EFECTOS DEL CESE DE UN PROGRAMA DE EJERCICIO FÍSICO AERÓBICO CON INTERVENCIÓN NUTRICIONAL EN PERSONAS ADULTAS CON HIPERTENSIÓN PRIMARIA, SOBREPESO/OBESIDAD Y FÍSICAMENTE INACTIVAS: ESTUDIO EXERDIET-HTA

EFFECTS OF THE CESSATION OF AN AEROBIC EXERCISE PROGRAM WITH NUTRITIONAL INTERVENTION IN ADULTS WITH PRIMARY HYPERTENSION, OVERWEIGHT/OBESITY AND PHYSICALLY INACTIVE: EXERDIET-HTA STUDY

Tesis doctoral • Vitoria-Gasteiz, 2020

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Dirigida por la Dra. Sara Maldonado Martín

A mi padre y a mi madre,

por apoyarme y educarme.

A Amaia,

por quererme y acompañarme.

PROGRAMA DE DOCTORADO

Ciencias de la Actividad Física y del Deporte

THESIS PROGRAM

Physical Activity and Sports Sciences

TESIS DOCTORAL

Efectos del cese de un programa de ejercicio físico aeróbico con intervención nutricional en personas adultas con hipertensión primaria, sobrepeso/obesidad y físicamente inactivas: estudio EXERDIET-HTA

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“La mejor medicina de todas es enseñar a la gente a no necesitarla”

Hipócrates

Esta tesis doctoral se ha realizado con la ayuda del Gobierno Vasco, del área de Educación, Política Lingüística y Cultura para el Programa Predoctoral, de Formación de Personal Investigador No Doctor. (2016-2020) [PRE_2015_1_0116].

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DECLARACIÓN

El autor 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 disfrutaron (Ilargi Gorostegi) o disfrutan (Aitor Mtz. de Aguirre) de una beca predoctoral del Gobierno Vasco.

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 presente tesis doctoral se ha realizado en forma de compendio de artículos. Por ello, aunque las publicaciones estén anexadas en el último apartado debido a los requerimientos de formato de la universidad, éstas son la parte central de la tesis.

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. A continuación, se seguirá con el segundo y tercer capítulo, el marco teórico y los objetivos e hipótesis, donde se inscribe el tema de la tesis y los objetivos de la misma, indicando en qué publicaciones se abordan. El cuarto capítulo son los métodos, donde se explican las herramientas metodológicas utilizadas.

Llegados a este punto, se debe complementar el quinto capítulo, donde se resumen los resultados obtenidos y la discusión, con el octavo capítulo, donde se encuentran las publicaciones completas, donde de manera más específica se expone la metodología utilizada para cada apartado, y donde se presentan de manera completa los resultados de cada estudio.

Tal y como indica la estructura que ordena la universidad, en el sexto capítulo se muestran las referencias bibliográficas utilizadas en todo el texto, y en el séptimo capítulo se presentan las conclusiones de la tesis doctoral.

Se trata de una tesis internacional, por lo que a lo largo de este documento el texto se va a encontrar escrito en dos lenguas, castellano e inglés. En las primeras páginas del documento se podrán leer dos listas de abreviaciones, una en castellano y otra en inglés.

ABREVIACIONES

6M: seis meses

AC: grupo de atención-control

AF: actividad física

ALT: alanina transaminasa

AST: aspartato transaminasa

CCR: capacidad cardiorrespiratoria

CV: cardiovascular

CRP: proteína C reactiva

DASH: del inglés, *Dietary Approaches to Stop Hypertension*

EF: ejercicio físico

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

GGT: gamma-glutamil-transferasa

HbA1c: hemoglobina glicosilada

HDL-C: colesterol de lipoproteína de alta densidad

HIIT: entrenamiento interválico de alta intensidad

HOMA-IR: modelo homeostático para evaluar la resistencia a la insulina

HTA: hipertensión arterial

HV-HIIT: entrenamiento interválico de alta intensidad y volumen alto

HV-MICT: entrenamiento continuo a intensidad moderada y volumen alto

IMC: índice de masa corporal

JCR: del inglés, *Journal Citation Reports*

LDL-C: colesterol de lipoproteína de baja densidad

LV-HIIT: entrenamiento interválico de alta intensidad y volumen bajo

MC: masa corporal

MET: equivalente metabólico

ObME: obesidad metabólicamente enferma

ObMS: obesidad metabólicamente sana

OMS: Organización Mundial de la Salud

PA: presión arterial

PAD: presión arterial diastólica

PAS: presión arterial sistólica

SobMS: sobrepeso metabólicamente sano

TC: colesterol total

TG: triglicéridos

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

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

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

ABBREVIATIONS

6M: six-months

ABMP: ambulatory blood pressure monitoring

AC: attention control group

ALT: alanine aminotransferase

AST: aspartate aminotransferase

BMI: body mass index

BM: body mass

BP: blood pressure

CPET: cardiopulmonary exercise test

CRF: cardiorespiratory fitness

CRP: C-reactive protein

DBP: diastolic blood pressure

GGT: gamma-glutamyl transpeptidase

HbA1c: haemoglobin A1c

HDL-C: high-density lipoprotein cholesterol

HOMA-IR: HOmeostatic Model Assessment-Insulin resistance index

HR: heart rate

HTN: arterial hypertension

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

HV-MICT: high-volume moderate-intensity continuous training

IPAQ: The Physical Activity Questionnaire

LDL-C: low-density lipoprotein cholesterol

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

SBP: systolic blood pressure

TC: total cholesterol

TG: triglycerides

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

VT1: ventilatory threshold 1

VT2: ventilatory threshold 2

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Resumen

Objetivos: esta tesis doctoral la componen distintos estudios que se centran en la relación de la capacidad cardiorrespiratoria (CCR) con el perfil bioquímico y en los efectos del cese de una intervención de 16 semanas con ejercicio físico (EF) aeróbico supervisado y dieta hipocalórica, 6 meses (6M) después de la misma, en participantes con hipertensión arterial primaria (HTA), sobrepeso u obesidad y físicamente inactivas. Por ello, los objetivos principales de este trabajo fueron: 1) establecer ,en esta población, las asociaciones entre la CCR y el perfil bioquímico; 2) determinar si las mejoras obtenidas después de una intervención de 16 semanas con dieta hipocalórica y EF aeróbico supervisado en CCR, presión arterial (PA) y composición corporal son mantenidas tras un periodo de 6M sin supervisión; y 3) determinar las diferencias en el perfil metabólico después de una intervención de 16 semanas con dieta hipocalórica y EF aeróbico supervisado y analizar si los cambios observados tras ese periodo son mantenidos tras un periodo de 6M sin supervisión.

Métodos: personas con HTA, sobrepeso u obesidad y físicamente inactivas (N = 224) participaron entre los años 2013-2018 en estudio EXERDIET-HTA. Los/las participantes fueron aleatoriamente asignados/as a uno de los tres grupos de intervención de EF aeróbico supervisado, o a un grupo atención-control. Todos los grupos siguieron una dieta hipocalórica. Después de 16 semanas de intervención, los/las participantes recibieron recomendaciones nutricionales y de AF para los próximos 6M, pero sin supervisión. Antes y después de la intervención y 6M tras la intervención, cada participante fue valorado con pruebas que incluían mediciones antropométricas, de la PA, de la CCR y del perfil bioquímico.

Resultados: 1) la CCR estaba independientemente e inversamente asociada a las concentraciones de aspartato aminotransferasa (AST; β= -0,328, p<0,05) y alanina aminotransferasa (ALT; β= -0,376, p<0,01). Estas relaciones fueron confirmadas por el análisis

de regresión logística y linear. La proteína C reactiva (CRP), la ratio AST/ALT, la gamma-glutamil transferasa (GGT), la ratio colesterol total (TC)/colesterol de proteína de alta densidad (HDL-C), la glucosa, la insulina y el modelo homeostático para evaluar la resistencia a la insulina (HOMA-IR) estaban asociados, pero no de manera independiente, con la CCR en modelos no ajustados de regresión linear y/o logística. Además, la glucosa estaba independientemente asociada al grupo de CCR moderada en el análisis de regresión logística. 2) Los beneficios inducidos por la intervención en la composición corporal y la CCR no fueron mantenidos 6M después del fin de la misma, pero los valores tras ese periodo eran mejores que los previos a la intervención. Después de 6M, los valores de masa corporal y circunferencia de cintura eran mayores (p<0,05) que al finalizar la intervención (Δ = 2,5% y Δ = 1,8%, respectivamente), pero inferiores (p<0,05) a los del inicio de la intervención (Δ = -5,1% y Δ = -4,7%, respectivamente). La CCR era superior (p<0,001) a los 6M respecto al inicio de la intervención (Δ = 17,1%), pero inferior (p<0,001) respecto al final de la intervención (Δ = -5,7%). En relación a las mejoras obtenidas en la PA después de la intervención, éstas se perdieron y regresaron los valores previos a la intervención. 3) En el inicio de la intervención los/las participantes presentaban un perfil de obesidad metabólicamente enferma (ObME) que tras la intervención mejoraba a un perfil de sobrepeso metabólicamente sano (SobMS), con descensos en el TC (Δ = -12,1 mg/dL), la ALT (Δ = -8,3 U/L), la glucosa (Δ = -5,5 mg/dL), la CRP (Δ = -1,4 mg/dL), la PA sistólica (PAS) e incrementos en la CCR. Sin embargo, después de 6M, el TC, la glucosa y la PAS regresaron a valores no saludables, con un perfil ObME.

Conclusiones: 1) la CCR se asoció con el perfil bioquímico en una población con HTA, sobrepeso/obesidad y físicamente inactiva. La asociación entre la CCR y el AST y ALT fue inversa e independiente, mientras que la influencia de la CCR estaba limitada por otras covariables en la asociación con la CRP, la ratio AST/ALT, la GGT, la ratio TC/HDL, la glucosa, la insulina y el HOMA-IR. 2) Las personas con HTA y sobrepeso/obesidad lograron mejoras significativas en la CCR, PA y composición corporal tras una intervención de 16 semanas con EF supervisado y dieta

hipocalórica. Después de 6M del fin de la intervención hubo pérdidas en las mejoras logradas cuando se proporcionaron recomendaciones sin ningún tipo de supervisión. Sin embargo, la CCR y composición corporal presentaron valores más saludables a los 6M en comparación con el inicio de la intervención (a pesar de la reducción de las mejoras respecto al fin de la intervención). Por lo contrario, las mejoras logradas en la PA no se mantuvieron y volvieron a los valores iniciales. 3) Una intervención de 16 semanas con EF supervisado y dieta hipocalórica fue efectiva para mejorar la salud cardiometabólica de los/las participantes desde ObME a SobMS. A los 6M, tras finalizar la supervisión, este estado resultó transitorio ya que el perfil regresó a ObME. 4) Los resultados sugieren que los programas de EF y dieta desarrollados de manera regular, sistemática y supervisada son necesarios para evitar el empeoramiento posterior en la salud cardiometabólica.

Abstract

Aim: This doctoral thesis is composed by three different studies focused on the association of cardiorespiratory fitness (CRF) with biochemical profile and the effects of cessation of a 16-week aerobic exercise program with nutritional intervention in physically inactive overweight/obese adults with primary hypertension (HTN), 6 months (6M) after the end of the intervention. Thus, the purposes of this study were: 1) to determine associations between CRF and biochemical profile in overweight/obese men and women diagnosed with HTN; 2) to determine whether the improvements in CRF, BP and body composition previously seen during a 16-week supervised exercise training intervention with hypocaloric diet are maintained following six months (6M) of unsupervised time; 3) to determine differences in metabolic profiles of overweight/obese, physically inactive individuals with HTN following a 16-week supervised aerobic exercise training intervention, and to analyse whether the changes observed after this period were maintained following 6M of unsupervised time.

Methods: Overweight/obese, physically inactive individuals with primary hypertension (HTN) (n = 224) were involved between 2013 and 2018 in the EXERDIET-HTA study. Participants were randomly assigned into an attention control group (physical activity recommendations) or one of three supervised exercise groups. All the groups followed a hypocaloric diet. After the 16-week intervention, all participants received diet and physical activity advice for the following 6M but no supervision. All anthropometric, blood pressure (BP), cardiorespiratory fitness (CRF) and biochemical profile measurements were taken pre and post the 16-week supervised intervention period, as well as after 6M of no supervision.

Results: 1) The CRF was independently and inversely associated with aspartate aminotransferase (AST; β= -0,328, p<.05) and alanine aminotransferase (ALT; β= -0,376, p<.01) concentrations. C-reactive protein (CRP), AST/ALT ratio, gamma-glutamyl transpeptidasa (GGT),

total cholesterol (TC)/high-density lipoprotein cholesterol ratio (HDL-C), glucose, insulin and insulin resistance index (HOMA-IR), were all associated, but not independently, with CRF in linear and/or unadjusted logistic regression models. Further, logistic regression revealed that glucose was associated independently with the moderate CRF group. 2) After 6M, body mass (BM) (Δ = 2.5%) and waist circumference (Δ = 1.8%) values were higher (p<.05) than postintervention values, but lower (p<.05) than preintervention values (BM, Δ = −5.1%; waist circumference, Δ = −4.7%, respectively). BP variables were higher (p<.001) compared to POST with no change from pre-intervention. CRF was higher (p<.001) compared to pre-intervention (Δ = 17.1%) but lower (p<.001) than POST (Δ = −5.7%). 3) From pre- to post-intervention, metabolically unhealthy obese (MUO) participants became metabolically healthy overweight (MHO) with lower TC (Δ = -12.1 mg/dL), ALT (Δ = -8.3 U/L), glucose (Δ = -5.5 mg/dL), CRP (Δ = -1.4 mg/dL), systolic BP (SBP), and higher CRF (CRF). However, after 6M, TC, glucose, and SBP returned to unhealthy values, and participants returned to MUO.

Conclusions: 1) CRF was associated with biochemical profile in a physically inactive population with HTN and overweight/obesity. The association between CRF and AST and ALT was inverse and independent, whereas the influence of CRF was limited by other covariates in the association with CRP, AST/ALT ratio, GGT, TC/HDL-C ratio, glucose, insulin and HOMA-IR. 2) People with HTN and overweight/obesity achieved significant improvements in CRF, BP and body composition following a 16-week supervised exercise intervention and hypocaloric diet. There was a significant reduction in the improvements following 6M, when the exercise and diet supervision was removed, and only recommendations were applied. CRF and body composition reduced the improvements following 6M, however, there were significant improvements from pre-intervention. By contrast, the attained improvements in BP were not maintained and BP returned to pre-intervention values. 3) A 16-week supervised exercise intervention with hypocaloric diet was effective to improve cardiometabolic health of participants with HTN and overweight/obesity from MUO to MHO. However, this was a transient stage as after 6M follow-

up, participants returned to MUO. 4) The results suggest that regular, systematic and supervised diet and exercise programs are necessary to avoid subsequent declines in cardiometabolic health.

