensive SBP values with slight, but concomitant variation (i.e. an upward trend in men compared with women), which has been shown to increase the risk for coronary heart disease and promote a poor cardiometabolic profile [17]. It seems that there is a cardioprotective effect of endogenous estrogens in premenopausal women, when compared with age-matched men, due to an enhanced HDL quality. However, in postmenopausal women there is a trend to present with a significantly increased BMI, BP, LDL-C, and total cholesterol, along with a reduction in absolute HDL-C concentration, with changes in the composition of HDL particles [17,18]. In the present study, 51.5% of women were premenopausal. Therefore, it should take into account that in the current study: (a) both men and women had normal HDL-C values (>40 mg/dl for men and >46 mg/dl for women) [4], along with obesity, hypercholesterolemia, and primary HTN diagnostic; (b) almost half of the women were postmenopausal; and (c) the sex-specific risk prediction model used in the Pooled Cohort Equation always calculates a higher risk in men compared with women, despite them having the same CVR values and regardless of age [9]. As such, women could show an underestimated CVR profile with less-aggressive treatment strategies. Nowadays, a greater number of women die annually from CVD compared with men [19]. Thus, although sex-related differences are well documented in the prevalence of CVR factors, the clinical manifestation and incidence of CVD and the impact of risk factors on outcomes [20] in women are often underestimated because of the misperception that females are 'protected' against CVD [21].

As expected, VA was significantly higher ($P = 0.001$) than CA (VA = 62 vs. CA = 54 years) (Table 2). As such, people with primary HTN and obesity are 'older' for their VA when compared with their CA. It is therefore likely that the health of the heart and blood vessels is more deteriorated than they should be in this population [11]. There is good evidence that CA is strongly and independently related to CVR, but this is not necessarily so for the VA. Repeated exposure to CVR factors across the lifespan leads to between-subject differences in VA and CA [22]. Previous research has shown that in apparently healthy and asymptomatic people, 72.45% of the individuals had a greater VA than CA, suggesting that this risk may be underestimated [23]. The current study suggests that key contributors of an increased VA in a hypertensive population are dyslipidemia, SBP, treatment for HTN, obesity and smoking (87.2% of them showing a greater VA than CA). Thus, VA seems to be a useful tool in communicating about risk to individuals, such as hypertensive and obese patients, who are at a greater risk for a CVD event and warrant early intervention of modifiable CVR factors (i.e. healthy eating, increasing physical activity, cessation of cigarette smoking and alcohol).

It is well recognized that physical activity is an important factor for reducing CVR and CVD [9,12]. Previous research has suggested that people with sedentary behaviors are at a higher risk for all-cause mortality compared with those who do at least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity per week, as recommended by WHO [12]. In the current study it was found that CRF alone does not significantly moderate CVR, because of no differences among the three CRF groups (Table 3). However, the mean difference and CI suggest that those who are in the low CRF group have meaningfully higher VA (although not significant) (Table 3), which suggests that CVR may in part be moderated by CRF but in conjunction with other CVR factors such as BMI and age. Aging and inactivity are associated with a decrease in both CRF and morphological changes in all layers of the vascular tree, and these are accompanied by increased arterial stiffness and aortic pressure, leading to a higher VA [24]. Furthermore, in the present study BMI explained 22.5% and age 6% of the variance between the CRF groups. The current study reinforces the evidence linking obesity, age and CRF level with VA in a primary hypertensive population [7,25], suggesting that low CRF could potentially be used in conjunction with other CVR factors to help determine predisposal of CVD, but not as a factor in its own right. Previous studies have concluded that physical activity is associated with beneficial changes in circulating lipids and lipoproteins, body mass, BP and insulin sensitivity, having a significant reduction in CVR [12,25]. In line with that, the last 2016 European Guidelines on CVD prevention in clinical practice highlight CRF as a factor that might influence the relationship between adiposity and clinical prognosis in the 'obesity paradox'. Thus, normal-weight individuals with a low CRF have a higher risk for mortality than fit individuals, regardless of their BMI [1,26].

Although our study has highlighted the importance of determining CVR factors in a hypertensive population, several limitations should be acknowledged. First, although our sample size was sufficient as an initial investigation into CVR and HTN, it would not be comparable to that of larger epidemiological studies, and future studies should consider large-scale investigations as well as determining the short-term and long-term effects of different interventions. Second, the current study had only 32.5% women, which does not represent an equal sex split. As this poses statistical issues, future studies, particularly those using interventions, should look to recruit equal numbers. Finally, although CRF did not sufficiently moderate CVR in the current study, the effects of physical activity in hypertensive patients with a broader range of VO_{2peak} should be further investigated in conjunction with other modifiable risk factors to determine the effectiveness of moderating CVR and VA. Additionally, future studies should look to determine whether VA and CVR can be used to more easily inform patients of their cardiovascular health than current methods.

Conclusion

Findings suggest that male non-Hispanic White overweight/obese individuals with diagnosed HTN have a higher risk of suffering a CV event in the following 10 years compared with women according to the greater CVR assessed using the Pooled Cohort Equations. However, CVR in women could be underestimated when both sexes present with the same CVR values and age. Those who are overweight/obese with HTN have an 'older' VA compared with their CA irrespective of sex. Finally, although CRF alone did not moderate CVR in the current study, further research into the effect of physical activity alongside additional modifiable CVR factors in HTN populations, particularly those who are the least active, is warranted. Predictions of CVR and VA estimation may represent a useful clinical tool for detecting patients at risk for a cardiac event, but estimation equations should be more focused on sex-related differences.

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Conflicts of interest

There are no conflicts of interest.

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Effects of different aerobic exercise programmes with nutritional intervention in sedentary adults with overweight/obesity and hypertension: EXERDIET-HTA study

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Abstract

Background: Both exercise training and diet are recommended to prevent and control hypertension and overweight/obesity.

Purpose: The purpose of this study was to determine the effectiveness of different 16-week aerobic exercise programmes with hypocaloric diet on blood pressure, body composition, cardiorespiratory fitness and pharmacological treatment.

Methods: Overweight/obese, sedentary participants ($n = 175$, aged 54.0 ± 8.2 years) with hypertension were randomly assigned into an attention control group (physical activity recommendations) or one of three supervised exercise groups (2 days/week: high-volume with 45 minutes of moderate-intensity continuous training (MICT), high-volume and high-intensity interval training (HIIT), alternating high and moderate intensities, and low-volume HIIT (20 minutes)). All variables were assessed pre- and post-intervention. All participants received the same hypocaloric diet.

Results: Following the intervention, there was a significant reduction in blood pressure and body mass in all groups with no between-group differences for blood pressure. However, body mass was significantly less reduced in the attention control group compared with all exercise groups (attention control –6.6%, high-volume MICT –8.3%, high-volume HIIT –9.7%, low-volume HIIT –6.9%). HIIT groups had significantly higher cardiorespiratory fitness than high-volume MICT, but there were no significant between-HIIT differences (attention control 16.4%, high-volume MICT 23.6%, high-volume HIIT 36.7%, low-volume HIIT 30.5%). Medication was removed in 7.6% and reduced in 37.7% of the participants.

Conclusions: The combination of hypocaloric diet with supervised aerobic exercise 2 days/week offers an optimal non-pharmacological tool in the management of blood pressure, cardiorespiratory fitness and body composition in overweight/obese and sedentary individuals with hypertension. High-volume HIIT seems to be better for reducing body mass compared with low-volume HIIT. The exercise-induced improvement in cardiorespiratory fitness is intensity dependent with low-volume HIIT as a time-efficient method in this population.

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Keywords

Obesity, hypertension, high-intensity interval training, low-volume training, blood pressure, cardiorespiratory fitness, body composition

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Introduction

Due to the recent changes in both eating habits and lifestyles (i.e. the abandonment of traditional dietary patterns and culinary techniques, increased sedentary time, and decreased volume and intensity of physical activity, which results in an imbalance in the energy balance), primary hypertension, overweight/obesity, and being sedentary often coexist in the same person.[1,2] Obesity has been considered the driving force of this response culminating in a significant increase in direct and indirect healthcare costs.[3] It is, therefore, important to develop cost-effective strategies for the treatment of obesity in order to reduce the prevalence of obesity-related hypertension.[2,4] The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) recommend appropriate lifestyle changes for the prevention and treatment of hypertension, alongside the use of drug therapy in individuals at high risk.[5] One benefit of losing body mass is the concomitant reduction in blood pressure (BP),[2,3,5] especially in individuals taking antihypertensive medication.[6] Although individual BP responses to a reduced body mass are variable depending on 'fat-sensitive' or 'fat-resistant' BP,[1] it has been demonstrated that combining exercise and diet may be the most effective treatment for reducing body mass. Consequently, the combination appears to be a logical step in facilitating a substantial improvement in cardiometabolic health, including hypertension.[2,5]

During the past two decades, several studies have shown the effectiveness of adherence to the dietary approaches to stop hypertension (DASH) dietary pattern.[4,7,8] In a population with hypertension, the combination of the DASH diet with aerobic exercise has resulted in a greater reduction in BP and improved cardiovascular biomarkers than the DASH diet alone.[9] Exercise guidelines recommend that both moderate-intensity and high-intensity aerobic training should be used to treat and reduce hypertension.[5] However, there is currently no agreement with respect to the optimal frequency, intensity, time, and type (FITT principle) of exercise prescription.[10] Previously, aerobic high-intensity interval training (HIIT) produced a significant improvement in BP and cardiorespiratory fitness (CRF) compared with moderate-intensity continuous training (MICT).[11–13] In addition, a dose–response curve for physical activity volume and intensity has previously been reported; this is especially important for sedentary individuals and those with a moderate level of physical condition,[14] suggesting that 'some is good but more is better'. There is also evidence to support the use of low-volume HIIT (i.e. ≤ 10 minutes of high-intensity effort) versus high-volume HIIT as a potent and time-efficient training method suggesting 'less is more'.[15]

Currently, no research has determined the effects of different exercise intensities and volumes combined with a hypocaloric diet intervention in overweight/obese, sedentary adults diagnosed with hypertension. Therefore, the aim of this study was to determine changes in BP, body composition, CRF and pharmacological treatment following three different (high-volume MICT, high-volume HIIT, low-volume HIIT) 16-week aerobic exercise programmes performed twice a week, all combined with a hypocaloric diet.