Capítulo 1/Chapter 1

Introducción/Introduction

1. Introducción

Desde la revolución industrial, el desarrollo de la tecnología ha ayudado a reducir el trabajo físico de las personas para sus labores diarias. A medida que han avanzado los años, la disposición de estas tecnologías ha sido cada vez más accesible para la población, por lo que los efectos sobre la actividad física (AF) y el consumo de energía han sido más notorios según ha pasado el tiempo.[1]

El objetivo del uso de las nuevas tecnologías era aumentar la productividad y reducir el trabajo físico, que en ocasiones podía causar la invalidez por su dureza.[1] Sin embargo, el cuerpo humano ha evolucionado de manera que la mayoría de sus sistemas orgánicos no son capaces de desarrollar su función de una manera óptima a no ser que sea estimulado con AF frecuente.[2] Se observa entonces que, si bien la revolución tecnológica ha traído grandes beneficios para las personas, también ha conllevado el aumento de la inactividad física,[1] que se define como la falta de cumplimiento de las recomendaciones mínimas internacionales de AF.[3,4] Estas recomendaciones son actualmente, según la organización mundial de la salud (OMS), realizar al menos 150 minutos de AF de intensidad moderada o 75 minutos de intensidad vigorosa a la semana y, al menos dos veces por semana, realizar actividades de fortalecimiento de los grandes grupos musculares.[5]

Se deben diferenciar los conceptos de AF y ejercicio físico (EF), así como la inactividad física y el sedentarismo, que, aunque son conceptos relacionados, no significan lo mismo. La AF se define como cualquier movimiento corporal producido por los músculos esqueléticos que produzca un gasto energético mayor al existente en reposo,[6] mientras que el EF sería la AF planificada, estructurada y repetida, cuyo objetivo es adquirir, mantener o mejorar la condición física.[6] Por su parte, en contraste a la definición de la inactividad física, la conducta sedentaria se define como la carencia de movimiento durante las horas de vigilia a lo largo del día, y es caracterizada por actividades que sobrepasan levemente el gasto energético basal (estar en posición acostada

o sentada, por ejemplo).[3] Es importante no confundir ambos términos, ya que una persona puede cumplir con las recomendaciones de AF, pero destinar la mayor parte del día a comportamientos sedentarios.[7,8]

En relación a la inactividad física, la OMS indica que es el cuarto factor de riesgo que más muertes provoca, por detrás de la hipertensión arterial (HTA), el tabaco y la hiperglucemia.[9] Por ello, es preocupante el nivel de inactividad física que existe en la actualidad. La OMS considera que el 23% de los hombres y el 32% de las mujeres del mundo no son físicamente activos.[10] Este problema se acentúa en los países con economías avanzadas, que superan en más del doble a los países con economías en vías de desarrollo en los porcentajes de inactividad física (37% *vs.* 16%).[10] En España, los niveles de inactividad física se sitúan en 25% en hombres y 30% en mujeres.[10]

Debido a estos porcentajes, la inactividad física ha emergido indiscutiblemente como uno de los principales factores de riesgo de padecer enfermedades no transmisibles (enfermedades cardiovasculares (CV), cáncer y diabetes, entre otras) y de mortalidad.[11] Los niveles de inactividad física a nivel global han provocado que la situación sea descrita como pandémica y que éste sea uno de los mayores desafíos de la salud pública del siglo XXI.[12,13] Se estima que la carga de responsabilidad de la inactividad física es del 6% en las enfermedades coronarias, del 7% en la diabetes tipo II, y del 10% en los cánceres de mama y colon.[14] También se calcula que la inactividad física es responsable de 3,2 millones de muertes al año a nivel mundial, que suponen un 5,5% del total.[15] Además, teniendo en cuenta que la inactividad física es una causa indirecta que como consecuencia tiene muchas enfermedades no transmisibles, la cifra mostrada en las estadísticas puede ser aún mayor.[16] Asimismo, la AF realizada está también muy relacionada con otros factores de riesgo.[17,18]

Los factores de riesgo son aquellos signos biológicos o hábitos adquiridos que se presentan con mayor frecuencia en las personas con una enfermedad concreta,[19] y que pueden ser clasificados

en dos grandes grupos, los no modificables y los modificables.[20,21] Entre los no modificables, se encuentran la edad, el sexo, y los antecedentes familiares, mientras que entre los modificables están el tabaquismo, la inactividad física, la dieta no saludable, el alto consumo de alcohol, la HTA, el sobrepeso/obesidad, la hiperlipidemia y la hiperglucemia.[21] Es sobre estos factores de riesgo sobre los cuales la AF puede actuar, ya que las guías internacionales recomiendan la AF como un importante factor que ayuda a prevenir y reducir la HTA,[17,22,23] el sobrepeso/obesidad,[18] la hiperlipidemia,[24,25] o la hiperglucemia.[25,26]

También se puede observar que existen evidencias claras de que unos niveles adecuados de AF están asociados a un menor riesgo de padecer enfermedades no transmisibles y, por tanto, a una mayor esperanza y calidad de vida.[14] Afortunadamente, parece que nunca es tarde para empezar a realizar AF. Para personas físicamente inactivas de mediana edad, comenzar a realizar AF de manera regular no solo está asociado con una ganancia de entre 1,2-3,7 años de vida, sino que también resulta ser efectivo para prevenir enfermedades CV.[27-29] Resultados similares fueron obtenidos en personas mayores.[30,31]

Junto a la AF, es importante destacar la dieta como un factor determinante en el riesgo de padecer enfermedades no transmisibles.[32] La prevalencia de obesidad era relativamente baja hasta la década de 1980, cuando comenzó un ascenso significativo.[33] En la contribución a este incremento, a parte de las facilidades del entorno para realizar cada vez menos AF, también hay que sumar la disponibilidad de comida barata, altamente procesada y, que juega un papel decisivo en el aumento de la prevalencia de obesidad.[34,35] Se calcula que el consumo de azúcar en Estados Unidos de América ha pasado de ser entre 1,8 y 2,7 kg de azúcar al año por persona a principios de 1800 a ser entre 68,0 y 77,1 kg al año por persona en la actualidad.[35] La mala alimentación no solo tiene como perjuicio las altas tasas de obesidad y sus problemas asociados, ya que distintos estudios epidemiológicos han demostrado también asociaciones fiables entre factores de la dieta y la morbilidad y mortalidad CV, diabetes tipo II o mortalidad por cualquier

causa.[32,36,37] En particular, el alto consumo de sodio, la carne procesada, las bebidas azucaradas y el bajo consumo de nueces, semillas, grasas omega-3, frutas y verduras han demostrado tener implicación en la mortalidad por causa cardiometabólica.[32]

Por tanto, vistos los efectos de los estilos de vida sobre la salud de la población, es un objetivo primordial poner el foco sobre ellos y promover una vida activa y una alimentación sana como dos ejes fundamentales en la prevención y el tratamiento de enfermedades.[17,18] En este sentido, hay que tener en cuenta que la supervisión de los/las profesionales debe ser un punto clave en este aspecto,[38,39] ya que esta supervisión profesional es una forma más efectiva de mejorar que las recomendaciones que puedan llegar a la población y sean posteriormente llevadas a cabo sin supervisión.[40,41] Se entiende como supervisión el seguimiento y control del proceso por un profesional especialista en el área, mientras que las recomendaciones son directrices que se aportan para animar y tratar de lograr los objetivos propuestos, pero no hay un seguimiento ni supervisión. Diferentes estudios que comparan grupos con EF supervisado por especialistas y grupos que solamente reciben recomendaciones de AF, demuestran que los/las participantes con EF supervisado obtienen mejoras superiores sobre factores de riesgo como el índice de masa corporal (IMC), la presión arterial (PA), la resistencia a la insulina o la capacidad cardiorrespiratoria (CCR).[40-42] De manera similar, el papel de los/las dietistas-nutricionistas está apoyado por la evidencia científica, y su contribución eficaz en la prevención, tratamiento o curación de las enfermedades está bien documentada, y su trabajo, a la vez que abarata el gasto sanitario evita el intrusismo, el sensacionalismo y los conceptos erróneos al respecto de la ciencia de la nutrición.[38,39]

Capítulo 2/Chapter 2

Marco teórico/Theoretical basis

2. Marco teórico

Las enfermedades CV son la primera causa de mortalidad en el mundo. En 2017 murieron 17,8 millones de personas por esta causa, lo que supone un 31,8% de todas las muertes.[43,44] En España la cifra en 2018 fue de 120 589 fallecidos, un 28,2% del total.[45] Entre los factores de riesgo CV, dos importantes factores modificables son la HTA y el sobrepeso/obesidad.

La HTA se define con valores superiores a 140 mmHg en la PA sistólica (PAS) y/o superiores a 90 mmHg en la PA diastólica (PAD) (Tabla 1), y también se considera a aquellas personas tratadas con medicación antihipertensiva como personas con HTA.[17] La HTA puede ser primaria o secundaria, entendiendo como HTA primaria aquella cuyas causas no son reconocibles, mientras que la HTA secundaria es debida a una causa identificable.[17] La HTA es un factor que contribuye en las muertes prematuras, estimándose que en 2015 contribuyó en casi 10 millones de muertes a nivel mundial,[46] mientras que en España se calcula que unas 40 000 muertes CV anuales son atribuibles a la HTA en personas con más de 50 años.[47] Además, desde 1990, se calcula que los años de vida ajustados por discapacidad atribuibles a la HTA han aumentado un 40%.[46] La PA tiene una relación independiente y continua con la incidencia de eventos CV (accidente cerebrovascular hemorrágico o isquémico, infarto de miocardio, muerte súbita, insuficiencia cardiaca y enfermedad arterial periférica).[48] De la misma forma, se ha demostrado relación entre la PA y la enfermedad renal en etapa terminal,[48] y la evidencia muestra que la HTA está vinculada a un mayor riesgo de desarrollar fibrilación auricular.[17] La relación continua entre la PA y el riesgo de eventos CV se ha demostrado a cualquier edad[49] y en cualquier grupo étnico.[50,51] Es importante tener estos datos en cuenta, ya que la prevalencia mundial de la HTA se estima que fue de 1 130 millones de personas en 2015,[52] y que globalmente la prevalencia en personas adultas está entre el 30% y el 45%.[53] En España se estima que el 42,2% de las personas adultas tiene HTA.[54] La HTA es más habitual cuanto mayor es la edad, con una prevalencia de más de un 60% en personas de más de 60 años.[53]

Tabla 1. Clasificación de la presión arterial y definición de los grados de hipertensión.

Categoría	PAS (mmHg)		PAD (mmHg)
Óptima	< 120	y	< 80
Normal	120 - 129	y/o	80 - 84
Normal - alta	130 - 139	y/o	85 - 89
Hipertensión grado 1	140 - 159	y/o	90 - 99
Hipertensión grado 2	160 - 179	y/o	100 - 109
Hipertensión grado 3	≥ 180	y/o	≥ 110
Hipertensión sistólica aislada	≥ 140	y	< 90

PAS: Presión arterial sistólica; PAD: Presión arterial diastólica. El grado de la hipertensión sistólica aislada se considera 1, 2 o 3 en función de los rangos indicados para los valores de PAS. Adaptado *Williams et al., 2018. 2018 ESC/ESH guidelines for the management of arterial hypertension.*[17]

Mientras la población siga envejeciendo, adoptando estilos de vida más sedentarios e incrementando la masa corporal (MC), la prevalencia de HTA seguirá creciendo, estimándose que en 2025 cerca de 1 500 millones de personas padecerán HTA.[55] Está demostrado que el sedentarismo y la inactividad física están relacionados con la HTA, ya que las personas que realizan menos AF tienden a tener la PA más alta.[22,56] Asimismo, tratamientos en estilos de vida que incluyen AF y dieta son capaces de reducir la PA, estando recomendados por las guías de control de la HTA,[17,22,23] y la evidencia científica concluye que la AF es capaz de reducir la PA tanto en personas hipertensas como en normotensas.[22] En un metanálisis se observó que programas de EF aeróbico conseguían descender la PAS en 3,84 mmHg y la PAD en 2,58 mmHg.[57]

Por su parte, el sobrepeso y la obesidad se definen como una acumulación anormal o excesiva de grasa que puede ser perjudicial para la salud.[58] El IMC es el indicador más utilizado para identificar el sobrepeso y la obesidad en personas adultas, considerándose sobrepeso cuando el IMC se encuentra entre 25 kg/m^2 y 29,9 kg/m^2 y obesidad cuando es igual o superior a 30 kg/m^2 (Tabla 2).[58] Aunque sea lo más utilizado, es importante tener otros factores en cuenta a la hora de diagnosticar el sobrepeso y la obesidad, ya que el IMC no nos indica la grasa corporal, a pesar de la buena correlación que existe entre ambas variables y la gran utilidad que tiene como

herramienta de seguimiento de la población.[59] Por ello, se recomienda también realizar otras mediciones como el perímetro de cintura, la bioimpedancia eléctrica, la pletismografía por desplazamiento de aire/agua o el DEXA para aportar una información más completa sobre la adiposidad corporal.[18,60] Diversos estudios demuestran que la obesidad aumenta el riesgo de padecer enfermedades CV, dislipidemia, diabetes tipo II, apnea de sueño, problemas respiratorios o algunos tipos de cáncer.[18,60] Asimismo, se asocia a un mayor riesgo de muerte por enfermedad CV o por cualquier causa.[18,60] Considerando estos datos, las cifras de sobrepeso y obesidad en la población son verdaderamente preocupantes. Según la OMS, en 2016 más de 1 900 millones de personas adultas tenían sobrepeso, de los cuales, más de 650 millones eran obesas; el 39% tenían sobrepeso y el 13% obesidad.[58] Entre 1975 y 2016, la prevalencia mundial de la obesidad se ha casi triplicado.[58] Por ello, la obesidad es considerada una pandemia global.[61] En España, los datos mostraban que en 2017 el 54,5% de la población adulta tenían un exceso de MC, un 37,1% sobrepeso y un 17,4% obesidad.[62]

Tabla 2. Clasificación de la Organización Mundial de la Salud del sobrepeso y la obesidad en base al IMC[58]

Clasificación	IMC (kg/m^2)	Riesgo
Normal	18,5 - 24,9	Promedio
Sobrepeso	25 - 29,9	Aumentado
Obesidad grado I	30 - 34,9	Moderado
Obesidad grado II	35 - 39,9	Severo
Obesidad grado III	≥ 40	Muy severo

IMC: Índice de masa corporal.