Methods

Study design

The EXERDIET-HTA study is a multi-arm parallel, randomised, single-blind controlled experimental trial comparing the effects of different 16-week aerobic exercise programmes (performed 2 days/week) combined with a dietary intervention in sedentary, overweight/obese individuals with hypertension (www.clinicaltrials.gov, number NCT02283047). The study protocol was approved by the ethics committee of the University of the Basque Country (UPV/EHU, CEISH/279/2014) and clinical investigation of Araba University Hospital (2015-030), and all participants provided written informed consent before any data collection. Medical staff were blinded to the participant randomisation process. The design, selection criteria and procedures for the EXERDIET-HTA study have been detailed previously.[16]

Participants

One hundred and seventy-five non-Hispanic white participants ($n = 120$ men and $n = 55$ women) were enrolled in the study from September 2013 to June 2016 in Vitoria-Gasteiz (Basque Country, Spain). Figure 1 presents a flow diagram of the study process. All participants were classified as overweight (body mass index (BMI) $> 25\,kg/m^2$) or obese (BMI $> 30\,kg/m^2$)[3] and diagnosed with stage 1 or 2 hypertension, defined as a systolic blood pressure (SBP) of 140–179 mmHg and/or a diastolic blood pressure (DBP) of 90–109 mmHg and/or under antihypertensive pharmacological treatment.[5] Physical activity behaviour was determined by the international physical activity questionnaire (IPAQ), and only participants who did not comply with the 'Global recommendations on physical activity for health'[17] by the World Health Organization were selected.

Measurements

The measurements for the study were taken pre (T0) and post (T1) each 16-week intervention period.

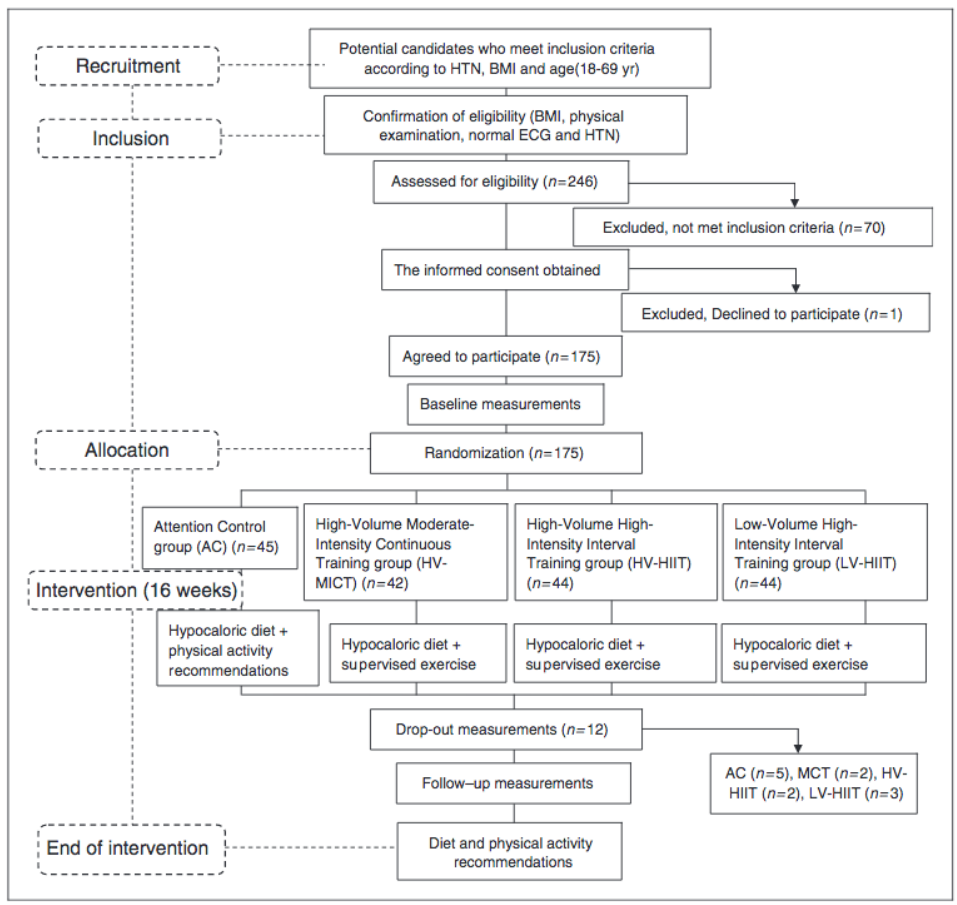

Figure 1. Flow diagram of the EXERDIET-HTA study from recruitment to the end of the intervention.

Blood pressure. Ambulatory blood pressure monitoring (ABPM) was conducted over a 24-hour period using an oscillometric ABPM 6100 (Welch Allyn, New York City, NY, USA) device to evaluate BP in line with the guidelines set by the ESH/ESC.[5] Blood pressure (ABPM) values are displayed as the mean of the day.

Cardiorespiratory fitness. A cardiopulmonary exercise test was used to determine peak oxygen uptake ($\dot{V}O_{2peak}$) and ventilatory thresholds (VT). The cardiopulmonary exercise test was performed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). The test protocol started at approximately 70 rpm and 40 W, with gradual increments of 10 W every minute applied until volitional exhaustion occurred. Continuous electrocardiogram monitoring was conducted throughout each test. Expired gas analysis was assessed using a commercially available metabolic cart (Ergo CardMedi-soft S.S, Belgium; Ref. USM001 V1.0). Achievement of $\dot{V}O_{2peak}$ criteria has previously been defined.[18] Ventilatory thresholds (i.e. VT1 and VT2) were assessed by standardised methods using the ventilatory equivalents.[18] After completion of the test, participants remained stationary on the bike for 5 minutes recovery with electrocardiogram and BP monitoring throughout. The identification of the two VT determined the three different exercise intensity domains, or ranges for the exercise intervention design (i.e. R1, light to moderate; R2, moderate to high; R3, high to severe).[18]

Dietary assessment. Habitual food consumption and nutrient intake were evaluated using three questionnaires: dietary history, food frequency questionnaire and two face-to-face non-consecutive 24-hour recalls. Trained dieticians conducted the necessary correction for within-subject variability in nutrient intake.[19] All nutritional data were calibrated in the Easy Diet computer program. Resting energy expenditure was calculated by the Mifflin St Jeor equation, which has previously been deemed the most appropriate for individuals who are overweight or obese.[20]

Medication. Prescribed medications were recorded and classified into the groups: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor

blockers (ARBs), diuretics, calcium antagonists, beta-blockers, statins, hypoglycaemic agents, antiplatelets and anticoagulants. Medical staff controlled all necessary changes to medication pre-, during and post-intervention.

Intervention

All participants underwent a hypocaloric diet. Following baseline data collection, participants were randomly allocated to one of the four intervention groups: the attention control (AC) group, or the three supervised exercise groups (high-volume MICT, high-volume HIIT, or low-volume HIIT). Each group was stratified by gender, SBP, BMI and age. All participants were asked to continue with their normal physical activity patterns outside of the study protocol. However, in addition to treatment for the hypocaloric diet, the AC group received the standard guidelines for physical activity recommendations in order to comply with ethical procedures regarding health.[5]

Intervention procedures. All exercise groups trained for two non-consecutive days per week under the supervision of exercise specialists. All sessions started and finished with BP monitoring, and training intensity was dictated by individual heart rate (HR) responses (Polar Electro, Kempele, Finland) and the rate of perceived exertion (Borg's 6–20 point). Each session included a 5–10-minute warm-up and a 10-minute cool-down. The core part of each training session consisted of a range of aerobic exercises, i.e. one day of the week on the treadmill, and the second one on the bike (BH Fitness equipment). The high-volume MICT group performed 45 minutes aerobic exercise, whereas the high- and low-volume HIIT groups performed 45 and 20 minutes, respectively. The intensity was individually tailored to each participant's HR at moderate (R2) or vigorous (R3) intensities, adjusting the speed and/or incline of the treadmill or the power and speed on the exercise bike. The rationale of mixing stationary exercise bike and treadmill was to avoid the osteoarticular impact of two treadmill days taking into account the nature of the HIIT programme and the impact derived from overweight/obese participants. The high-volume MICT group performed 45 minutes of continuous steady training at R2. Supervised exercise training protocols have previously been explained in full.[16]

Considering the average $\dot{V}O_{2peak}$ at baseline for all participants (2.01 ± 0.5 L/min), the total work performed by the three exercise groups was calculated using the $\dot{V}O_2$–time relationship. As such, the moderate intensity at R2 was taken as 65% of $\dot{V}O_{2peak}$ (1.3 L/min) and the high intensity at R3 as 90% of $\dot{V}O_{2peak}$ (1.8 L/min). Thus, the high-volume MICT group performed 45 minutes at R2 twice per week representing approximately 117 L. The high-volume HIIT group performed 45 minutes twice per week, one day on the treadmill (4×4 minutes at 1.8 L/min at R3 and 29 minutes at 1.3 L/min at R2, representing approximately 66.5 L), and one day on the exercise bike (18×30 seconds at R3 and 36 minutes at R2 representing approximately 63 L/min resulting in a total work of approximately 129.5 L). The low-volume HIIT group performed 20 minutes twice per week, exercising one day on the treadmill (2×4 minutes at R3 and 12 minutes at R2 representing approximately 30 L) and one day on the exercise bike (9×30 seconds at R3 and 15:30 minutes at R2 representing approximately 28 L resulting in a total work of approximately 58 L). A criterion for completing the study was set at 100%. Thus, all participants in the supervised exercise groups performed 32 sessions; if a session was missed (a maximum of four were allowed), these were added on to the end of the 16-week programme, maintaining the two sessions per week.

Diet intervention. A hypocaloric and controlled sodium diet (3–6 g/day) was prescribed for each participant. The diet was designed to provide 25% less energy than their daily energy expenditure and to achieve a weekly loss in body mass of between 0.5 and 1.0 kg in accordance with the recommendations of the American Diabetes Association and the Spanish Society for the Study of Obesity.[21] The diet contained approximately 30% fat, 15% protein and 55% carbohydrates and was designed in accordance with the DASH diet.[7] Every 2 weeks participants were weighed and received encouragement and advice alongside nutritional counselling in order to aid compliance.

Statistical analysis

Descriptive statistics were calculated for all variables. Data are expressed as mean ± standard deviations (SD) and the range. All variables that were not normally distributed using a Kolmogorov–Smirnov test were log transformed prior to any analysis. Analysis of variance was used to determine if there were significant pre-intervention between-group differences. The comparison of frequencies in categorical variables among groups was performed using the chi-square test. A two sample *t*-test was used to determine whether there was a significant difference in the recorded data between pre- and post-intervention within each group. Analysis of covariance was used to examine the delta (Δ) score for each group (AC, high-volume MICT, high-volume HIIT, low-volume HIIT), adjusting for age, sex, changes in body mass and the initial value of each of the dependent variables. Helmert contrasts were

performed to analyse the difference between the three exercise groups pooled together and the AC group. Bonferroni correction was used to determine the level of significance when a significant main effect was found. Data were analysed according to the intention-to-treat principle. Statistical significance was set at $P < 0.05$. All statistical analyses were performed with SPSS version 22.0. Power calculation was completed using the G*Power 3 analysis program.[22] The required sample size was determined for the primary outcome variable (SBP). It was identified that adequate power (0.80) to evaluate differences in our design consisting of four experimental groups would be achieved with 164 people (41 each group, $\alpha = 0.05$, effect size $f = 0.27$) based on the pilot study with an SD of 9 mmHg.

Results

Baseline characteristics

Participants and medications were classified by groups and are presented in Table 1. Baseline data for all

Table 1. Physical, physiological and pharmacological therapy characteristics at baseline for each group of participants ($N = 175$).

	AC ($N = 45$)	HV-MICT ($N = 42$)	HV-HIIT ($N = 44$)	LV-HIIT ($N = 44$)	*P* value
Sex (men/women)	30/15	28/14	32/12	30/14	0.9
Age (years)	53.1 ± 8.3	54.7 ± 7.6	53.5 ± 9.1	54.7 ± 8.8	0.7
Body mass (kg)	91.2 ± 15.9	93.4 ± 16.4	90.3 ± 15.6	91.6 ± 14.6	0.8
BMI (kg/m^2)	31.9 ± 4.6	32.2 ± 4.4	31.2 ± 3.6	32.0 ± 4.6	0.7
Waist (cm)	103.1 ± 11.6	105.5 ± 12.6	102.0 ± 11.0	103.5 ± 10.4	0.6
Hip (cm)	107.5 ± 9.7	108.8 ± 9.4	106.2 ± 7.6	108.9 ± 10.7	0.5
Waist/hip ratio	0.96 ± 0.7	0.97 ± 0.1	0.96 ± 0.8	0.96 ± 0.1	0.8
FFM (%)	66.2 ± 8.1	64.6 ± 8.6	67.7 ± 6.3	67.0 ± 8.1	0.3
FBM (%)	33.7 ± 8.1	35.4 ± 8.6	32.3 ± 6.4	32.9 ± 8.1	0.3
FFM/FBM	2.14 ± 0.8	1.98 ± 0.7	2.2 ± 0.6	2.18 ± 0.7	0.5
Rest SBP (mmHg)	139 ± 13	133 ± 12	133 ± 10	135 ± 13	0.06
Rest DBP (mmHg)	79 ± 8	76 ± 8	79 ± 7	77 ± 9	0.1
Rest HR (beats/min)	69 ± 10	74 ± 9	70 ± 11	69 ± 10	0.08
Rest MBP (mmHg)	99 ± 9	94 ± 8	97 ± 7	97 ± 10	0.1
$\dot{V}O_{2peak}$ (L/min)	2.04 ± 0.59	2.01 ± 0.55	2.0 ± 0.5	2.01 ± 0.5	0.9
$\dot{V}O_{2peak}$ (mL/kg/min)	22.5 ± 6.0	21.6 ± 5.2	22.4 ± 4.8	22.0 ± 5.6	0.9
VT1 (mL/kg/min)	13.1 ± 5.8	12.2 ± 3.9	12.7 ± 4.6	12.7 ± 4.4	0.8
VT2 (mL/kg/min)	17.1 ± 6.6	17.7 ± 5.6	17.9 ± 6.5	17.8 ± 6.4	0.9
MET	6.4 ± 1.7	6.13 ± 1.4	6.4 ± 1.4	6.3 ± 1.6	0.8
Medication (%)	84	93	82	89	0.6
ACEI (%)	37.8	45.3	40.9	29.5	0.5
ARB (%)	46.7	40.5	27.3	50.0	0.1
Diuretics (%)	33.3	38.1	34.1	31.8	0.9
Calcium antagonists (%)	8.9	21.4	13.7	18.2	0.4
Beta-blockers (%)	13.3	11.9	9.1	4.5	0.5
Statins (%)	11.1	16.7	16.0	11.4	0.8
Hypoglycaemic agents (%)	6.7	2.4	2.3	13.6	0.09
Antiplatelets + anticoagulants (%)	4.4	9.5	2.3	2.3	0.3
Cigarette smoking (%)	2.2	9.8	20.9	9.3	0.08
DM (%)	4.4	4.9	7.0	11.6	0.5

Values are mean ± SD, percentage (%) or number.
AC: attention control group; HV: high volume; LV: low volume; MICT: moderate-intensity continuous training group; HIIT: high-intensity interval training group; BMI: body mass index; FFM: fat-free mass; FBM: fat body mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MBP: mean blood pressure; $\dot{V}O_{2peak}$: peak oxygen uptake; VT: ventilatory threshold; MET: metabolic equivalent of task; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; DM: diabetes mellitus.
Blood pressure (BP) values show the mean BP calculated by 24-hour ambulatory blood pressure monitoring.
$P < 0.05$.

participants have previously been published.[23] At baseline, 86.9% of participants were taking medication irrespective of group. The percentage of participants who took one, two, three or more than four medications was 40%, 26.3%, 13.1% and 7.4%, respectively. With respect to medication type, 32.3% of participants took ACEIs, 41.1% ARBs, 34.3% diuretics, 15.4% calcium antagonists, 9.8% beta-blockers, 13.7% statins, 6.3% hypoglycaemic agents, 4.6% antiplatelets and 1.1% anticoagulants. There were no significant between-group differences observed for anthropometric, body composition, haemodynamic, cardiorespiratory and pharmacological treatment at baseline. No major complications or cardiac events occurred during any part of the study.