La AF es un factor clave en la prevención y el tratamiento del sobrepeso o la obesidad.[18] Una mayor MC está estrechamente relacionada a un estilo de vida sedentario y a una insuficiente AF.[60,63] Al igual que la HTA, éste es un factor de riesgo modificable y las principales recomendaciones para el tratamiento de la obesidad incluyen la AF y la dieta[18,60,64]. Se ha demostrado que programas de EF aeróbico eran efectivos a la hora de descender la MC en personas con obesidad.[18,60]

En la intervención del estudio EXERDIET-HTA se comprobó que en población con HTA y sobrepeso u obesidad, la combinación de una dieta hipocalórica y EF aeróbico supervisado dos veces por semana era una herramienta no farmacológica óptima para el descenso tanto de la PA como de la MC y mejora de la composición corporal.[65]

2.1. Relación entre hipertensión arterial y sobrepeso y obesidad

La HTA y el sobrepeso o la obesidad coexisten frecuentemente en una misma persona y la combinación de ambas está reconocida como una causa preeminente de riesgo CV.[66,67] Así, se estima que al menos el 75% de la incidencia de la HTA está directamente relacionada con la obesidad.[68] Entre las personas con obesidad se mostró que un 42,5% tenían HTA, en personas con sobrepeso este porcentaje era del 27,8%, mientras que en personas con normopeso era del 15,3%.[69] Varios estudios han demostrado también la importancia de la ganancia de MC en la elevación de la PA y de la bajada de MC en la reducción de la PA.[66] A través de modelos de regresión, un estudio calculó que la PAS incrementaba 1 mmHg por cada ganancia de 1,7 kg/m^2 y 4,5 cm en hombres o 1,3 kg/m^2 y 2,5 cm en mujeres en el IMC y el perímetro de cintura, respectivamente.[70]

Son varios los posibles mecanismos que provocan un aumento de la PA en las personas con obesidad. La estimulación del sistema nervioso simpático es uno de estos mecanismos, ya que se observa que su actividad está aumentada en las personas obesas, estimulando la termogénesis y el metabolismo basal como intento de estabilizar la MC, lo cual se ve acompañado por una estimulación simpática renal (retención de sodio), mayores niveles plasmáticos de catecolaminas y una vasoconstricción que provocarían el aumento de la PA.[66,71,72] Otro de los mecanismos responsables es el aumento de la activación del sistema renina-angiotensina-aldosterona, que está provocado por una mayor resistencia a la insulina y producción de angiotensina en el tejido adiposo, y que resulta en una retención de sodio y agua

e incremento del volumen circulante, provocando un incremento de la PA.[66,67,71] Otros mecanismos que también pueden provocar el aumento de la PA serían las alteraciones sobre el metabolismo lipídico, el aumento de ácidos grasos libres, la resistencia parcial a la leptina (que estimula el sistema nervioso simpático), la disfunción del tejido adiposo y la disfunción endotelial.[66,71,72]

2.2. El perfil cardiometabólico y bioquímico

Además de coexistir con la HTA, habitualmente la obesidad coexiste con enfermedades como la diabetes tipo II, dislipidemias, etc.[73] No obstante, no todas las personas con obesidad tienen alteraciones metabólicas. Se calcula que entre un 10% y 25% de ellas no presentan ni resistencia a la insulina, ni dislipidemias, ni ningún otro factor de riesgo que con frecuencia está relacionado con la obesidad.[73] Cuando esto sucede, se plantea el concepto de la obesidad metabólicamente sana (ObMS). Se podría indicar, por tanto, que la ObMS es la de una persona que se presenta con un IMC > 30 kg/m^2, pero que no tiene ningún desorden cardiometabólico definido. De todas formas, hay que tener en cuenta que el concepto de ObMS no quiere decir que las personas en esta condición estén completamente sanas, ya que se debe recordar que la obesidad es por sí misma perjudicial para la salud, pues se relaciona independientemente con el riesgo CV o de muerte por cualquier causa.[18,64] Se ha podido concluir que la ObMS no es una condición benigna, pues respecto a las personas con normopeso metabólicamente sanas existe un mayor riesgo de muerte o de evento CV.[74]

Se presentan diferentes criterios a la hora de definir la ObMS, concepto del cual deriva una forma de clasificar a las personas, teniendo en cuenta varios marcadores cardiometabólicos.[75] De este modo, la clasificación enmarca diferentes tipos en función de las variables analizadas: personas con ObMS, con obesidad metabólicamente enfermas (ObME), con sobrepeso metabólicamente sanas (SobMS), con sobrepeso metabólicamente enfermas, con normopeso

metabólicamente sanas o con normopeso metabólicamente enfermas.[75] Entre las distintas clasificaciones tenemos las de Wildman, Wildman modificada y Consensus Societies (Tabla 3).[75]

El porqué de este concepto es cuestionar si la morbimortalidad de las personas con ObMS es igual que la de las personas con normopeso. La revisión sistemática de Eckel nos muestra que las personas con ObMS siguen teniendo un riesgo mayor que las personas con normopeso metabólicamente sanas.[74] Sin embargo, su riesgo era menor que el de las personas con ObME y también de las personas con normopeso metabólicamente enfermas. Estos datos revelan que las personas con obesidad, HTA e inactivas deberían tener como un objetivo prioritario lograr ser metabólicamente sanos, siendo una primera meta en la mejora de salud la ObMS o el SobMS.[76,77] Un metanálisis encontró que las personas con ObMS tenían niveles de AF y de CCR superiores a las personas con ObME, y que pasaban menos tiempo en comportamientos sedentarios, por lo que se sugería que un perfil metabólico sano podría ser debido a un estilo de vida más saludable.[78] Por ello, diferentes autores/as consideran que la CCR debe ser un criterio a tener en cuenta en la salud metabólica, y que podría ayudar a identificar a las personas con ObMS.[74]

Tabla 3. Clasificaciones de Wildman, Wildman modificada y Consensus Societies para la obesidad metabólicamente sana.

WILDMAN	WILDMAN MODIFICADA	CONSENSUS SOCIETIES Síndrome metabólico
ANORMALIDADES CARDIOMETABÓLICAS	**ANORMALIDADES CARDIOMETABÓLICAS**	**ANORMALIDADES CARDIOMETABÓLICAS**
1- PA elevada: PAS/PAD ≥ 130/85 mmHg o uso de medicación antihipertensiva	**1- PA elevada**: PAS/PAD ≥ 130/85 mmHg o uso de medicación antihipertensiva	1- **Circunferencia de cintura elevada:** ≥ 94 cm en hombres y ≥ 80 cm en mujeres
2- Nivel de triglicéridos elevado: nivel de triglicéridos en ayunas ≥ 150 mg/dL	**2- Nivel de triglicéridos elevado**: nivel de triglicéridos en ayunas ≥ 150 mg/dL	**2- Nivel de triglicéridos elevado**: nivel de triglicéridos en ayunas ≥ 1,7 mmol/L
3- Nivel de HDL-C reducido: nivel de HDL-C < 40 mg/dL en hombres o < 50 mg/dL en mujeres o uso de medicación hipolipemiante	**3- Nivel de HDL-C reducido**: nivel de HDL-C < 40 mg/dL en hombres o < 50 mg/dL en mujeres o uso de medicación hipolipemiante	**3- Nivel de HDL-C reducido**: nivel de HDL-C < 1 mmol/L en hombres o < 1,3 mmol/L en mujeres
4- Nivel de glucosa elevado: nivel de glucosa en ayunas ≥ 100 mg/dL o uso de medicación antidiabética	**4- Nivel de glucosa elevado**: nivel de glucosa en ayunas ≥ 100 mg/dL o uso de medicación antidiabética	**4- Nivel de glucosa elevado**: nivel de glucosa en ayunas ≥ 5,6 mmol/L o tratamiento farmacológico
5- Resistencia a la insulina: HOMA-IR > 5,13 (*i.e.*, el percentil 90)	**5- Resistencia a la insulina**: HOMA-IR ≥ 3,8 (*i.e.*, el percentil 90)	**5- PA elevada**: PAS/PAD ≥ 130/85 mmHg o uso de medicación antihipertensiva o antecedentes de hipertensión
6- Inflamación sistémica: niveles de CRP > 0,1 mg/L (*i.e.*, el percentil 90)	**6- Inflamación sistémica**: niveles de CRP > 3 mg/L (*i.e.*, el percentil 90)	----------
Categorías en base a las anormalidades y el IMC	**Categorías en base a las anormalidades y el IMC**	**Categorías en base a las anormalidades y el IMC**
Normopeso metabólicamente sano: IMC < 25 kg/m^2 y < 2 anormalidades cardiometabólicas	**Normopeso metabólicamente sano**: IMC < 25 kg/m^2 y < 2 anormalidades cardiometabólicas	**Normopeso metabólicamente sano**: IMC < 25 kg/m^2 y < 3 anormalidades cardiometabólicas
Normopeso metabólicamente enfermo: IMC < 25 kg/m^2 y ≥ 2 anormalidades cardiometabólicas	**Normopeso metabólicamente enfermo**: IMC < 25 kg/m^2 y ≥ 2 anormalidades cardiometabólicas	**Normopeso metabólicamente enfermo**: IMC < 25 kg/m^2 y ≥ 3 anormalidades cardiometabólicas
Sobrepeso metabólicamente sano: IMC 25,0 - 29,9 kg/m^2 y < 2 anormalidades cardiometabólicas	**Sobrepeso metabólicamente sano**: IMC 25,0 - 29,9 kg/m^2 y < 2 anormalidades cardiometabólicas	**Sobrepeso metabólicamente sano**: IMC 25,0 - 29,9 kg/m^2 y < 3 anormalidades cardiometabólicas
Sobrepeso metabólicamente enfermo: IMC 25,0 - 29,9 kg/m^2 y ≥ 2 anormalidades cardiometabólicas	**Sobrepeso metabólicamente enfermo**: IMC 25,0 - 29,9 kg/m^2 y ≥ 2 anormalidades cardiometabólicas	**Sobrepeso metabólicamente enfermo**: IMC 25,0 - 29,9 kg/m^2 y ≥ 3 anormalidades cardiometabólicas
Obesidad metabólicamente sana: IMC ≥ 30 kg/m^2 y < 2 anormalidades cardiometabólicas	**Obesidad metabólicamente sana**: IMC ≥ 30 kg/m^2 y < 2 anormalidades cardiometabólicas	**Obesidad metabólicamente sana**: IMC ≥ 30 kg/m^2 y < 3 anormalidades cardiometabólicas
Obesidad metabólicamente enferma: IMC ≥ 30 kg/m^2 y ≥ 2 anormalidades cardiometabólicas	**Obesidad metabólicamente enferma**: IMC ≥ 30 kg/m^2 y ≥ 2 anormalidades cardiometabólicas	**Obesidad metabólicamente enferma**: IMC ≥ 30 kg/m^2 y ≥ 3 anormalidades cardiometabólicas

PA: Presión arterial; PAS: PA sistólica; PAD: PA diastólica; HDL-C: Colesterol de lipoproteína de alta densidad; HOMA-IR: Modelo homeostático para evaluar la resistencia a la insulina; CRP: Proteína C reactiva; IMC: Índice de masa corporal. Adaptada de *Martínez-Larrad et al., 2014. Profile of individuals who are metabolically healthy obese using different definition criteria. A population-based analysis in the Spanish population.*[75]

Unido al perfil cardiometabólico se encuentra el análisis del perfil bioquímico, que es de una gran importancia para la población general y aún más para la población con HTA y sobrepeso u obesidad, debido al riesgo añadido que supone esta condición a la hora de tener una anormalidad en el perfil.[75] Como se observa en la Tabla 3, la valoración de algunos componentes del perfil bioquímico es fundamental a la hora de categorizar a las personas como metabólicamente sanas o enfermas. Además, es conocido que las concentraciones de las distintas variables extraídas en un análisis del perfil bioquímico y las anormalidades en sus componentes se asocian a un mayor riesgo de padecer distintas enfermedades (enfermedades CV, síndrome metabólico o diabetes tipo II, entre otras).[24,79,80] En ocasiones, los componentes del perfil bioquímico son parte del diagnóstico de algunas enfermedades, como es el caso de la esteatosis hepática no alcohólica (enzimas hepáticas),[81] la diabetes tipo II (glucosa, insulina, hemoglobina glicosilada (HbA1c)),[82] o las dislipidemias (variables del perfil lipídico).[83]

Entre los componentes del perfil bioquímico está la proteína C reactiva (CRP), un marcador inflamatorio que es frecuentemente utilizado como predictor de eventos CV,[84] y que también ha demostrado tener relación con el síndrome metabólico cuando los niveles de la CRP son elevados.[85,86] Hay varios estudios que observan relación positiva entre la MC y la CRP y que demuestran que una bajada en la MC produce reducciones en la concentración de CRP.[87-89]

Las enzimas hepáticas son otro componente del perfil, entre las que encontramos la aspartato transaminasa (AST), alanina transaminasa (ALT) y la gamma-glutamil-transferasa (GGT). Éstas son índices primarios utilizados para reflejar el nivel graso del hígado,[90,91] y se ha mostrado que un nivel elevado en las enzimas hepáticas es predictor de numerosos problemas de salud, incluyendo el síndrome metabólico, la diabetes tipo II, enfermedades CV y la muerte prematura.[80,90,92-95] Estas enzimas son marcadores de inflamación hepática, y la inflamación hepática está asociada con la inflamación sistémica, lo cual ayuda a explicar el mayor riesgo de

morbilidad y mortalidad que existe cuando los niveles sanguíneos de las enzimas hepáticas son elevados.[96,97]