Physiological changes

Following the 16-week intervention, resting SBP, DBP, mean BP and HR decreased ($P < 0.05$) (Table 2). Furthermore, in all groups, CRF expressed as $\dot{V}O_{2peak}$ (L/min) (AC, $\Delta = 10\%$; $P < 0.05$; high-volume MICT, $\Delta = 15\%$; high-volume HIIT, $\Delta = 25\%$; and low-volume HIIT, $\Delta = 25\%$; $P < 0.001$), $\dot{V}O_{2peak}$ (mL/kg/min) and metabolic equivalents of task (METs) ($P < 0.001$) increased. All groups increased at least one MET (Table 2 and Figure 2). However, at VT1 and VT2 (mL/kg/min) improvements were observed in high-volume HIIT for VT1 ($P = 0.003$) and both HIIT exercise groups for VT2 (high-volume HIIT, $P < 0.001$ and low-volume HIIT, $P = 0.016$). In contrast, no significant changes were seen in the AC and high-volume MICT groups for either VT1 or VT2. Following Bonferroni correction, there were no significant between-group differences in any haemodynamic variables (i.e. BP and HR) (Table 2). However, the AC group showed a smaller but significant improvement in $\dot{V}O_{2peak}$ ($P < 0.001$) compared with all exercise groups (high-volume MICT, mean difference 0.606, 95% confidence interval (CI) –2.193–3.405 mL/kg/min; high-volume HIIT, mean difference 3.215, 95% CI 0.418–6.012 mL/kg/min; and low-volume HIIT, mean difference 2.846, 95% CI 0.082–5.610 mL/kg/min) and METs ($P < 0.001$). Furthermore, both HIIT groups showed a greater ($P = 0.008$) $\dot{V}O_{2peak}$ and MET ($P = 0.018$) than the high-volume MICT group. In contrast, there were no significant between-group differences in any VT variables.

Anthropometric and body composition

Following 16 weeks intervention body mass, BMI, waist and hip circumferences, waist-to-hip ratio (WHR), and fat body mass (FBM) decreased ($P < 0.05$) in all groups (Table 2). In addition, fat-free mass (FFM) and the FFM/FBM ratio increased ($P < 0.05$). Following Bonferroni correction, there were significant between-group differences in anthropometric and body composition. The AC group had a smaller body mass reduction (T0 vs. T1 difference%, $\Delta = -6.6\%$; $P = 0.029$) and change in BMI ($\Delta = 6.7\%$; $P = 0.030$) compared with those in all exercise groups: high-volume MICT ($\Delta = -8.3\%$); high-volume HIIT ($\Delta = -9.7\%$); and low-volume HIIT ($\Delta = -6.9\%$). Furthermore, the high-volume HIIT group had a greater reduction in body mass ($P = 0.011$, mean difference 2.436, 95% CI –4.972–0.099 kg) and BMI ($P = 0.015$, mean difference 0.805, 95% CI –0.066–1.675 kg/m^2) compared with the low-volume HIIT group. However, there were no significant between-group differences observed for WHR. With respect to body composition, there were no significant differences in %FFM between the AC and all exercise groups ($\Delta = 4.0\%$; $P = 0.062$): high-volume MICT ($\Delta = 6.2\%$); high-volume HIIT ($\Delta = 6.8\%$); and low-volume HIIT ($\Delta = 4.6\%$). However, the %FFM gain in the high-volume HIIT group was greater than the AC group ($P = 0.039$). Similarly, there were no significant differences in %FBM when exercise groups were compared together with the AC group ($\Delta = -8.1\%$; $P = 0.062$): high-volume MICT ($\Delta = -11.3\%$); high-volume HIIT ($\Delta = -14.1\%$); and low-volume HIIT group ($\Delta = -9.6\%$). However, the high-volume HIIT group had a greater reduction of %FBM than the AC group ($P = 0.038$).

Pharmacological therapy

Following the 16-week intervention, medication was reduced from 86.9% to 79.3%. Furthermore, 37.7% of participants who still took medication had their dose reduced. The percentage of participants who took one, two, three or more than four medications was also reduced to 35.4%, 29.9%, 8.5% and 5.4%, respectively. In particular, 32.3% of participants took ACEIs, 39 % ARBs, 30.5% diuretics, 15.2% calcium antagonists, 6.1% beta-blockers, 11.0% statins, 6.7% hypoglycaemic agents, 3.7% antiplatelets and 1.2% anticoagulants. The chi-square test revealed that there were no significant between-group differences in medication reduction.

Discussion

To our knowledge, this is the first known study to investigate the impact of exercise programmes, which use different intensities and volumes in conjunction with a dietary intervention in overweight/obese, sedentary adults diagnosed with hypertension. The main findings of the study were: (a) all groups significantly

Table 2. Physiological data and body composition for all groups before and after intervention period.

	AC ($N=40$)	HV-MICT ($N=40$)	HV-HIIT ($N=42$)	LV-HIIT ($N=41$)	*P* value AC vs. EG	*P* value Intergroups	*F*-value	%Variance
Rest SBP (mmHg)								
T0	140.0 ± 13.2	132.7 ± 12.7	131.7 ± 10.4	135.6 ± 13.2				
T1	133.0 ± 15.3*	125.4 ± 8.9*	127.1 ± 9.7*	127.1 ± 10.5*	0.897	0.418	1.611	1.9
Rest DBP (mmHg)								
T0	79.9 ± 7.2	75.4 ± 8.0	79.0 ± 6.9	78.2 ± 8.2				
T1	75.1 ± 9.1*	72.0 ± 6.7*	74.1 ± 6.2*	73.9 ± 7.4*	0.544	0.762	0.050	0.8
Rest HR (beats/min)								
T0	68.9 ± 9.9	73.6 ± 9.2	70.5 ± 11.0	69.2 ± 10.5				
T1	65.2 ± 9.2*	68.1 ± 8.1*	63.7 ± 8.8*	64.4 ± 10.0*	0.747	0.485	0.819	1.7
Rest MBP (mmHg)								
T0	99.9 ± 8.4	94.5 ± 8.5	96.6 ± 7.2	97.3 ± 9.1				
T1	94.4 ± 10.4*	89.8 ± 6.2*	91.8.4 ± 6.9*	91.6 ± 7.6*	0.694	0.808	0.567	0.7
V?O_{2peak} (L/min)								
T0	2.0 ± 0.6	2.0 ± 0.6	2.0 ± 0.4	2.0 ± 0.5				
T1	2.2 ± 0.7*	2.3 ± 0.7*$^{\times}$	2.5 ± 0.7*$^{\times\$}$	2.5 ± 0.6*$^{\times\$}$	0.001	0.001	5.329	9.8
V?O_{2peak} (mL/kg/min)								
T0	22.6 ± 6.1	21.6 ± 5.2	22.4 ± 4.9	22.3 ± 5.2				
T1	26.3 ± 8.3*	26.7 ± 7.4*$^{\times}$	30.6 ± 8.5*$^{\times\$}$	29.1 ± 6.7*$^{\times\$}$	0.009	0.003	4.828	8.6
MET								
T0	6.4 ± 1.7	6.1 ± 1.5	6.4 ± 1.4	6.4 ± 1.5				
T1	7.5 ± 2.4*	7.6 ± 2.1*$^{\times}$	8.7 ± 2.4*$^{\times\$}$	8.3 ± 1.9*$^{\times\$}$	0.011	0.007	4.209	7.6
VT1 (mL/kg/min)								
T0	13.1 ± 5.8	12.2 ± 3.9	12.7 ± 4.6	12.7 ± 4.4				
T1	13.3 ± 7.2	12.9 ± 5.8	15.7 ± 6.8*	14.2 ± 7.0	0.754	0.238	1.4	2.7
VT2 (mL/kg/min)								
T0	17.1 ± 6.6	17.7 ± 5.6	17.9 ± 6.5	17.8 ± 6.4				
T1	19.5 ± 10.2	19.7 ± 8.6	24.5 ± 9.6*	21.6 ± 10.3*	0.843	0.057	2.6	4.7
Body mass (kg)								
T0	89.5 ± 14.8	94.0 ± 16.6	90.5 ± 15.7	91.2 ± 14.6				
T1	83.6 ± 14.9*	86.2 ± 15.8*$^{\times}$	81.7 ± 14.0*$^{\times}$	84.9 ± 13.6*$^{\times\ddagger}$	0.029	0.010	3.909	6.9
BMI (kg/m^2)								
T0	31.2 ± 3.9	32.4 ± 4.4	31.2 ± 3.6	31.6 ± 4.3				
T1	29.1 ± 4.1*	29.7 ± 4.1*$^{\times}$	28.2 ± 3.4*$^{\times}$	29.4 ± 4.1*$^{\times\ddagger}$	0.030	0.012	3.846	6.7
Waist (cm)								
T0	102.2 ± 11.3	105.1 ± 11.7	102.1 ± 11.1	102.8 ± 10.0				
T1	96.2 ± 11.3*	97.6 ± 10.5*	93.8 ± 11.4*	96.2 ± 8.7*	0.146	0.279	1.480	2.4
Hip (cm)								
T0	107.0 ± 8.8	108.8 ± 9.1	106.2 ± 7.7	107.3 ± 8.2				
T1	103.4 ± 8.9*	103.9 ± 9.1*	102.6 ± 7.2*	103.4 ± 7.2*	0.456	0.510	0.440	1.5
Waist/hip ratio								
T0	0.96 ± 0.08	0.97 ± 0.09	0.96 ± 0.08	0.96 ± 0.09				
T1	0.93 ± 0.08*	0.94 ± 0.08*	0.91 ± 0.08*	0.93 ± 0.07*	0.461	0.188	1.388	3.1
FFM (%)								
T0	66.8 ± 7.9	64.6 ± 8.6	67.5 ± 6.4	67.7 ± 7.0				
T1	69.5 ± 8.2*	68.6 ± 8.4*	72.1 ± 7.0*$^{\times}$	70.8 ± 8.1*	0.062	0.035	2.935	5.3
FBM (%)								
T0	33.2 ± 7.9	35.4 ± 8.6	32.5 ± 6.4	32.3 ± 7.7				
T1	30.5 ± 8.2*	31.4 ± 8.3*	27.9 ± 7.0*$^{\times}$	29.2 ± 8.1*	0.062	0.034	2.959	5.4

(continued)

Table 2. Continued

	AC (N = 40)	HV-MICT (N = 40)	HV-HIIT (N = 42)	LV-HIIT (N = 41)	P value AC vs. EG	P value Intergroups	F-value	%Variance
FFM/FBM								
T0	2.1 ± 0.8	2.0 ± 0.7	2.2 ± 0.6	2.2 ± 0.7				
T1	2.5 ± 1.0*	2.4 ± 0.9*	2.8 ± 0.9*	2.6 ± 1.0*	0.061	0.067	2.439	4.5

Mean ± SD.

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; MBP: mean blood pressure; V?O_{2peak}: peak oxygen uptake; MET: metabolic equivalent; VT: ventilatory threshold; BMI: body mass index; FFM: fat-free mass; FBM: fat body mass; AC: attention control group; HV-MICT: high-volume and moderate-intensity continuous training group; HV-HIIT: high-volume and high-intensity training group; LV-HIIT: low-volume and high-intensity training group; EG: exercise groups.

Blood pressure (BP) values show the mean BP calculated by 24-hour ambulatory blood pressure monitoring.

*P value < 0.05 from T0. $^{\times}P$ value < 0.05 from the AC. $^{\$}P$ value < 0.05 from the HV-MICT. $^{\ddagger}P$ value < 0.05 from the HV-HIIT.

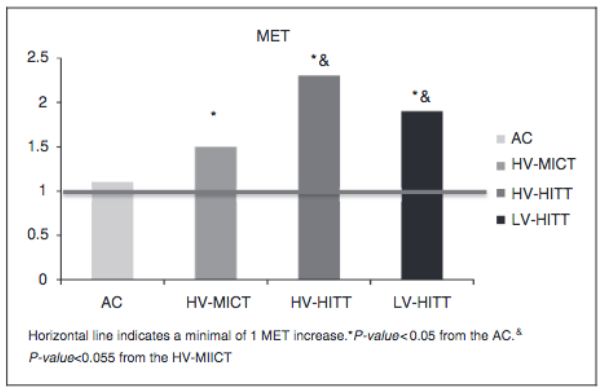

Figure 2. Peak metabolic equivalent of task (MET) differences after the 16-week intervention period for each group.

improved BP, CRF, body composition following 16 weeks intervention; (b) a substantial decrease of pharmacological treatment was observed; (c) hypocaloric diet and 2 days of supervised exercise showed improved body mass and CRF compared with a diet only intervention (AC group), but no significant between-group differences were observed in BP; (d) the high-volume HIIT exercise elicited a greater improvement in body mass and body composition than the low-volume HIIT exercise; and (e) the exercise-induced improvement in CRF is more dependent on intensity than volume.

In this study, a 16-week lifestyle intervention significantly improved cardiovascular risk factors (i.e. BP, CRF and adiposity) in all groups, and pharmacological therapy was largely reduced or removed completely. Hence, the hypocaloric DASH diet along with both supervised aerobic exercise and no supervised physical activity recommendations could offer an optimal non-pharmacological tool in the management of hypertension. As such, this could result in a cost-effective model for cardiovascular disease prevention[8] and healthcare cost reduction. These results corroborate those of previous investigations that suggested overweight/obese people with above normal BP could improve BP and body mass, vascular and autonomic function when they combine exercise and the DASH diet with calorie restriction.[9,24] Furthermore, we provide evidence that the combined effects of physical activity and hypocaloric diet enhance BP and reduce the need for pharmacological therapy.[25] To this end, contrary to our hypothesis, all supervised exercise groups had a reduced BP similar to the AC group post-intervention (7–9 mmHg in SBP and 3–5 mmHg in DBP). As such, the potential of the DASH diet to elicit significant improvements in SBP and DBP in individuals with hypertension who are overweight/obese is confirmed,[8] and it appears to be independent of the FITT principle. However, the lack of between-group differences in BP in the current study could in part be explained by: (a) the role physical activity plays in augmenting baroreflex dysfunction, which may result in a reduced sympathetic outflow with a lowered BP and HR response;[26,27] (b) the different exercise interventions appear to be medication dependent with similar BP reduction following all exercise intensities (i.e. MICT or HIIT);[11] and (c) 2 days of supervised exercise may not be enough to differentiate between exercise modalities over the 16-week period. Previously, it has been reported that there is greater antihypertensive effect seen in response to high-intensity exercise when compared with lower exercise intensities.[11] Previous research found that HIIT three times a week elicited greater significant reductions in BP than MICT and a control group following a 12-week intervention.[12] However, it should be noted that participants using the antihypertensive drug in the mentioned study performed a wash-out before inclusion and so a greater effect may have been seen.

To achieve a negative energy balance is to challenge and target specific pathways in order to produce beneficial changes in the pathogenesis of obesity-related hypertension.[2] In the present study, despite the antihypertensive medication and the metabolic potential side

effects,[1,4] a dual treatment of hypocaloric diet combined with supervised exercise twice a week was the optimal way to reduce body mass compared with the AC group. More specifically, high-volume HIIT significantly enhanced body mass reduction (kg, ↓9.7%), and fat distribution the most (%FFM ↑6.8 and %FBM ↓14.1). Given that, high-volume MICT and low-volume HIIT exercise programmes were performed with the same frequency but a reduced intensity and volume, respectively, the improvements seen in high-volume HIIT compared with the other two exercise programmes were likely to be caused by enhanced energy expenditure. These data suggest that sedentary people with overweight/obesity and hypertension can adapt and respond to exercise training during an energy-deficit programme with a dose–response curve related to volume and intensity. Furthermore, it has been shown that high levels of moderate to vigorous intensity physical activity are associated with long-term body mass loss maintenance,[28] despite the probable adaptive metabolic response caused by the compensatory downregulation in resting energy expenditure following exercise-induced body mass loss.[29]

CRF is an independent predictor of all-cause and disease-specific mortality in various populations irrespective of BMI.[30] Thereby, the fat-but-fit paradigm has been given much attention with respect to reducing the risk of illness and death.[31,32] Thus, in the present study (Table 1), while all participants were overweight/obese and considered unfit at baseline with CRF classified as poor (<24.4 mL/kg/min in men and <19 mL/kg/min in women),[23,33] following the 16-week intervention CRF was improved and classified as 'fair to good'.[33] Furthermore, all groups improved by at least 1 MET (Figure 2) during the course of the intervention. As such, although participants were still classified as overweight their CRF increased by 16–36%, which is associated with a considerable improvement in cardiovascular risk and reduced all-cause mortality.[34] In addition, the magnitude of change in CRF improvement was significantly different between exercise groups. In particular, both HIIT programmes elicited significantly greater improvements in CRF than the high-volume MICT and AC (Table 2 and Figure 2) groups. In addition, the HIIT groups showed significant improvements in submaximal variables such as VT (Table 2). These enhanced improvements in CRF may be due to stress adaptations, which have previously been shown to cause notable cellular, vascular and metabolic adaptations during HIIT.[35] One remarkable finding of the present study was that HIIT improved CRF irrespective of the training volume (low vs. high volume). Our findings reinforce previous studies, which suggest low-volume HIIT is a time-efficient and effective protocol in clinical populations answering the question 'Can less be more'?[36,37] As such, it may be that low-volume HIIT is more appealing for individuals who do not have enough time to train for long periods, or for those who have medical conditions which prevent them from performing exercise for prolonged periods of time.[13,35] However, taking into account the urgent need of increasing caloric expenditure and CRF in this population, low-volume HIIT could be an option to tailor supervised exercise along with daily recommendations of lower-intensity physical activities.[38]

Although the current study has provided clear evidence for the benefits of combining a hypocaloric DASH diet with exercise, there are some limitations which should be considered: (a) although every effort was made to manage unsupervised time, physical activity performed by participants in the AC group could not be controlled, and (b) it is difficult to regulate and monitor the adherence of participants to the diet.

Conclusions

In summary, the present study has shown that the combination of the hypocaloric DASH diet with different supervised aerobic exercise programmes twice a week offers an optimal non-pharmacological tool in the management of risk factors in sedentary individuals with overweight/obesity and hypertension. Benefits include an enhanced control of BP, body mass composition, CRF and pharmacological treatment. A dose–response curve related to volume and intensity in the form of 2-weekly bouts of high-volume HIIT provided significantly greater reductions in body mass compared with low-volume HIIT. However, the key to enhancing CRF in this population appears to be linked with exercise intensity irrespective of duration. As such, low-volume HIIT may be a time-efficient and effective method of improving health.