Por su parte, estudios epidemiológicos han demostrado los efectos independientes de las anormalidades lipídicas como factores de riesgo de enfermedad CV.[98,99] Se ha encontrado una relación directa entre los niveles de colesterol de lipoproteína de baja densidad (LDL-C) y la tasa de aparición de enfermedades coronarias,[24] y la reducción de estos niveles ha demostrado ser una forma de disminuir el riesgo de padecer eventos CV.[100] El alto nivel de triglicéridos (TG) también se asocia a un mayor riesgo CV,[101] y las concentraciones bajas de colesterol de lipoproteína de alta densidad (HDL-C) aumentan el riesgo de padecer o morir por enfermedades coronarias.[24] Aunque niveles altos de LDL-C o de TG y niveles bajos de HDL-C han demostrado ser por sí mismos aterogénicos, no es raro que estas tres anormalidades se presenten simultáneamente dando lugar a la tríada lipídica, la cual tiene un riesgo añadido.[24]

Por otro lado, los niveles sanguíneos de glucosa, insulina y HbA1c son parte del diagnóstico de la diabetes tipo II,[82] y son también considerados factores de riesgo CV,[102,103] aparte de que sus alteraciones aumentan el riesgo de cáncer o de muerte por cualquier causa.[104,105] La resistencia a la insulina, medida a través del modelo homeostático para evaluar la resistencia a la insulina (HOMA-IR), también ha demostrado ser un predictor de eventos CV y de mortalidad a tener en cuenta.[106-108]

Afortunadamente, los componentes del perfil bioquímico son factores de riesgo modificables, y se ha demostrado la posibilidad de mejorar a través de estilos de vida saludables que incluyen la práctica regular de AF y una dieta equilibrada.[24,25,109]

2.3. Capacidad cardiorrespiratoria

La CCR es descrita como la capacidad que tienen los sistemas respiratorio y circulatorio de suministrar oxígeno a la musculatura esquelética durante una AF continuada.[110,111] La CCR es uno de los componentes de la condición física vinculada a la salud que más relevancia científica y clínica ha adquirido.[111,112] La medida principal de la CCR es el consumo máximo de oxígeno ($\dot{V}O_{2max}$), que se define como el máximo volumen de oxígeno que el organismo es capaz de absorber, transportar y consumir en un tiempo determinado durante un EF extenuante.[110]

Se ha comprobado que un nivel bajo de CCR está asociado con un mayor riesgo de padecer enfermedades CV y mortalidad por cualquier causa, así como a un mayor ratio de mortalidad atribuible a varios tipos de cáncer, especialmente el de mama o el de colon/tracto digestivo.[113-116] También se ha observado que por cada incremento de un equivalente metabólico (MET) en la CCR el riesgo de mortalidad por cualquier causa descendía entre un 10% y un 25%,[110,111,117] y que una CCR menor a 5 METs está asociada a un mayor riesgo de mortalidad, mientras que niveles superiores a 8-10 METs, ya se asocian a una protección relativa y mayor supervivencia.[117-122] Por todo ello, la CCR está considerada un signo vital y una variable clave de interés para médicos y pacientes.[110,111]

Además, en algunos estudios se ha observado que la CCR también parece estar asociada al perfil bioquímico, ya que en la población general se ha observado que una CCR alta previene de la aparición de diabetes tipo II o el síndrome metabólico.[123,124] También se ha relacionado una mayor CCR a concentraciones menores de CRP, AST y ALT en personas con sobrepeso,[87,90] así como a una mayor concentración de HDL-C y a una menor incidencia de hipercolesterolemia.[125] Estas relaciones que se han hallado en distintas poblaciones no se han estudiado específicamente en una población con HTA y sobrepeso/obesidad, por lo que se requiere más investigación para poder concluir qué relaciones existen entre la CCR y el perfil bioquímico.

Factores que influencian la CCR son la edad, el sexo, la etnia o los estilos de vida, que es el punto principal en el que fijarse cuando se busca la mejora de la CCR.[126] En especial la práctica de EF regular es un componente fundamental a la hora de mejorar la CCR, y el EF aeróbico es el más adecuado para conseguir una mayor mejora,[111] lo cual disminuye el riesgo CV debido a diferentes adaptaciones fisiológicas.[110] Una de ellas es el aumento de las cavidades del corazón, que mejora su capacidad de llenado, incrementando el volumen cardiaco. Debido a este incremento, también aumenta el volumen sistólico, y con ello la cantidad de sangre expulsada por el corazón por minuto (gasto cardiaco). Esto resulta en un descenso de la frecuencia cardiaca de reposo y submáxima, ya que cada latido es capaz de expulsar más sangre y aportar más oxígeno a la musculatura esquelética. En consecuencia, en un mismo esfuerzo mecánico se consiguen descender las pulsaciones tras un periodo de entrenamiento. Además, también se pueden conseguir descensos en la PA de reposo y valores submáximos, experimentando incrementos más suaves durante el EF. Igualmente, el EF aeróbico produce una vasodilatación que provoca la disminución de las resistencias vasculares periféricas y, por tanto, reducir la PA durante el EF.[127]

Por todo lo explicado, la valoración de la CCR a través de pruebas de esfuerzo es clínicamente relevante en la evaluación del riesgo CV.[110] Existen muchas pruebas para la valoración directa o indirecta de la CCR, siendo el método de referencia a través de descriptores fisiológicos que determinan la intensidad del esfuerzo metabólico ($\dot{V}O_{2max}$ o consumo de oxígeno pico, $\dot{V}O_{2pico}$), la prueba cardiopulmonar limitada por síntomas.[110,111,128] Los métodos directos son los más precisos para determinar el $\dot{V}O_{2pico}$, bajo condiciones controladas en laboratorio y con aparatos de ergometría que permitan analizar los gases ($\dot{V}O_2$ y producción de dióxido de carbono, $\dot{V}CO_2$) de la persona que realiza la prueba.[111]

2.4. Tratamiento dietético

Entre los cambios en el estilo de vida que se recomiendan para la prevención y el tratamiento del riesgo CV se encuentra una alimentación saludable. La alimentación es clave en el descenso o mantenimiento de la MC y de la PA y en el control de otros factores de riesgo.[17,22,23]

En personas con sobrepeso/obesidad la reducción calórica es el componente más importante a la hora de lograr la pérdida de MC, así como el aumento y mantenimiento de la AF es de vital importancia a la hora de mantener la pérdida lograda previamente en la MC. Esta pérdida es dependiente fundamentalmente de la reducción de la ingesta calórica total, no de las proporciones de los macronutrientes (hidratos de carbono, grasas y proteínas),[129] que deben ser determinadas por el/la dietista-nutricionista en conformidad a la situación clínica de la persona valorada.[130] La calidad y composición de la dieta es un factor de riesgo modificable con efectos probados en la prevención de enfermedades CV y la mortalidad.[131]

A este respecto, la dieta DASH (siglas del inglés, *Dietary Approaches to Stop Hypertension*) ha demostrado ser efectiva para reducir la PA, pero los beneficios no están únicamente limitados a esta reducción, ya que también se han registrado mejoras significativas en la resistencia a la insulina, concentración de glucosa, el perfil lipídico o prevención de enfermedades CVs y reducción en la mortalidad por todas las causas.[132,133] La dieta DASH es un patrón dietético que promueve el consumo de frutas, verduras y productos lácteos bajos en grasa, y que incluye granos enteros, pescado, aves y frutos secos. A su vez, intenta reducir el consumo de carne roja, dulces, bebidas azucaradas, grasa total, grasas saturadas y colesterol.[134] Por tanto, la dieta DASH promueve una mayor ingesta de nutrientes protectores como el sodio, calcio, magnesio, fibra y proteínas vegetales, al mismo tiempo que limita los hidratos de carbono refinados y grasas saturadas.[135] La dieta es en cuanto a la distribución de los macronutrientes baja en grasa (<30% de la energía), tiene un mayor aporte de energía derivada de las proteínas respecto a las recomendaciones habituales (≈18% de la energía), y algo superior de lo habitual en hidratos de

carbono (≈55% de la energía).[134] Además, se ha mostrado que la reducción del aporte de sal en la dieta DASH aumenta la eficacia en la reducción de la PA.[135] Así, la dieta DASH está recomendada por las distintas guías americanas y europeas de prevención y tratamiento de la HTA.[22,23,135]

2.5. Ejercicio físico como tratamiento

Realizar EF de manera regular está altamente recomendado para la prevención y tratamiento tanto de la HTA como de la obesidad, y todas las guías internacionales promueven la práctica de EF para el descenso del riesgo CV y de la mortalidad.[17,18,20,136] El EF afecta de forma favorable a varios factores de riesgo CV: reduce la PA, la MC, la adiposidad visceral y total, el perímetro de cintura, provoca un aumento en el uso de la glucosa e incremento de la sensibilidad a la insulina, de concentraciones de lipoproteínas de alta densidad, reducción de concentraciones de lipoproteínas de baja densidad y aumento de la CCR.[20,23,136,137]

En la literatura se encuentran estudios que analizan la respuesta al EF de la PA, composición corporal, perfil bioquímico y CCR con EF de diferente frecuencia (sesiones/semana), intensidad (ligera, moderada, vigorosa), tiempo (duración del programa de EF y de los entrenamientos) y tipo (resistencia, fuerza, velocidad, flexibilidad o coordinación). Estos cuatro componentes forman el principio FITT.[138,139] Para reducir la PA, las recomendaciones de las instituciones internacionales presentan el EF aeróbico como principal método de entrenamiento.[17,22,23] El EF aeróbico se puede diseñar de forma continua o interválica. El EF aeróbico continuo se lleva a cabo en un periodo de tiempo de forma continua a una intensidad constante; y el EF aeróbico interválico alterna periodos a diferentes intensidades.[139,140]

En general, parece haber un consenso en recomendar el EF aeróbico continuo de intensidad moderada como terapia antihipertensiva, pero las últimas guías de práctica clínica europeas y americanas también avalan el EF interválico de intensidad vigorosa, a la vez que recomiendan

complementar el entrenamiento aeróbico con el de fuerza para beneficios adicionales.[17,23,138-140] Para el tratamiento de la obesidad las guías aconsejan combinar el entrenamiento aeróbico, para la disminución de la MC, con tres sesiones de entrenamiento de fuerza no consecutivas a la semana, que ayuden a mejorar la composición corporal, aumentando masa muscular y disminuyendo masa grasa.[18,141]

Las directrices de las guías se basan fundamentalmente en mejorar los indicadores de riesgo CV más conocidos, como la PA, composición corporal, el perfil lipídico, la resistencia a la insulina o la CCR.[17,23,138,140] En el caso de la CCR, varios estudios han demostrado que el EF aeróbico interválico de intensidad vigorosa la mejora en mayor medida que el EF aeróbico continuo de intensidad moderada.[142-145]

En términos del principio FITT, las recomendaciones actuales de EF aeróbico para la prevención de riesgo CV son:[17,20,139]

- Frecuencia: al menos 3 sesiones a la semana, preferiblemente a diario.
- Intensidad: moderada (64-76% de la frecuencia cardiaca máxima) o vigorosa (77-93% de la frecuencia cardiaca máxima).
- Tiempo: mínimo 150 minutos de AF moderada o 75 minutos de AF vigorosa por semana. Es posible combinar intensidades, y para un control más exhaustivo de la MC se recomienda mayor volumen, sesiones de mayor duración (60-90 minutos al día).
- Tipo: EF continuo y EF interválico (caminar, nadar, bicicleta…).

Asimismo, se recomienda realizar entrenamiento de fuerza muscular dinámica (calistenia, bandas elásticas…) al menos dos veces a la semana, realizando 2-3 series de 8-12 repeticiones al 60-80% de la repetición máxima individual. También se recomienda, sin una dosis específica, el trabajo de equilibrio, agilidad, coordinación y marcha.[17,20]

2.6. Ejercicio físico supervisado y no supervisado

En el estudio EXERDIET-HTA ya se demostró que en personas con sobrepeso/obesidad e HTA, una intervención de 16 semanas con EF aeróbico y dieta hipocalórica mejoraba la composición corporal, la PA y la CCR y, por ello, la salud cardiometabólica, en todos sus grupos.[65] Además, el grupo de atención-control (AC, dieta hipocalórica, pero solo recomendaciones de AF) no mejoraba tanto como los tres grupos que sumado a la dieta incluían EF supervisado, siendo estos: 1) grupo con EF de alto volumen e intensidad moderada de tipo continuo (HV-MICT, 45 minutos), 2) grupo con EF de alta intensidad de tipo interválico y volumen alto (HV-HIIT), y 3) grupo con EF de alta intensidad de tipo interválico y volumen bajo (LV-HIIT, 20 minutos).[65] Estos resultados vienen refrendados por distintos estudios que demuestran que realizar EF supervisado y dieta es eficaz para mejorar los distintos factores de riesgo CV.[17,25,109]

Estos datos son de gran valor y se puede concluir que este tipo de intervenciones son efectivas para las personas con sobrepeso/obesidad e HTA a la hora de mejorar la salud cardiometabólica, pero un objetivo importante que debe perseguirse es que el cambio no sea temporal y que los estilos de vida sean saludables de una manera sostenida en el tiempo.[17,18] Por tanto, sería interesante analizar los efectos que puede tener el cese del EF supervisado, y así saber si el efecto de las intervenciones, cuando éstas finalizan y no hay supervisión por parte de profesionales, es duradero a largo plazo. Los efectos del cese del EF supervisado o desentrenamiento han sido estudiados en deportistas de alto nivel,[146-148] pero no existen muchos datos en otras poblaciones, y además los resultados de los estudios son en ocasiones discordantes. Por ejemplo, un estudio en personas prehipertensas y con obesidad observaba que, tras dos semanas del cese del EF supervisado, los niveles de PA que había conseguido descender tras el programa de EF volvían a ascender.[149] Sin embargo, personas con síndrome metabólico conseguían mantener los niveles de PA un mes después del cese del

entrenamiento.[150] De forma similar, mientras un estudio en personas con enfermedad arterial coronaria veía como las mejoras se revertían en la composición corporal tras un periodo sin EF supervisado,[151] en otro estudio, mujeres con diabetes tipo II no variaban su composición corporal tras el cese del EF supervisado.[152]

Esta discrepancia en los resultados puede deberse a las características de cada estudio en cuanto a la población estudiada, la duración de la intervención, el tipo de EF realizado o la duración del tiempo sin supervisión hasta la realización de nuevas pruebas, ya que existe poca homogeneidad en estos aspectos en los estudios existentes. Se requiere más investigación y añadir nuevos resultados para poder extraer conclusiones más claras acerca de la influencia del cese de intervenciones que incluyen EF sobre la salud cardiometabólica. Asimismo, no se encuentran datos en personas con hipertensión y sobrepeso/obesidad, lo cual pone en relieve el valor de estudiar los efectos del cese de una intervención de EF aeróbico y dieta hipocalórica.