Author contribution

SMM conceived the study, acquisition of data and drafted the manuscript. IGA contributed to the design, intervention of exercise, acquisition, and analysis of data and drafted the manuscript. PC and AMAB contributed to the design, intervention of exercise and acquisition of data. JPA and GRA are members of the medical staff. SMF drafted the manuscript. All the authors critically reviewed the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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ORIGINAL ARTICLE

Effects on Cardiovascular Risk Scores and Vascular Age After Aerobic Exercise and Nutritional Intervention in Sedentary and Overweight/Obese Adults with Primary Hypertension: The EXERDIET-HTA Randomized Trial Study

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Abstract

Introduction The EXERDIET-HTA study was a multi-arm parallel, a randomized, single-blind controlled experimental trial comparing the effects of 16 weeks of different aerobic exercise programs two days per week, and dietary intervention in a hypertensive, overweight/obese and non-physically active population.

Aim To evaluate the influence of diet and aerobic exercise program intervention on cardiovascular risk (CVR) factors and predicted CVR and vascular age (VA) profiles in overweight/obese people with primary hypertension (HTN), and to analyze the potential sex differences in the ability to predict VA and CVR via different methods.

Methods The CVR and VA determined ($n = 167$, 53.7 ± 7.8 years) using the Framingham Risk Score (FRS) and the new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk, before and after the 16-week intervention period (different aerobic exercise programs + hypocaloric diet). The sex-specific risk factors considered were age, high-density lipoprotein cholesterol (HDL-C), total cholesterol, systolic blood pressure (SBP), diabetes mellitus (DM) and smoking status.

Results From baseline to follow-up, participants reduced ($p \leq 0.001$) FRS-CVR score and VA, and SBP. Total cholesterol decreased significantly, but specifically in men ($p \leq 0.001$), and antihypertensive medication (%) in women ($p = 0.047$). No significant differences over time were observed for HDL-C, smoking, DM overall for either sex. For ASCVD-CVR there was no overall change or for either sex. After the intervention, women had a lower CVR score than men ($p \leq 0.001$), irrespective of the calculation method.

Conclusions The improvement in CVR factors after 16-week lifestyle changes reduced the risk of suffering a cardiovascular event in overweight/obese adults with HTN through the FRS estimation tool, but not with the ASCVD score. The risk score algorithms could underestimate CVR in women. In contrast, VA could be a useful and easier tool in the management of individuals with CVR factors.

Keywords Lifestyle intervention · Gender · Systolic blood pressure · Vascular age · Cardiovascular risk score · Obesity · Overweight

This article is part of the topical collection on Nutraceuticals in Hypertension & Cardiovascular Prevention.

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1 Introduction

Cardiovascular disease (CVD) is a non-communicable disease, which represents the main cause of disability and death in the world, including Europe [1, 2]. Globally, between 2006 and 2016 deaths from CVD increased by 14.5%, although the age-standardized death rate decreased [3]. These data suggest that this condition needs to receive greater priority in prevention policy to reduce avoidable risk factors [2, 3]. Healthy lifestyle behavior promotion in the general population should directly target unhealthy lifestyles, such as poor-quality diet, physical inactivity, and smoking, at the individual level [2]. Cardiovascular risk (CVR) factors assessment is the first step guiding therapeutic strategy for the prevention of CVD [2], and strategy effectiveness depends on each patient's CVR profile and predictive risk [4].

There are several risk factor assessment tools for estimating a patient's 10-year risk of developing CVD [2, 4]. However, the most well-established risk score algorithm is the Framingham Risk Score (FRS), which was initially validated in 1998 to predict CVR [5, 6] and subsequently revised [7]. Recently, the American College of Cardiology and the American Heart Association developed a new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk, the called "Pooled Cohort Risk Equations" [8, 9]. This new tool was aimed at providing sex- and race-specific estimation of the 10-year risk of ASCVD for African-American and non-Hispanic white men and women aged 40–70 years old [8, 9]. On the other hand, vascular age (VA, i.e., the age of the vascular system of a person with different CVR factors, calculated as the age a person would be with the same calculated CVR but whose risk factors were all within normal ranges [10]) is an easily understood concept related to CVR and calculated according to the definition of D'Agostino from FRS [7].

The common prediction factors for CVR models that have a relationship with cardiovascular events and premature death are age, sex, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP, including treated or untreated status), diabetes mellitus (DM), and current smoking status [8].

Many observational studies have demonstrated graded associations between primary hypertension (HTN) and increased CVD risk [11] Additionally, adults with HTN usually present other modifiable CVR factors such as obesity, hypercholesterolemia, DM, smoking, physical inactivity, and unhealthy diet [12]. Therefore, correcting the dietary habits, lack of exercise and excessive consumption of alcohol through nonpharmacological interventions alone or in combination with pharmacological therapy is fundamental for the management of HTN [12].

A previous study evaluating CVR using the "Pooled Cohort Equations" (sex-specific risk prediction model) and VA in overweight/obese people with HTN found that CVR was significantly higher in men than in women despite them having the same CVR values, whereas no differences were found between sexes in VA [13]. As such, women could have an underestimated CVR profile based on the misperception that women are "protected" against CVD [14]. Hence, one of the biggest criticisms of the prediction scales of CVR accuracy is their capacity to overestimate or underestimate the risk [15]. Currently, there is no known research that measures the effects of an aerobic exercise program with nutritional intervention on CVR and VA in sedentary and overweight/obese adults with HTN. Considering the importance of CVR assessment, the objectives of this study were: (1) to evaluate the influence of 16-week diet and different aerobic exercise programs intervention on CVR factors and predicted CVR and VA profiles in sedentary and overweight/obese people with HTN, and (2) to analyse the potential sex differences in the ability to predict VA and CVR via different methods resulting from changes in lifestyle.

2 Methods

The EXERDIET-HTA study was a multi-arm parallel, a randomized, single-blind controlled experimental trial comparing the effects of 16 weeks of different aerobic exercise programs two days per week, and dietary intervention in a hypertensive, overweight/obese and non-physically active population (http://www.clinicaltrials.gov, NCT02283047) [16, 17]. The design, selection criteria, and procedures for the EXERDIET-HTA study have been previously detailed [16]. The study protocol was approved by the Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital (2015-030), and all participants provided written informed consent prior to any data collection. All follow-up examinations were performed in the same laboratory setting and by the same researchers as the baseline measurements. Medical staff was blinded to participant randomization.

One hundred and sixty-seven non-Hispanic white participants (n = 108 men and n = 59 women) with stage 1 or 2 HTN [≥ 140 SBP and ≥ 90 diastolic blood pressure (DBP)] and/or under antihypertensive pharmacological treatment [16, 18, 19], and classified as overweight (body mass index (BMI) ≥ 25 kg/m^2 or obese (BMI ≥ 30 kg/m^2) [20]. Participants were recruited from cardiology services and via local media and were enrolled in the study in Vitoria-Gasteiz (Basque Country, Spain).

The measurements for CVR factors used in the present study to determine the CVR and VA of participants were

taken before (T0) and after (T1) the 16-week intervention period and were defined as follows:

Ambulatory blood pressure monitoring was conducted over a 24 h period using an oscillometric ABPM 6100 recorder (Welch Allyn, New York, USA) to evaluate SBP (as used to determine CVR) [8]. The device was used in line with the recommendations set by the European Society of Hypertension and the European Society of Cardiology guidelines. As such, BP was measured at 30-min intervals during awake-time and at 60-min intervals during the sleep period. Data were only used if at least 75% of the awake-time and sleep periods were successfully recorded [16, 18].

Fasting venous blood (12.5 mL) was collected from each participant following an overnight fast. Diabetes mellitus was defined as fasting glucose of ≥ 126 mg/dL [21] and/or under pharmacological glycemic control treatment. Additionally, measurements of glucose and lipid profile (total-, and HDL-C) were assayed (ABBOTT, Architect c16000, Orlando, FL, USA). The intra- and inter-assay coefficients of variation were: for glucose 0.65% and 0.84%; for total cholesterol 0.6% and 0.8%; and for HDL-C 1.7% and 1.1%, respectively.

Age and cigarette smoking status were assessed by self-report. All medicines being taken were ascertained from the participant's physician.

Cardiovascular risk and vascular age parameters' assessment have been previously analyzed in the sample at baseline, and the same procedures were applied for the follow-up study [13]. Briefly, the Framingham Heart Study assesses the absolute risk to the individual with a percentage score (i.e., 10% means that there is a 10% chance of having a cardiovascular event within the next 10 years, < 6% = low risk; 6–20% = medium risk, and ≥ 20% = high risk) [7]. The Pooled Cohort Risk Equations to estimate the 10-year risk was described as a series of steps [8]. The Framingham method was used to determine the VA of all participants [7], which indicates the biological age of the individual's vascular system, as the age a person would be with the same calculated CVR, but whose risk factors were all within normal ranges. The sex-specific risk factors considered were age, HDL-C, total cholesterol, SBP, DM, and smoking status. Each variable received a weighted score; the sum of the score for each variable was then translated into the risk of a CV event in 10 years and VA [7].

After baseline data collection, participants were randomly allocated to one of the four intervention groups stratified by sex, SBP, BMI and age using a time-blocked computerized randomization program by the principal investigator and blind to medical staff. Detailed descriptions of the exercise and diet intervention procedures have been already reported [16, 17]. Briefly, the intervention groups were: (1) Attention Control group with physical activity recommendations (i.e., at least 30 min of moderate-intensity aerobic exercise 5–7 days per week and some dynamic resistance exercises); and three supervised aerobic exercise groups training two nonconsecutive days under supervision by exercise specialists, (2) high-volume moderate-intensity continuous training group, 45 min at moderate intensity; (3) high-volume high-intensity interval training group, 45 min alternating with different protocols moderate-to-high intensity; and (4) low-volume high-intensity interval training group, 20 min alternating with different protocols moderate-to-high intensity. All participants received treatment with a hypocaloric "Dietary Approaches to Stop Hypertension" (DASH) diet. The diet was designed to provide 25% less energy than their daily energy expenditure and to achieve a weekly loss of body mass between 0.5 and 1.0 kg. Approximately 30% of their energy intake came from fat, 15% from protein, and 55% from carbohydrates and was designed in accordance with the DASH diet [22]. This diet is rich in plant foods (i.e., *a* rich source of polyphenols) due to its favourable effect of BP [23]. Every two weeks, participants were weighed and received encouragement and advice alongside nutritional counseling to aid adherence.

Descriptive statistics were calculated for all variables. Data are expressed as means ± standard deviations (SD) and the range. ANOVA was used to determine if there were significant pre-intervention differences between sexes for the variables: age, BMI, SBP, total cholesterol, HDL-C, antihypertensive medication, cigarette smoking, DM, CVR, and VA. The comparison of frequencies between sexes was performed using a Chi-Square test. Repeated measures within-between participants ANOVAs were used to determine whether there was a significant difference in the recorded data between pre- and post-intervention for all participants and any time × sex interaction effects, i.e. to examine whether the change due to the intervention differed between men and women. A pre- and post-intervention mean difference for each variable was calculated. Statistical significance was set at $p < 0.05$. All statistical analyses were performed on an intention-to-treat basis using the SPSS version 22.0. The required sample size was determined for the primary outcome variable (SBP) and previously published [16, 17].

3 Results

Baseline characteristics of CVR factors classified by sex are presented in Table 1. The sample was the same as the previous study [13], but the number of participants is reduced because only those with follow-up values were included. The mean age (±SD) was 53.7 ± 7.8 years old with 64.7% being men, 12.8% of the participants were smokers, and 9.6% of the sample was suffering from DM. The results indicated that there were no significant differences between sexes for all CVR factors at baseline, except for total cholesterol,

Table 1 Characteristics of risk factors and cardiovascular risk classified by sex. Values are mean ± SD or percentage (%)

Dependent variable	All participants ($n=167$)	Men ($n=108$)	Women ($n=59$)	p_{M-W}	Effect size
Age (years)	53.7 ± 7.8	54.5 ± 7.8	52.4 ± 7.5	0.09	0.135
SBP (mmHg)	135.8 ± 12.1	135.8 ± 11.8	135.7 ± 12.6	0.96	0.004
Total cholesterol (mg/dL)	205.9 ± 39.8	201.3 ± 40.8	214.4 ± 36.8	0.04	0.166
HDL-C (mg/dL)	50.0 ± 32.9	49.8 ± 39.6	52.1 ± 14.4	0.44	0.038
Antihypertensive medication (%)	92.2	89.8	96.6	0.12	
Cigarette smoking (%)	12.8	13.2	12.1	0.84	
DM (%)	9.6	11.1	6.8	0.36	
ASCVD-CVR (%)	8.3 ± 6.8	10.5 ± 7.3	4.5 ± 3.1	< 0.001	0.471
FRS-CVR (%)	17.9 ± 10.9	21.6 ± 11.1	11.3 ± 6.7	< 0.001	0.489
Vascular age	71.3 ± 14.6	70.3 ± 13.5	73.1 ± 16.3	0.2	0.093

SBP systolic blood pressure, *HDL-C* high density lipoprotein cholesterol, *DM* diabetes mellitus, *ASCVD* atherosclerotic cardiovascular disease, *FRS* Framingham Risk Score, *CVR* cardiovascular risk

which was higher in women (mean difference = 13.1; 95% CI 25.4–0.85 mg/dL) than in men, with both sexes exceeding cut-off values set by the European Society of Hypertension and the European Society of Cardiology guidelines [24]. The mean HDL-C was similar in men and women with both sexes remaining within the healthy cut-off values suggested by the European Society of Hypertension and the European Society of Cardiology guidelines [24].

The absolute CVR score was significantly different ($p < 0.001$) between sexes with women having a lower CVR than men, irrespective of calculation method (ASCVD-CVR: mean difference = 6.0, 95% CI 4.0–8.0%, $p < 0.001$; FRS-CVR: mean difference = 10.2, 95% CI 7.1–13.4%, $p \leq 0.001$, Table 1). Additionally, in accordance with the ASCVD-CVR score, men were considered to be at medium risk (10.5%), whereas women were considered to be at low risk (4.5%). However, using the FRS-CVR score, men were considered to be at high risk (> 20%) whereas women were considered to be at medium risk (11.3%). Consequently, significant differences were found between CVR score calculators for CVR prediction ($p < 0.001$, mean difference = 9.6, 95% CI 10.6–8.6%). In contrast, there was no sex difference in VA (mean difference = 2.8, 95% CI −7.5 to 1.8 years old, $p = 0.23$), but VA was significantly higher ($p < 0.001$) than chronological age (CA) (mean difference = 17.5, 95% CI 19.4–15.7 years old), irrespective of sex, ($p < 0.001$).

Table 2 shows CVR factors, CVR scores and VA values at baseline and follow-up. After the intervention, all participants showed decreased SBP, total cholesterol, antihypertensive medication usage (%), CVR score predicted by FRS, and VA ($p < 0.05$). ANOVA showed that SBP decreased in both sexes (T0 vs. T1 difference %, men $\Delta = 7.4\%$; women, $\Delta = 6.0\%$, $p \leq 0.001$). Significant time × sex interaction effects revealed that mean total cholesterol significantly reduced in men ($\Delta = 13.6\%$, $p \leq 0.001$), but not in women ($\Delta = 6.5\%$, $p = 0.12$), and antihypertensive medication (%) significantly decreased in women ($\Delta = 10.2\%$, $p = 0.047$), but not in men ($\Delta = 4.6\%$, $p = 0.30$). No significant differences were observed in HDL-C, smoking habit and suffering from DM after 16-weeks intervention period. When CVR score and VA were analyzed, FRS-CVR and VA decreased overall, and in both sexes (FRS-CVR: men $\Delta = 4.0\%$; $p \leq 0.001$; women, $\Delta = 2.0\%$; $p = 0.01$) and (VA: men $\Delta = 5.6\%$, $p \leq 0.001$; women, $\Delta = 6.5\%$; $p \leq 0.001$, Fig. 1). However, no significant changes over time were observed in ASCVD-CVR overall or for either sex (men $\Delta = 0.8\%$, $p = 0.30$; women $\Delta = 0.5\%$, $p = 0.08$). Finally, the magnitude of change in each CVR variable due to the intervention was not significantly different from each other between sexes, despite some single factor reductions being significant only for men or women, as described above. However, after intervention period, the CVR score remained significantly different ($p < 0.001$) between sexes (at follow-up) with women having a lower CVR than men, irrespective of calculation method (ASCVD-CVR: mean sex difference = 5.6, 95% CI 3.0–8.2%, $p < 0.001$; FRS-CVR: mean sex difference = 8.1, 95% CI 5.1–11.2%, $p \leq 0.001$, Table 2).