Capítulo 3/Chapter 3

Hipótesis y objetivos/Hypotheses and objectives

3. Objetivos e hipótesis

Por todo lo expuesto anteriormente, los objetivos principales de la investigación y las hipótesis planteadas en base a estos objetivos, abordadas en las tres publicaciones que forman parte de esta tesis, fueron:

- En el primer artículo, titulado "*Is cardiorespiratory fitness independently associated with the biochemical profile in overweight/obese adults with primary hypertension? The EXERDIET-HTA study*",[153] el objetivo fue establecer las asociaciones entre la CCR y el perfil bioquímico en personas adultas con HTA, sobrepeso u obesidad y físicamente inactivas. La hipótesis fue que una mayor CCR estaría asociada a un mejor perfil bioquímico, y que esta asociación sería independiente.
- En el segundo artículo, titulado "*Long-Term Effects in the EXERDIET-HTA Study: Supervised Exercise Training vs. Physical Activity Advice*",[154] el objetivo principal fue determinar si, en esta población, las mejoras obtenidas después de una intervención de 16 semanas con dieta hipocalórica y EF aeróbico supervisado en CCR, PA y composición corporal son mantenidas tras un periodo de 6 meses (6M) sin supervisión. Además, el objetivo secundario fue establecer si el tipo de EF aeróbico realizado durante las 16 semanas de intervención afecta a los cambios que se producen tras el periodo de 6M sin supervisión. Las hipótesis fueron que después de las 16 semanas de intervención, la CCR, la PA y la composición corporal empeorarían tras un periodo de 6M sin supervisión, pero los datos serían mejores que los previos a la intervención, y que las personas participantes que durante la intervención realizaban EF interválico de alta intensidad empeorarían menos que aquellas que realizaban EF continuo a intensidad moderada o aquellas de grupo control, con solo dieta y recomendaciones de AF.
- En el tercer artículo, titulado "*A Metabolically Healthy Profile Is a Transient Stage When Exercise and Diet Are Not Supervised: Long-Term Effects in the EXERDIET-HTA Study*",[155]

el objetivo fue determinar, en esta población, las diferencias en el perfil metabólico después una de intervención de 16 semanas con dieta hipocalórica y EF aeróbico supervisado y analizar si los cambios observados tras ese periodo son mantenidos tras un periodo de 6M sin supervisión. La hipótesis fue que el perfil metabólico de las personas participantes en la investigación evolucionaría de ser ObME antes de la intervención a SoMS después de la intervención. Tras el periodo de 6M no supervisado, el perfil regresaría a ObMS.

Capítulo 4/Chapter 4

Métodos/Methods

4. Methods

4.1. Study design

The EXERDIET-HTA study is a multi-arm parallel, randomized, single-blind controlled experimental trial (www.clinicaltrials.gov, number NCT02283047). The longitudinal data were collected between September 2013 and January 2018. The Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) and Clinical Investigation of Araba University Hospital (2015-030) approved the study design, protocols, and informed consent.

After baseline measurements, participants were randomly allocated in one of the four intervention groups stratified by sex, systolic blood pressure (SBP), body mass index (BMI), and age using a time-blocked computerized randomization program. The participants were followed during the intervention for 16 weeks, and after the intervention, all participants received diet and physical activity advice for the following six months (6M). In that period, participants were not supervised. All 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. The study design is graphically explained in Figure 1.

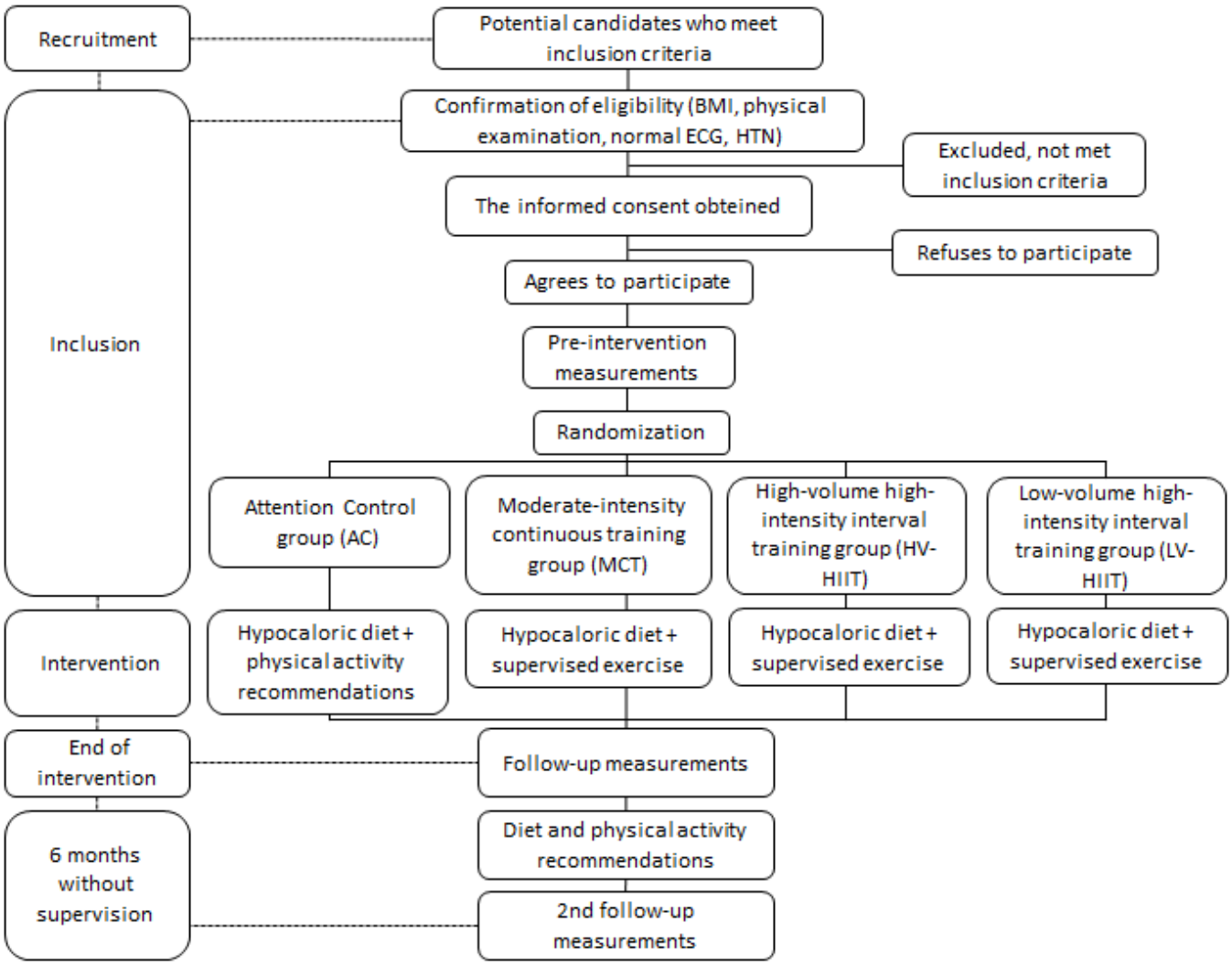

Figure 1. Flow diagram of the EXERDIET-HTA study from recruitment to the end of the intervention. Adapted from *Maldonado-Martín et al., 2016. Effects of Different Aerobic Exercise Programs with Nutritional Intervention in Primary Hypertensive and Overweight/Obese Adults: EXERDIET-HTA Controlled Trial*[156].

4.2. Participants

Adults with primary hypertension (HTN), overweight/obesity, and non-physically active took part in the EXERDIET-HTA study. All participants volunteered to participate in the study, located in Vitoria-Gasteiz (Araba/Álava, Basque Country, Spain), and they recruited from the cardiology services and local media. All candidates of the study completed the informed consent process before any test. After it, the candidate underwent anthropometric assessment and was selected for the study if BMI > 25 kg/m^2. The Physical Activity Questionnaire (IPAQ) was conducted to

ensure that participants were non-physically active according to the global recommendations on physical activity for health by the World Health Organization.[157] Participants with no diagnosis of HTN were evaluated with ambulatory blood pressure monitoring (ABMP) to make certain the HTN status by the cardiologist, defined as SBP of 140–179 mmHg and/or diastolic blood pressure (DBP) of 90–109 mmHg and/or under antihypertensive pharmacological treatment.[23] All other inclusion and exclusion criteria are specified in Table 4.

Table 4. Inclusion and exclusion criteria for EXERDIET-HTA study.

Inclusion criteria	Age: 18 – 65 years old
	Diagnosis of primary HTN, 1-2 stage defined as SBP 140-179 mmHg and/or DBP 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; anaemias, bleeding disorders, chronic thrombotic disorders, or hypercoagulable states; malignancies in the past 5 years, except for skin cancer therapeutically controlled; endocrine and metabolic disorders; including type 1 diabetes; 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 for more than 2 weeks
	To have participated in a diet-weight-loss program during last year

Adapted from *Maldonado-Martín et al., 2016. Effects of Different Aerobic Exercise Programs with Nutritional Intervention in Primary Hypertensive and Overweight/Obese Adults: EXERDIET-HTA Controlled Trial.*[156]

The number of participants varied slightly in each article due to the data availability and the moment when the study was performed. The first published article (*i.e.*, "*Is cardiorespiratory fitness independently associated with the biochemical profile in overweight/obese adults with primary hypertension? The EXERDIET-HTA study*")[153] was analyzed and written in 2017, and the available data at that moment was taken from the 2013-17 years of the EXERDIET-HTA study. Further, as the first article only considered the pre-intervention data, nine participants from a previous pilot-study that meeting the inclusion criteria were added to the analysis. Thus, the number of participants of the first article was 214 (n = 138 men, n = 76 women).

The data of the second article (*i.e.*, *"Long-term effects in the EXERDIET-HTA study: supervised exercise training vs. physical activity advice")*[154] were taken from the 2013-18 years of the EXERDIET-HTA study. Two-hundred and twenty-four participants took part in the study. However, 15 participants left the study during the intervention and 19 more did not attend the 6M assessment. Therefore, 190 participants (n = 126 men and n = 64 women) completed all three visits and were included in all analyses.

The third article (*i.e., "A metabolically healthy profile is a transient stage when exercise and diet are not supervised: long-term effects in the EXERDIET-HTA study")*[155] analyzed the metabolic profile of participants, and some participants did not have the data, taken from the 2013-18 years of the EXERDIET-HTA study. Two-hundred and nineteen participants were considered at pre-intervention, and 177 participants (n = 114 men and n = 63 women) completed all three visits and were included in all analyses.

4.3. Measurements

4.3.1. Anthropometry and body composition

Measurements were taken in accordance with guidelines from the International Society for the Advancement of Kinanthropometry. Stature (SECA 213, Hamburg, Germany), total body mass (BM, SECA 869, Hamburg, Germany), BMI, waist and hip circumferences, and waist-to-hip ratio (SECA 200, Hamburg, Germany). Fat-free mass, total body water, and fat body mass were estimated using a Tanita bio-impedance device (BF 350, Tokyo, Japan), according to the general instructions by the manufacture and the theory and fundamentals of bioimpedance analysis.[158]

4.3.2. Blood pressure

An ABPM recorder (6100-Welch Allyn, New York, USA) was used during a 24-hr period. Following the European guidelines,[23] measures were taken at 30 min intervals during the daytime and 60 min during night time. Participants self-disclosed their typical bedtime and wake up time, and this was used to define the automated 30 min and 60 min day/night time intervals.[156] Recorded data were downloaded with the participant`s presence in order to ensure the actual bedtime and wake-up time and to correct it in case of change. The recording was accepted when at least 75% of the recordings were obtained.

4.3.3. Cardiorespiratory fitness

Participants' cardiorespiratory fitness (CRF), defined as peak oxygen uptake ($\dot{V}O_{2peak}$) was assessed by a symptom-limited cardiopulmonary exercise test (CPET) on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). The testing protocol started with 40W with gradual increments of 10W every minute to exhaustion with continuous electrocardiogram monitoring, cadence was maintained at ~70 rpm throughout. During the CPET, participants were encouraged verbally by the laboratory technician and a medical doctor. $\dot{V}O_{2peak}$ was determined using a commercially available metabolic cart (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. 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 of ≥ 1.1, 3) achieving >85% of age-predicted maximum heart rate (HR), and 4) a plateau in oxygen uptake and/or HR.[128] Blood pressure was assessed every two minutes (Lode Excalibur automated BP module), and self-reported Borg scale (6 to 20 scale) was recorded at the end of each stage. After completion of the test, participants remained on the bike for five minutes of passive recovery with electrocardiogram and BP monitoring. Ventilatory thresholds (*i.e.*, VT1 and VT2) were assessed by standardized methods using the V-slope and ventilator equivalents.[128] The identification of the thresholds determined the three exercise intensity ranges for exercise design. 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. R3: high to severe intensity exercise intensity with HR values up to VT2 to peak intensity. When the identification of the VT2 was not possible, exercise intensity ranges were designed considering percentages of HR reserve. Moderate intensity was defined between as 50-75% of HR reserve, and high intensity between 76-95% of HR reserve.[128]

4.3.4. Biochemical profile

In a separate visit, a morning fasting blood sample (12.5 mL) was obtained from each participant at the Clinical Trials Unit of Tecnalia (HUA, Vitoria-Gasteiz). That sample was used to determine the biochemical profile and the metabolic profile, which consisted of C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), glucose, insulin, and haemoglobin A1c (HbA1c). The AST/ALT and TC/HDL-C ratios were calculated and the HOmeostatic Model

Assessment-Insulin resistance index (HOMA-IR) was determined by fasting serum insulin (µU/mL) x fasting plasma glucose (mg/dL)/405.[159]

According to previous research, the cut-off points of parameters related to cardiometabolic abnormalities were: Concentrations of CRP when >3 mg/L.[160] Hepatic enzymes when AST>30 U/L, ALT>30 U/L, GGT>50 U/L and AST/ALT>1.[90] With respect to the lipid profile, the Adult Treatment Panel III considers that the concentrations were not optimal when TC>200 mg/dL (52 mmol/L), LDL-C>100 mg/dL (26 mmol/L), HDL-C<40 mg/dL (10.4 mmol/L), TG>200 mg/dL (2.28 mmol/L) and TC/HDL-C ratio>3.5.[24] Based on the Diabetes Federation Statement,[161] high levels were considered when glucose>100 mg/dL (5.55 mmol/L). The HOMA-IR ratio cut point was established at 3.8; insulin cut point at 16.7 mU/L and HbA1c at 6%.[162,163]

4.4. Intervention

After baseline, participants were randomized to the attention control group (AC) or one of the three exercise intervention groups. The medical staff was blinded to participant randomization assignment.

4.4.1. Groups

Attention Control group: the AC group received treatment only with a hypocaloric diet and standard recommendations about regular physical activity for people with HTN and overweight/obesity. Specifically, the recommendations were to participate in at least 30 min of moderate-intensity dynamic aerobic exercise 5-7 days per week. Aerobic interval training and dynamic resistance exercise were also advised.[23] Participants received information on HR values (calculated in the CPET) regarding moderate and high-intensity ranges for the self-monitoring of exercise intensity.

The three exercise groups received treatment with a hypocaloric diet and supervised exercise twice a week during the 16 weeks.

High-volume moderate-intensity continuous training (HV-MICT) group: participants of this group performed moderate-intensity (HR in the R2 intensity range) continuous exercise and high volume increasing gradually from 20 to 45 min. Treadmill and bike training protocols are detailed in Table 5.

High-volume high-intensity interval training (HV-HIIT) group: participants alternate high-intensity (HR in the R3 intensity range) and moderate-intensity through interval training and high volume increasing gradually from 20 to 45 min. Treadmill and bike training protocols are detailed in Tables 6 and 7, respectively.

Low-volume high-intensity interval training (LV-HIIT) group: participants alternate high-intensity and moderate-intensity through interval training and the volume was always maintained in 20 min. Treadmill and bike training protocols are detailed in Tables 6 and 7, respectively.

4.4.2. Exercise intervention

Participants exercised two non-consecutive days per week under supervision by exercise specialists. HR monitoring (Polar Electro, Kempele, Finland) monitored all the exercise sessions, and Borg's original scale was used to rate the perceived exertion of participants. Every session included 10 min warm-up and 10 min cool-down periods. The main part of the session consisted of aerobic exercise training, one day of the week on the treadmill, the other one on the bike. The intensity was individually tailored thanks to the intensity ranges calculated in the CPET, and an exercise specialist controlled the speed and incline of the treadmill and the speed and power of the bike to achieve the planned HR for each participant.

Table 5. Intervention program for HV-MICT group. Volume and intensity progression.

	HV-MICT	
Weeks	Total Volume (min)	Intensity (%HRres)
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%

HV-MICT: High-volume moderate-intensity continuous training; HRres: Heart rate reserve. Adapted from *Maldonado-Martín et al., 2016. Effects of Different Aerobic Exercise Programs with Nutritional Intervention in Primary Hypertensive and Overweight/Obese Adults: EXERDIET-HTA Controlled Trial.*[156]

Treadmill protocol: The high-intensity aerobic exercise groups carried out a 5 min warm-up period at moderate-intensity on the treadmill, before walking intervals of 4 min at high-intensity. Between the high-intensity intervals, 3 min of walking at moderate-intensity was conducted. The treadmill session finished with a 1-4 min cool-down period at moderate-intensity. The progress in volume (only in HV-HIIT group) and intensity is specified in Table 6.

Bike protocol: The high-intensity aerobic exercise groups carried out a warm-up period at moderate-intensity on the bike, 10 min for the HV-HIIT group, and 5-10 min for the LV-HIIT group. After that, participants cycled intervals of 30 s at high-intensity and 1 min at moderate-intensity. The bike session finished with a 5-10 min cool-down period at moderate-intensity. The progress in volume (only in HV-HIIT group) and intensity is specified in Table 7.

Table 6. Intervention program for HV-HIIT and 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

HV-HIIT: High-volume high-intensity; LV-HHIT: Low volume high-intensity; HRres: Heart rate reserve. Adapted from *Maldonado-Martín et al., 2016. Effects of Different Aerobic Exercise Programs with Nutritional Intervention in Primary Hypertensive and Overweight/Obese Adults: EXERDIET-HTA Controlled Trial.*[156]

Table 7. Intervention program for HV-HIIT and 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

HV-HIIT: High-volume high-intensity; LV-HHIT: Low volume high-intensity; HRres: Heart rate reserve. Adapted from *Maldonado-Martín et al., 2016. Effects of Different Aerobic Exercise Programs with Nutritional Intervention in Primary Hypertensive and Overweight/Obese Adults: EXERDIET-HTA Controlled Trial.*[156]

4.4.3. Diet intervention

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.[164,165] 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 Mifflin St Jeor equation was used to calculate the resting energy expenditure, to be the most appropriate for people who are overweight or obese,[166,167] and the coefficient of 1.5 corresponds to the factor of physical activity for light physical activity level or sedentary individuals. The design of the diet was performed by following the proportions and amounts of food groups recommended by the dietary pattern of the DASH diet.[168] Further, participants received nutritional advice regarding the restriction of foods high in sodium according to the recommendations of the European Societies of Hypertension and Cardiology.[23] Guidance menus and the most appropriate culinary techniques were facilitated to achieve 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.

4.5. 6-Month Post-Intervention Follow-up

After the 16-week intervention, participants received diet and exercise recommendations for the following 6M. However, no further intervention or attention was given from any of the research staff. Regarding physical activity, they were advised with the same recommendations that the AC group received at the beginning of the intervention, including regular physical activity. Participants also received information related to HR values regarding moderate and

high exercise intensity domains for self-monitoring of exercise intensity. They were asked to try to have similar dietary intakes during this period and to follow the recommendations by the Spanish Society of Dietetics and Food Sciences and the Spanish Society of Community Nutrition. After this 6M period, all the aforementioned measurements were taken again.

Capítulo 5/Chapter 5

Resumen de resultados y discusión/Summary of results and discussion

5. Resumen de resultados y discusión

5.1. Estudio 1: *"Is cardiorespiratory fitness independently associated with the biochemical profile in overweight/obese adults with primary hypertension? The EXERDIET-HTA study"*

Referencia:

Corres P, Maldonado-Martín S, Gorostegi-Anduaga I, et al. Is cardiorespiratory fitness independently associated with the biochemical profile in overweight/obese adults with primary hypertension? The EXERDIET-HTA study. *Scand J Clin Lab Invest*. 2018;78(7-8):613-620.

En este estudio el objetivo fue determinar las asociaciones entre la CCR y el perfil bioquímico en personas adultas con sobrepeso/obesidad, HTA y físicamente inactivas. Tras el análisis estadístico, los principales hallazgos del estudio fueron:

1) La CCR estaba independientemente e inversamente asociada a las concentraciones de AST y ALT. Estas relaciones fueron confirmadas por el análisis de regresión logística y linear.

2) La CRP, la ratio AST/ALT, la GGT, la ratio TC/HDL-C, la glucosa, la insulina y el HOMA-IR estaban asociados, pero no de manera independiente, con la CCR en modelos no ajustados de regresión linear y/o logística. Además, la glucosa estaba independientemente asociada al grupo de CCR moderada en el análisis de regresión logística. De esta forma, este grupo tenía menos posibilidades de tener la glucosa elevada en comparación con el grupo de CCR baja. En el grupo de CCR alta se observó una tendencia a la significación en esa misma asociación.

Coincidiendo con el presente estudio, en anteriores investigaciones, niveles más elevados de CCR y de AF fueron inversamente asociados con las enzimas hepáticas, y concretamente con la AST y la ALT, siendo esta relación independiente respecto a la composición corporal.[90,169] Cuando el análisis no estaba ajustado, la GGT mostró una asociación inversa y la ratio AST/ALT una asociación directa con la CCR, pero esta relación era dependiente de otras covariables. Otras

investigaciones describieron resultados similares, indicando que la composición corporal mediaba en la relación.[170] Se conoce que las enzimas hepáticas se encuentran no solo en el hígado sino también en el músculo esquelético y cardiaco. Sin embargo, mientras la ALT y la GGT se encuentran predominantemente en el hígado y, por tanto, están relacionadas con la grasa hepática y abdominal, la AST está más presente que las anteriores en el músculo esquelético y cardiaco. Por ello, una baja CCR debida a la falta de EF aeróbico regular puede tener efectos adversos en las enzimas hepáticas y en la capacidad oxidativa del músculo, así como en las concentraciones de AST, ALT (en el presente estudio el grupo de CCR alta tenía un 96% y un 85% menos de probabilidad de tener concentraciones elevadas que el grupo de CCR baja, en el modelo completamente ajustado, respectivamente) y de GGT (en el modelo sin ajuste el grupo de CCR alta tenía un 80% menos de probabilidad de tener su concentración elevada respecto al grupo de CCR baja).[90] Estos resultados podrían estar asociados a la presencia de esteatosis hepática no alcohólica.[171]

Previamente, se ha sugerido en poblaciones sin sobrepeso u obesidad que una CCR alta podría atenuar el riesgo de incidencia de HTA en personas con altas concentraciones de marcadores inflamatorios como la CRP.[172] Por ello, se han observado resultados que asocian una mayor CCR con concentraciones más reducidas de CRP incluso en modelos ajustados con IMC y masa grasa.[87,173] Además, una mejor composición corporal se ha asociado a concentraciones menores de CRP,[174] y una CCR mayor con una composición corporal mejorada.[175] Los resultados del presente estudio apoyan la asociación inversa entre la CCR y la CRP (en el modelo sin ajustar), aunque el análisis ajustado solo mostrara una tendencia a la significación. En consecuencia, podría existir algún mecanismo subyacente que explicara esta relación, aunque aún no se entienda del todo.[173] Las concentraciones circulantes de los marcadores inflamatorios, en particular de la CRP, aumentan el riesgo de desarrollar ateroesclerosis, y por tanto la CRP sería un predictor fiable de eventos CV.[176]

Aunque las posibles explicaciones están fuera del alcance de este estudio, estudios anteriores han presentado posibles vías para explicar la relación entre la CCR y la CRP: 1) la producción hepática de CRP es estimulada por la interleukina-6 y, en menor grado, por la interleukina-1 y el factor de necrosis tumoral α, que a su vez están estimulados por el tejido adiposo visceral;[87] 2) la AF regular y el EF agudo han demostrado disminuir las concentraciones en reposo de interleukina-6 y del factor de necrosis tumoral α, por lo que, potencialmente, también de la CRP;[87,173] 3) la estimulación simpática aumentada está relacionada a la inflamación. Por lo tanto, las reducciones en los marcadores inflamatorios ocurren cuando la CCR y la actividad del sistema nervioso autónomo es mejor, a través de vías antiinflamatorias colinérgicas inducidas por el EF.[177]

No se encontraron asociaciones entre la CCR y ningún marcador del perfil lipídico en este estudio, a excepción de la ratio TC/HDL-C. Los/las participantes con una CCR alta tenían menos opciones de tener una ratio TC/HDL-C elevado (un 62% menos de opciones que el grupo de CCR baja), pero la asociación no era independiente y desaparecía cuando se ajustaba el análisis. La ratio TC/HDL-C es un índice de la presencia de un perfil de dislipemia aterogénico relacionado con la resistencia a la insulina.[178] La ausencia de EF o la baja CCR está unida a una mayor disfunción endotelial (*i.e.*, una vasodilatación reducida junto con un mayor índice de marcadores proinflamatorios y protrombóticos), HTA y una ratio TC/HDL-C aumentada.[179] Por contra, el EF ha demostrado remodelar positivamente los vasos sanguíneos.[179] Asimismo, estudios previos encontraron una asociación entre la CCR y el perfil lipídico, directa con el HDL-C e inversa con los TG y la ratio TC/HDL-C,[123,180] mientras que el LDL-C no parece estar vinculado a la CCR. Un estudio longitudinal ha observado que la composición corporal (el IMC o la circunferencia de cintura, por ejemplo), está más asociada al perfil lipídico que la CCR.[180] Por ello, una mejor composición corporal podría mejorar el perfil lipídico, mientras que la influencia de la CCR sería limitada.[180] Sin embargo, se requiere de más investigación para confirmar esta ausencia de asociación en personas con sobrepeso/obesidad e HTA.

Los indicadores de la tolerancia a la glucosa y de resistencia a la insulina (específicamente glucosa, insulina y HOMA-IR) estuvieron inversamente relacionados con la CCR en el presente estudio, aunque la HbA1c no mostró ninguna asociación con la CCR. En previas investigaciones, se ha observado una asociación inversa entre la CCR y la tolerancia a la glucosa y la resistencia a la insulina, que además era independiente de la composición corporal.[181,182] En este estudio, la concentración de glucosa también mostró una asociación independiente con el grupo de CCR moderada en el análisis de regresión logística (*i.e.*, menor probabilidad de tener la glucosa elevada que el grupo de CCR baja). Sin embargo, no todos los estudios consultados muestran que la relación sea independiente a la composición corporal,[124] y por ello se requiere de más investigación para clarificar las potenciales asociaciones entre estos parámetros, particularmente en una población con sobrepeso/obesidad e HTA. Aun así, de acuerdo con anteriores estudios, parece claro que una mayor CCR en personas adultas con obesidad tiene efectos positivos sobre la sensibilidad a la insulina.[182]

Este estudio muestra la importancia de la CCR en el mantenimiento de un perfil bioquímico saludable. Debido a las relaciones entre la CCR, el perfil bioquímico y el riesgo CV y de mortalidad,[80,110,176] los resultados del presente estudio evidencian la utilidad de la CCR como una herramienta de control en el ámbito de la salud pública, ya que una detección temprana de niveles bajos de CCR podría significar la detección temprana de personas con mayores posibilidades de desarrollar enfermedades CVs.[110,125]

5.2. Estudio 2: *"Long-Term Effects in the EXERDIET-HTA Study: Supervised Exercise Training vs. Physical Activity Advice"*

Referencia:

Corres P, MartínezAguirre-Betolaza A, Fryer SM, et al. Long-Term Effects in the EXERDIET-HTA Study: Supervised Exercise Training vs. Physical Activity Advice. *Res Q Exerc Sport*. 2020;91(2):209-218.