4 Discussion

To our knowledge, this is the first study investigating the impact of a 16-week intervention (hypocaloric DASH diet plus aerobic exercise) on CVR factors, CVR score calculators and VA in sedentary overweight/obese and hypertensive adults. The main findings of the study were that after aerobic exercise and hypocaloric DASH diet intervention: (1) participants significantly improved SBP, total cholesterol and decreased antihypertensive medication usage; (2) CVR and VA using the FRS model was significantly reduced in both sexes but not CVR estimated by ASCVD Pooled Cohort Equations; (3) regardless of the CVR

Table 2 Cardiovascular risk factors, cardiovascular risk and vascular age data classified by sex before and after intervention period. Values are mean ± SD or percentage (%)

Dependent variable	All participants ($n=167$)	p T0 vs. T1	Effect size η^2	Men ($n=109$)	Women ($n=58$)	p_M vs. W at T1	Effect size η^2	p Time × sex	Effect size η^2
SBP (mmHg)									
T0	135.8 ± 12.1			135.8 ± 11.8	135.7 ± 12.6				
T1	128.9 ± 11.8*	< 0.001	0.277	128.5 ± 11.5*	129.7 ± 12.4*	0.531	0.05	0.54	0.049
Total cholesterol (mg/dL)									
T0	205.9 ± 39.8			201.3 ± 40.8	214.4 ± 36.8				
T1	194.8 ± 36.9*	< 0.001	0.143	187.7 ± 35.7*	207.9 ± 35.9	0.001	0.271	0.21	0.454
HDL-C (mg/dL)									
T0	50.0 ± 32.9			49.8 ± 39.6	52.1 ± 14.4				
T1	47.7 ± 11.6	0.35	0.046	45.8 ± 11.1	51.0 ± 11.8	0.006	0.221	0.71	0.033
Antihypertensive medication (%)									
T0	92.2			89.8	96.6				
T1	85.6*	0.05		85.2	86.4*	0.826		0.15	
Cigarette smoking (%)									
T0	13.8			13.9	13.6				
T1	13.8	1.00		13.9	13.6	0.860		1.00	
DM (%)									
T0	9.0			11.1	6.8				
T1	9.0	1.00		11.1	6.8	0.268		1.00	
ASCVD-CVR %									
T0	8.3 ± 6.8			10.5 ± 7.3	4.5 ± 3.1				
T1	7.6 ± 8.6	0.18	0.045	9.6 ± 9.4	4.0 ± 3.1	< 0.001	0.371	0.21	0.041
FRS-CVR %									
T0	17.9 ± 10.9			21.6 ± 11.1	11.3 ± 6.7				
T1	14.7 ± 10.2*	< 0.001	0.149	17.6 ± 10.9*	9.4 ± 5.9*	< 0.001	0.423	0.13	0.126
Vascular age									
T0	71.3 ± 14.6			70.3 ± 13.5	73.1 ± 16.3				
T1	65.4 ± 15.2*	< 0.001	0.194	64.7 ± 15.1*	66.6 ± 15.7*	0.448	0.061	0.62	0.40

SBP systolic blood pressure, *HDL-C* high density lipoprotein cholesterol, *DM* diabetes mellitus, *ASCVD* atherosclerotic cardiovascular disease, *FRS* Framingham Risk Score, *CVR* cardiovascular risk

*p value < 0.05 from T0

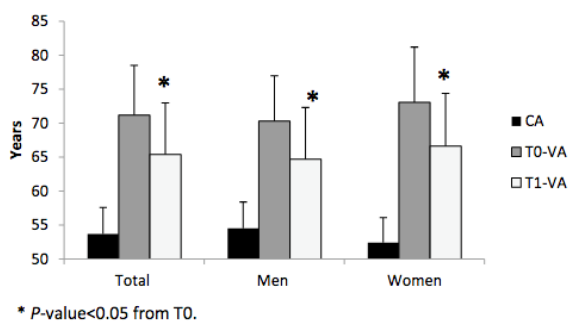

Fig. 1 Vascular age (VA) values at baseline (T0) and follow-up (T1) periods compared to chronological age (CA). *p value < 0.05 from T0

assessment tool, men showed significantly higher values than women post-intervention albeit no differences in percentage change resulting from the intervention, and 4) VA could better identify the effect of a non-pharmacological intervention in both sexes than other CVR tools.

Based on a rigorous approach to the validation of equations, the American College of Cardiology and the American Heart Association guideline strongly recommends the use of Pooled Cohort Equations in non-Hispanic African Americans and non-Hispanic whites (40–79 years old) for the assessment of the 10-year risk of a first hard ASCVD event [8]. However, although the ASCVD-CVR equations have been developed from the FRS [7, 8], and the role of the major variables in the development of CVR was similar in both score calculators, in the present study, after the exercise and diet intervention, CVR was still 7.1% lower with ASCVD-CVR than with FRS-CVR ($p < 0.001$) in all participants (Table 2). Thus, the observed and predicted risks for participants in this study at follow-up were 9.6% and 17.6% (medium risk) in men and 4.0% (low risk) and 9.4% (medium risk) in women for the ASCVD-CVR and FRS-CVR, respectively. Hence, it could be considered that

the ASCVD-CVR score calculator by the American College of Cardiology and the American Heart Association would identify the least number of participants with CVR (i.e., underestimation), or the FRS-CVR would stratify a maximum number of individuals with high CVR (i.e., overestimation) [6]. This difference could likely be caused by the objective of each score; the FRS estimates CVR for a large combination of CVD outcomes and the ASCVD tool estimates risk mainly for myocardial infarction (fatal and nonfatal) and stroke only [25] and does not consider family history, which influences mortality [25].

An appropriate lifestyle change, including diet and exercise, has been shown to effectively improve markers of CV health [18, 19] and CVD prevention [2]. Likewise, previous studies have proven that a dose-response curve for physical activity and HTN has a clinically meaningful role in primary prevention of HTN [26], along with a diet rich in polyphenols [23]. Related to that, in the current study, the decreases ($p < 0.05$, before-after intervention) in SBP ($\Delta = 7.3$ mmHg in men and $\Delta = 6$ mmHg in women), total cholesterol in men ($\Delta = 13.6$ mg/dL) and antihypertensive medication use in women ($\Delta = 10.5\%$) could rightfully be considered the reason underlying the reduction in the FRS-CVR score and VA. However, given that drug therapy for primary prevention of CVD is nowadays based on absolute CVD risk, where the BP-lowering drug treatment is determined by BP level along with other CVR factors (i.e., sex, age, total cholesterol, HDL-C, DM, and smoking status) [27], and that a reduction of 5 mmHg in SBP was associated with a lower risk of CVD mortality [28], it seems that the ASCVD-CVR estimation tool does not have enough sensitivity to show the benefits of a lifestyle intervention. Hence, the lack of significant changes in ASCVD-CVR estimation, in the presence of other CVR factor improvements, could have a negative effect on the advice to treat individuals with an ASCVD-CVR > 7.5% with statins [15]. It is important, therefore, to note that treatment decisions should be individualized (i.e., after a clinician-patient risk/benefit discussion addressing optimal lifestyle), as suggested by the latest cholesterol guidelines [29], and not just absolute CVR estimation.

On the other hand, the present study showed that after 16-week of intervention with diet and aerobic exercise, absolute CVR remained higher in men than in women for both CVR scores (ASCVD, 5.6%; FRS, 8.2%). As such, the straightforward discussion would claim that men have a higher risk of suffering a CV event in the following 10 years, underlining the sex differences in life expectancy and quality of life, due, in part, to unhealthy behaviors [30]. However, a deeper analysis of data and literature revealed that in the current study after lifestyle intervention: (1) there were no differences in the percentage change after intervention between men and women (ASCVD, $p = 0.73$; FRS, $p = 0.09$); (2) post-intervention women showed higher total cholesterol values with hyperlipidemia > 190 mg/dL, with no differences in HDL-C (normal values > 40 mg/dL), antihypertensive medication use, smoking habit or DM compared to men; (3) the new cholesterol guidelines have no sex-specific differences in recommendations [31], and (4) menopausal status in women is not taken into account when CVR is estimated irrespective of tool (in this study 50% were post-menopausal women). Given this, and that deaths from CVD have been greater in women compared with men over the past 30 years, with CVR increases during the menopausal transition and after menopause mainly marked by progressive endothelial dysfunction [32], would be logical to conclude that CVR is underestimated in women.

Noting the imprecise previous tools for calculating the CVR, mainly due to the various underlying mathematical models used to calculate the scores, VA could be a useful tool in the management of individuals with CVR factors, and easier to use and understand the effect of an intervention in terms of life years [10]. Thus, in the present study after 16-week lifestyle intervention, VA decreased in all participants (Table 2, Fig. 1) with no differences between sexes. These results could identify biologically plausible mechanisms underlying exercise and diet-induced effects on CVD risk reduction irrespective of sex. Overall, the CVR factors-associated arterial wall thickening, which contributes to vascular stiffening, are sensitive to a non-pharmacological lifestyle intervention [33].

Although the present study has highlighted the importance of determining CVR factors in a hypertensive population after a lifestyle intervention, several limitations should be acknowledged. Firstly, although the sample size was sufficient as an initial investigation into CVR and HTN; it would not be comparable to that of larger epidemiological studies, and future studies should consider large-scale investigations. Secondly, the current study only had 35.3% of women which does not represent an equal gender split. As this poses statistical issues, future studies should look to recruit equal numbers, or even to study effects only in women.

5 Conclusions

The improvements in CVR factors after a 16-week lifestyle change intervention reduced the risk of suffering a CV event in the following 10 years in overweight/obese adults with HTN assessed with the FRS estimation tool. However, the ASCVD-CVR score calculator was not sensitive enough to show the benefits of diet and exercise. The risk score algorithms (FRS and ASCVD) might underestimate the CVR in women as they always consider men to be higher risk irrespective of age. Therefore, VA could be a useful tool in the management of individuals with CVR factors, and easier to

apply and understand the effect of an intervention in terms of life expectancy.

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Compliance with Ethical Standards

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent All participants provided written informed consent prior to any data collection.

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10.3. Anexo 3. Publicaciones relacionadas con la tesis

En revistas internacionales

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