Para contextualizar este estudio debemos referirnos a un artículo publicado anteriormente que forma parte del estudio EXERDIET-HTA, publicado por Gorostegi-Anduaga et al.[65] En esta publicación se analizaban los efectos de los diferentes programas de 16 semanas de intervención con EF aeróbico junto con la dieta hipocalórica DASH. Los/las investigadores/as observaron que este tipo de intervención era una herramienta no farmacológica óptima para el control de los factores de riesgo cardiometabólico en personas adultas con sobrepeso/obesidad e HTA. Tras la intervención, la composición corporal, la PA y la CCR mejoraron significativamente en todos los grupos (también en el grupo AC, sin EF supervisado, solamente recomendaciones de AF). El estudio reveló que existían diferencias entre grupos, con mejoras superiores en los grupos de EF supervisado que en el grupo AC para la composición corporal y la CCR. Sin embargo, no existieron diferencias entre grupos para la PA.[65]

Este segundo estudio de la presente tesis doctoral tenía como objetivo determinar si las mejoras que se obtenían en una intervención de 16 semanas con EF aeróbico supervisado y dieta hipocalórica respecto a la CCR, PA y composición corporal eran mantenidas después de un periodo de 6M sin supervisión en personas adultas con sobrepeso/obesidad, HTA y físicamente inactivas. El objetivo secundario era determinar si existían diferencias entre los grupos de la

intervención (grupos de EF supervisado *vs*. grupo AC) en los efectos del periodo de 6M no supervisado.

Los hallazgos principales del estudio fueron:

1) Los beneficios inducidos por la intervención en la composición corporal y la CCR no fueron mantenidos 6M después del fin de la misma, pero los valores tras ese periodo eran mejores que los previos a la intervención. Respecto a las mejoras obtenidas en la PA, éstas desaparecían y regresaban los valores previos a la intervención.
2) No se encontraron diferencias entre grupos en los efectos del cese de la intervención, excepto por una diferencia entre el grupo HV-HIIT y el grupo AC en la MC. La diferencia era favorable al grupo HV-HIIT, que reducía en menor medida los beneficios obtenidos en esa variable.

El síndrome de desentrenamiento es un término que se refiere al momento en el que las personas que se encontraban en un entrenamiento sistemático y/o EF supervisado cesan su actividad durante más de cuatro semanas. Este síndrome presenta las consecuencias fisiológicas del insuficiente estímulo de EF, que provoca pérdidas en las adaptaciones conseguidas mediante el EF.[146,147] En el presente estudio, el cese del EF aeróbico supervisado, seguido de 6M sin supervisión en los que los/las participantes solo recibían recomendaciones al inicio del periodo, resultó en un empeoramiento de las adaptaciones positivas logradas previamente en la intervención en todos los grupos. Tras la retirada de la supervisión, se observó un empeoramiento respecto al fin de la intervención tanto en la composición corporal (*i.e*., MC, % diferencia, Δ = 2,5%; IMC, Δ = 2,7%; circunferencia de cintura, Δ = 1,8%; y masa libre de grasa, Δ = -2,2%) y la CCR ($\dot{V}O_{2pico}$; Δ = -5,7%). Sin embargo, cabe destacar que los valores eran mejores que los previos a la intervención. Estos hallazgos concuerdan con estudios previos en otras poblaciones (en personas con enfermedad arterial coronaria, mujeres con el síndrome del ovario poliquístico y sobrepeso, mujeres con hipertensión parental, personas con síndrome

metabólico, mujeres con diabetes tipo II y hombres sanos) que desarrollaron intervenciones con diferentes tipos de EF, duración de la intervención y del periodo sin supervisión (de 4 semanas a 4 meses).[150-152,183-186]

Otro resultado interesante que se observó en el presente estudio fue que, tras el periodo de 6M sin supervisión, el grupo HV-HIIT presentó una mayor reducción significativa (*P* = 0,034) en la MC respecto a los valores previos a la intervención (Δ = -6,4 kg) en comparación al grupo AC (Δ = -3,5 kg). Estos datos podrían ayudar a confirmar que el mayor gasto energético debido al entrenamiento de intensidades moderadas-vigorosas y volumen alto está relacionado a un mantenimiento en la pérdida de MC a largo plazo.[187] Estudios anteriores han apoyado esta hipótesis y han mostrado que el HIIT es un estímulo efectivo para reducir la masa grasa en personas con obesidad.[188,189] Los posibles mecanismos que inducen al HIIT a reducir la masa grasa incluirían: 1) un nivel más elevado de respuesta de las catecolaminas, y 2) un mayor $\dot{V}O_2$ post-ejercicio que conduce a un aumento de la oxidación de las grasas.[190,191]

Respecto al presente estudio, es importante señalar que retirar la supervisión en el entrenamiento durante 6M no condujo a una pérdida total de las ganancias de CCR ($\dot{V}O_{2pico,}$ Δ = 18% comparando el seguimiento a los 6M con los valores previos a la intervención), en ninguno de los grupos de la intervención. Además, se conoce que un incremento de 1 MET en la CCR está asociado con un aproximadamente un 13-15% menos de riesgo de mortalidad CV y por cualquier causa.[110] Teniendo en cuenta este dato y comparando el seguimiento a los 6M y los datos previos a la intervención, los grupos de entrenamiento supervisado conseguían preservar a los 6M una ganancia superior a 1 MET, mientras que el grupo AC no (AC, Δ = 0,7 MET; HV-MICT = 1,0 MET; HV-HIIT = 1,5 MET, LV-HIIT = 1,2 MET). Aunque la adherencia a la intervención de 16 semanas fue muy alta en los grupos de entrenamiento supervisado, 6M más tarde únicamente el 51% de los/las participantes realizaban AF más de 2 veces a la semana y cumplían las recomendaciones

que se les aportaba (datos no publicados del estudio EXERDIET-HTA). Este hecho sugiere que el EF supervisado es necesario para obtener mejores resultados.

En concordancia con investigaciones previas,[192] tras retirar el EF supervisado durante 6M la PA volvía a los niveles previos a la intervención. Este hallazgo es importante, ya que la PA es un marcador clínico sensible y robusto, que está asociado con los cambios en MC,[193] debido a un aumento de la adiposidad visceral (en este estudio, en el seguimiento a los 6M comparado con el final de la intervención, la MC Δ = 2,5% y la circunferencia de cintura Δ = 1,8%). Es posible que varios factores fisiológicos y mecanismos biológicos estén involucrados en el aumento de la respuesta de la PA que se observa en el presente estudio, como la compresión física de los riñones por la grasa, la sobreactivación del sistema renina-angiotensina-aldosterona y una mayor activación del sistema nervioso simpático.[194] A pesar de la evidencia existente sobre la eficacia de la dieta DASH, la pérdida de MC y el EF sobre el descenso de la PA,[65,195] parece que la adherencia a la dieta DASH resulta difícil de seguir para las personas con HTA, e incluso se encuentran niveles menores de adherencia a la dieta DASH en aquellos/as que también tienen obesidad.[196] Por ello, en esta población, el EF supervisado junto con una supervisión dietética parecen necesarias para optimizar las capacidades reductoras de la PA del EF y de la dieta.[137,197]

5.3. Estudio 3: "*A Metabolically Healthy Profile Is a Transient Stage When Exercise and Diet Are Not Supervised: Long-Term Effects in the EXERDIET-HTA Study*"

Referencia:

Corres P, Fryer SM, MartínezAguirre-Betolaza A, et al. A Metabolically Healthy Profile Is a Transient Stage When Exercise and Diet Are Not Supervised: Long-Term Effects in the EXERDIET-HTA Study. *Int J Environ Res Public Health*. 2020;17(8):2830.

Los objetivos de este estudio fueron analizar los cambios en el perfil cardiometabólico de personas con sobrepeso u obesidad, HTA y físicamente inactivas después de una intervención de 16 semanas con EF supervisado y un grupo AC, ambos con dieta hipocalórica, y realizar un seguimiento de los cambios tras 6M del final de la intervención, cuando la supervisión en el EF y la dieta se retiraba. Este estudio mostró que dicha intervención mejoraba significativamente el perfil cardiometabólico de los/las participantes, que pasaban de ser ObME a SobMS. Sin embargo, este estado era transitorio, ya que tras los 6M no supervisados el perfil metabólico regresaba a ObME.

Actualmente hay cada vez más evidencias de que las personas con obesidad con un estilo de vida saludable podrían tener un riesgo CV similar al de las personas sanas sin obesidad, ya que la adherencia al EF y a una dieta saludable conduce a cambios beneficiosos para la composición corporal y el perfil cardiometabólico.[198] El presente estudio mostró que los/las participantes del estudio EXERDIET-HTA tenían un perfil de ObME al inicio de la intervención (obesidad, HTA, glucosa en ayunas > 100 mg/dL, LDL-C > 100 mg/dL, TC > 200 mg/dL, ALT > 30 U/L, CRP > 3 mg/L y baja CCR, 22,4±5,4 $mL \cdot kg^{-1} \cdot min^{-1}$), que era significativamente peor que el del grupo HEALTHY, compuesto por una muestra control de personas sanas no obesas. Estos resultados confirman que la obesidad y la inactividad física son factores que contribuyen en gran medida a la

dislipidemia, manifestada por el LDL-C y los TG elevados,[199] induciendo la inflamación crónica y la activación del sistema renina-angiotensina, aumentando de esta manera, consecuentemente, la activación simpática y la PA.[200]

En anteriores publicaciones del estudio EXERDIET-HTA se revelaron los cambios tras realizar una intervención de 16 semanas de EF y dieta hipocalórica, que mejoraban significativamente la composición corporal y la CCR.[65,154] Estos cambios podrían estar asociados a un efecto protector metabólico, que mejoraría la resistencia a la insulina, el perfil lipídico y la PA, tal y como muestran los resultados del presente estudio. De hecho, los/las participantes disminuyeron también la concentración de CRP (Δ = -1,4 mg/L), que se explicaría por diferentes mecanismos, incluyendo un descenso en la producción de citoquinas por el tejido adiposo, el músculo esquelético, y las células endoteliales y mononucleares de la sangre; una mejora en la sensibilidad a la insulina y en la función endotelial; y un posible efecto antioxidante.[173] Después de las 16 semanas de intervención, únicamente el grupo de EF supervisado mostraba cambios beneficiosos en todas las variables excepto en el HDL-C. La concentración disminuyó en las enzimas hepáticas ALT (Δ = -9,1 U/L) y GGT (Δ = -9,1 U/L), que en concentraciones elevadas ambas están relacionadas a la grasa abdominal y del hígado y son predictores del fenotipo ObME, la diagnosis de la esteatosis hepática no alcohólica, la diabetes tipo II y la ateroesclerosis subclínica.[171] Previamente, intervenciones con EF y dieta hipocalórica han demostrado mejorar la composición lipídica del hígado a través de diferentes mecanismos.[201] Así, algunos estudios sugieren que el EF podría modular la grasa del hígado alterando directamente la oxidación lipídica del hígado y la lipogenesis,[202] y que esta mejora podría estar dirigida por la adiponectina y la mejora en la sensibilidad a la insulina.[203] Por tanto, esto podría explicar en parte los cambios favorables que se muestran tras las 16 semanas de intervención, incluyendo la menor concentración de glucosa (Δ = -6,8 mmol/L), insulina (Δ = -2,2 mU/L), HOMA-IR (Δ = -0,9) y HbA1c (Δ = -0,2%). Estos marcadores han mostrado previamente ser algunas de las adaptaciones al EF crónico, tras la mejor regulación de la proteína GLUT4 del músculo, el aumento de la capacidad

enzimática y la capilarización muscular.[204] De forma similar a estudios previos que investigaban los beneficios del EF supervisado,[199,205] el presente estudio observó que tras la intervención se redujeron las concentraciones en el perfil lipídico de TC (Δ = -13,9 mmol/L), LDL-C (Δ = -9,4 mmol/L), TG (Δ = -20,9 mmol/L) y la ratio TC/HDL-C (Δ = -0,3). Por el contrario, en este estudio no se encontraron cambios en el HDL-C (los valores previos a la intervención eran normales). En otros estudios en los que se realizaba EF supervisado sin intervención dietética es normal encontrar que las concentraciones de HDL-C aumenten.[150,183,185,199] Una posible explicación a este hecho es la dieta DASH hipocalórica que se sigue en este estudio, ya que se ha revelado que la dieta DASH disminuye los niveles de HDL-C junto con el TC, LDL-C y TG.[206-208] El efecto de esta dieta en la intervención debe ser considerado, ya que también se ha indicado que es efectiva para cambiar el perfil bioquímico, reduciendo niveles de CRP, AST, ALT, insulina y HOMA-IR.[208-210] Además de los beneficios que se producen en el perfil bioquímico, la intervención del estudio EXERDIET-HTA mejora notablemente la CCR y la composición corporal.[65,154] Dada la fuerte relación de la CCR con el riesgo metabólico,[111] parece razonable incluir el nivel de CCR en el pronóstico de la ObMS, para mejorar la estratificación de las personas con obesidad,[78] dando valor al EF supervisado y al paradigma “fat-but-fit”.[211]

Aunque los resultados previamente mencionados muestran los beneficios que el EF aeróbico podría añadir a la dieta DASH hipocalórica respecto al perfil bioquímico (descenso en las concentraciones de glucosa, insulina, HOMA-IR, LDL-C, TC, TG, TC/HDL-C, ALT, GGT, CRP), en el presente estudio, cuando se llevó a cabo el análisis ANCOVA, no se observaron diferencias significativas entre el grupo AC y los grupos de EF supervisado en las diferencias de los valores previos y posteriores a la intervención. Sin embargo, el menor número de participantes del grupo AC (n = 43) que los de EF supervisado (n = 134), podría afectar a la potencia estadística y, por tanto, se necesita más investigación para confirmar o denegar esta ausencia de diferencias entre grupos. En cualquier caso, en el análisis intragrupo, el grupo AC solamente lograba un descenso significativo en la CRP.

En base a los hallazgos del presente estudio y de los anteriormente presentados por el grupo de investigación,[65,154] la intervención de 16 semanas fue efectiva cambiando el perfil cardiometabólico de los/las participantes de ObME a SobMS, de acuerdo a los siguientes criterios: descenso de obesidad a sobrepeso con menor grasa corporal; los valores de TC, ALT, glucosa y CRP pasaron de ser no saludables a ser óptimos según los puntos de corte establecidos, reflejando una ausencia de anormalidades metabólicas y menor nivel en los mediadores de la inflamación sistémica; y la CCR evolucionó de estar por debajo del percentil 50 a estar por encima en los valores de $\dot{V}O_{2pico.}$[212] Además, los/las participantes redujeron sus valores de PA (-5,4% de reducción en la PA media), y más del 7% de los/las participantes dejaron de tomar medicación, mientras que un 25% de ellos/as redujo su dosis bajo supervisión médica.[65,154]

Aunque hubo una mejora significativa en el perfil cardiometabólico tras de la intervención, una vez retirado el EF supervisado se observó un empeoramiento en el perfil cardiometabólico en el seguimiento a los 6M. El perfil de SobMS no se mantuvo en los/las participantes y tras los 6M regresaron a la ObME. Se observaron cambios no favorables en el perfil lipídico, glucémico y hemodinámico, lo cual es consistente con los resultados mostrados en estudios previos en diferentes poblaciones con distintos tipos de EF, duración de la intervención y del tiempo de no supervisión.[183,185,201,213] Estos efectos negativos pueden ser secundarios a las ganancias inducidas por el desentrenamiento en la grasa corporal, lo que favorece un estado más inflamatorio y una disminución de la CCR, como se observó en los/las participantes. Estudios previos han mostrado la fisiopatología de la obesidad relacionada a la HTA.[66] De este modo, un aumento en el índice cintura-cadera, paralelamente a un mayor nivel de insulina, leptina y del sistema renina-angiotensina-aldosterona parece estimular el sistema nervioso simpático con la concomitante subida en la PA.[66] Además, ya se ha podido establecer que una CCR más baja, promovida por el cese del EF, aumenta el riesgo de sufrir síndrome metabólico y efectos perjudiciales para el sistema cardiovascular, como la peor regulación de la PA, la variabilidad de la frecuencia cardiaca, la demanda de oxígeno en el miocardio, la función endotelial y la inflamación sistémica,

junto con un almacenamiento de grasa ineficaz.[77] Por lo tanto, parece claro que los niveles de AF difieren entre la ObMS y ObME en personas adultas.[78,214]

Estos datos sugieren que la supervisión o estrategias alternativas para realizar EF son necesarias para que la ObMS no sea un estado transitorio hacia el deterioro cardiometabólico y como consecuencia, desarrollar un mayor riesgo de enfermedad CV.[215,216] Así, en el presente estudio, aunque la adherencia al EF durante la intervención supervisada fue muy alta en el grupo de EF supervisado, 6M más tarde solo el 51% de los/las participantes realizaban AF más de 2 veces a la semana y cumplían las recomendaciones que se les aportaba (datos no publicados del estudio EXERDIET-HTA). Sin embargo, es interesante apuntar que las concentraciones de HDL-C fueron superiores tras el periodo de 6M sin supervisión que en los datos previos a la intervención (Δ = 2,4 mmol/L) y posteriores a la intervención (Δ = 2,5 mmol/L). Esto podría deberse a los efectos de la no supervisión en la dieta, que es un factor clave en los cambios de HDL-C, tal y como se ha discutido anteriormente hablando de la dieta DASH.[206,207]

Capítulo 6/Chapter 6

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Capítulo 7/Chapter 7

Conclusiones/Conclusions

7. Conclusions

- CRF was associated with biochemical profile in a physically inactive population with HTN and overweight/obesity. The association between CRF and AST and ALT was inverse and independent, whereas the influence of CRF was limited by other covariates in the association with CRP, AST/ALT ratio, GGT, TC/HDL-C ratio, glucose, insulin and HOMA-IR.
- Inactive people with HTN and overweight/obesity achieved significant improvements in CRF, BP, and body composition following a 16-week supervised exercise intervention with diet restriction. There was a significant reduction in the improvements following 6M when the exercise and diet supervision was removed, and only recommendations were applied. CRF and body composition reduce the improvements following 6M, however, there were significant improvements from pre-intervention. By contrast, the attained improvements in BP were not maintained and BP returned to pre-intervention values.
- A 16-week supervised exercise intervention with diet restriction was effective to improve cardiometabolic health of physically inactive participants with HTN and overweight/obesity from metabolically unhealthy obesity to metabolically healthy overweight. However, this was a transient stage as after 6M follow-up, participants returned to metabolically unhealthy obesity.
- The type of aerobic exercise performed during the intervention did not influence 6M follow-up, there were no differences between groups when the supervision was removed and only recommendations were applied.
- The results suggest that regular, systematic and supervised exercise programs are necessary to avoid subsequent declines in cardiometabolic health of inactive people with HTN and overweight/obesity.

Capítulo 8/Chapter 8

Limitaciones y propuestas de futuro/Limitations and future directions

8. Limitaciones y propuestas de futuro

Una de las limitaciones de este trabajo ha sido el tamaño de la muestra, especialmente para el primer estudio, que es un estudio transversal en el cual una muestra superior sería conveniente para lograr una mayor potencia estadística. Para el segundo y tercer estudio, teniendo en cuenta que se lleva a cabo una intervención, la muestra es considerable, y aunque algunos estudios epidemiológicos tengan muestras mayores, el estudio EXERDIET-HTA cumple con la potencia estadística para un estudio aleatorizado experimental. Aunque se realizaron esfuerzos para que todos/as los/las participantes que realizaron la intervención hicieran la visita de los 6M, algunos/as participantes no acudieron, provocando que la muestra fuese menor. Asimismo, debido al menor número de mujeres que han participado en el estudio, no se pueden estimar los efectos de cada tipo de EF dependiendo del sexo.

Por otro lado, existen algunos factores de confusión que pueden influir en los resultados obtenidos, como la AF que los/las participantes realizaban al margen de lo que se les supervisaba durante la intervención o la imposibilidad de controlar completamente la adherencia a la dieta. Además, aunque los análisis se ajustaban con las medicaciones que tomaban los/las participantes y se tenía en cuenta si fumaban o no, es difícil establecer cuál es la influencia de estos factores sobre los resultados.

Hay que considerar también que durante los 6M no supervisados cada participante realizaba la AF que consideraba, por lo que las diferencias inter-individuales que existen en el grupo se pueden ver enmascaradas por las técnicas de análisis de datos cuantitativas.

En futuros estudios se podrían usar distintos métodos de investigación para ayudar a interpretar cuáles son las razones detrás de los cambios que se han observado en los resultados. Además, futuras investigaciones podrían determinar si el EF y la dieta supervisada continuada pueden mantener las ganancias conseguidas en la salud cardiometabólica, comparando 6M sin

supervisión y 6M con supervisión. Por otra parte, se podría considerar realizar un seguimiento a la muestra de utilizada en esta tesis para poder establecer curvas de mortalidad en esta población, aunque el número de participantes sea pequeño para este tipo de cálculos. Este estudio se llevó a cabo en personas con HTA, sobrepeso u obesidad y físicamente inactivas, por lo que los hallazgos no se deben extrapolar a poblaciones distintas. Para conocer si los resultados podrían ser semejantes en otras poblaciones, se debería realizar experimentos con las mismas.

Capítulo 9/Chapter 9

Publicaciones/Publications

9. Publicaciones

9.1. Anexo 1: *"Is cardiorespiratory fitness independently associated with the biochemical profile in overweight/obese adults with primary hypertension? The EXERDIET-HTA study"*

Los indicadores de calidad de la revista del primer artículo publicado, según *Journal Citation Reports* (JCR) y el *Cite Score* de Scopus en el año 2019 son los siguientes:

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ORIGINAL ARTICLE

Is cardiorespiratory fitness independently associated with the biochemical profile in overweight/obese adults with primary hypertension? The EXERDIET-HTA study

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ABSTRACT

Cardiorespiratory fitness (CRF) is positively associated with enhanced cardiovascular health. This cross-sectional study aimed to determine associations between CRF and the biochemical profile of overweight/obese adults diagnosed with primary hypertension (HTN). Does cardiorespiratory fitness (exposure) positively affect the biochemical profile (outcome) in overweight/obese individuals suffering from HTN? Assessment with anthropometric, ambulatory blood pressure monitoring (24 h), CRF (peak oxygen uptake, VO_{2peak}) and biochemical analysis was performed on 214 participants (138 men, 76 women). A series of linear and logistic regression analyses were conducted. Participants were divided into CRF tertiles (classified as low, moderate and high CRF). The CRF was independently and inversely associated with aspartate aminotransferase (AST; $\beta = -0.328$, $p < .05$) and alanine aminotransferase (ALT; $\beta = -0.376$, $p < .01$) concentrations. C-reactive protein, AST/ALT ratio, gamma-glutamyl transpeptidase, total cholesterol/high-density lipoprotein cholesterol ratio, glucose, insulin and insulin resistance index (HOMA-IR), were all associated, but not independently, with CRF in linear and/or unadjusted logistic regression models. However, independently, logistic regression revealed that glucose was associated with the moderate CRF group. Findings suggest that a lower CRF is associated with an unhealthy biochemical profile in non-physically active and overweight/obese individuals with HTN. As such, this population should look to increase physical activity in order to improve their CRF and biochemical profile.

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Cardiorespiratory fitness; hypertension; overweight; aspartate aminotransferase; alanine aminotransferase

Introduction

Primary hypertension (HTN) and overweight/obesity are modifiable cardiovascular (CV) risk factors and two of the most common causes of premature death in developed countries [1,2]. Approximately one in three adults have elevated blood pressure (BP), and the body mass index (BMI) has dramatically increased in all countries over recent decades [2]. Previously, in patients without HTN but overweight/obesity, risk factors such as C-reactive protein (CRP), dyslipidemia, insulin resistance and hepatic enzymes have been all associated with metabolic syndrome, type II diabetes and CVD [3–5]. In addition, approximately half the population of the Western World has at least one lipid abnormality [6]. Further, there is strong evidence to suggest that obesity-related disorders such as insulin resistance and type II diabetes are strongly associated with an increased risk of HTN [1,7].

Although CVD, HTN, type II diabetes and dyslipidemia are all causes of early morbidity, they are cardio-metabolic lifestyle factors that can be altered by adopting healthy lifestyle [2]. Cardiorespiratory fitness (CRF) (i.e. aerobic capacity) is positively associated with enhanced cardiovascular health and a reduction in all-cause mortality [8]. Thus, high CRF has been shown to suppress the onset of type II diabetes, metabolic syndrome and CVD in the general population [9,10]. More specifically, enhanced CRF has been associated with lower concentrations of CRP in overweight men [11], aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in overweight women and men [12], as well as higher concentrations of high-density lipoprotein cholesterol (HDL-C), and a reduced incidence of hypercholesterolemia adjusted to BMI [13].

As such, it could be expected that an enhanced CRF may be positively associated with a better biochemical profile in overweight/obese individuals suffering from HTN. Adding to that, in order to reduce the obesity epidemic, we need to further enhance our understanding of the biochemical profile associated with overweight/obese individuals with HTN. This would allow clinicians and research scientists to further understand the complexity surrounding the associations and

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causes of CVD. Therefore, the question may be-"Does cardiorespiratory fitness positively affect the biochemical profile in overweight/obese individuals suffering from HTN?" Thus, the aim of the study was to determine associations between CRF and biochemical profile in overweight/obese men and women diagnosed with HTN.

Methods

Participants

Two-hundred and fourteen participants (138 men, 76 women) volunteered to participate in the EXERDIET-HTA study (Trial Registration: NCT02283047) located in the town of Vitoria-Gasteiz (Araba/Álava, Basque Country, Spain) and recruited from the cardiology services and local media. Inclusion criteria were having overweight (BMI >25 kg·m^{-2}) or obesity (BMI >30 kg·m^{-2}) [14], and diagnosed with HTN, defined as systolic BP (SBP) of 140–179 mmHg and/or diastolic BP (DBP) of 90–109 mmHg and/or under antihypertensive pharmacological treatment [1]. 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'* by the World Health Organization (i.e. at least 150 min of moderate-intensity aerobic physical activity throughout the week *or* do at least 75 min of vigorous-intensity aerobic physical activity throughout the week *or* an equivalent combination of moderate- and vigorous-intensity activity) were selected [15].

All participants' demographic data, smoking and medication data are presented in Table 1. All other inclusion and exclusion criteria have been previously published in the study protocol [16]. Study design, protocols and informed consent were 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).

Measurements

Anthropometry measurements for the assessment of body composition included stature (SECA 213, Hamburg, Germany), total body mass (SECA 869, Hamburg, Germany) and BMI. Total body water (TBW) and fat mass (FM) were estimated using bioelectrical impedance (Tanita, BF 350, Tokyo, Japan) according to the general instructions by the manufacture and the theory and fundamentals of bioimpedance analysis [17]. An ambulatory BP monitor (ABPM) (6100 Welch Allyn, New York, USA) used to determine SBP and DBP at 30 min intervals during the daytime and at 60 min intervals during night-time during for a 24 h period according to report's recommendations by the European Society of Hypertension/European Society Cardiology guidelines [1]. Participants 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 [16].

Participants' CRF, defined as peak oxygen uptake (VO_{2peak}) was assessed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). Initial power was 40 W increasing in 10 W increments every minute until exhaustion, cadence was maintained at ~70 rpm throughout. Peak oxygen uptake was determined using a commercially available metabolic cart (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 data were measured continuously during exercise and reported in 60-s averages. Achievement of VO_{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 (VCO_2/VO_2) ≥ 1.1, (3) achieving >85% of age predicted maximum heart rate (HR) and (4) failure of VO_2 and/or HR to increase with further increases in work rate [18]. During the test, continuous electrocardiogram was monitored throughout. Blood pressure was assessed every 2 min (Lode Excalibur automated BP module), and self-

Table 1. Demographic and descriptive characteristics of the participants split by sex.

	All ($N = 214$)	Men ($N = 138$)	Women ($N = 76$)	p
Age (years)	53.5 ± 7.7	54.4 ± 7.9	52.0 ± 7.3	.03*
BMI (Kg/m^2)	32.0 ± 4.5	31.9 ± 4.2	32.0 ± 5.0	.9
TBW (%)	48.4 ± 6.5	50.7 ± 4.6	44.3 ± 7.2	<.001***
FM (%)	34.3 ± 8.5	30.8 ± 7.7	40.8 ± 5.7	<.001***
SBP (mmHg)	136.2 ± 12.8	136.8 ± 12.2	135.2 ± 14.0	.4
DBP(mmHg)	78.4 ± 8.3	79.7 ± 7.6	76.1 ± 8.9	.003**
VO_{2peak} (mL·kg^{-1}·min^{-1})	22.5 ± 5.4	24.1 ± 5.3	19.6 ± 4.4	<.001***
CRP (mg/L)	4.3 ± 4.3	3.8 ± 4.0	5.0 ± 4.6	.1
AST (U/L)	25.3 ± 11.6	26.8 ± 12.7	22.4 ± 8.6	.01*
ALT (U/L)	32.2 ± 20.9	35.3 ± 22.1	26.6 ± 17.4	.002**
AST/ALT	0.90 ± 0.4	0.86 ± 0.49	0.98 ± 0.3	.08
GGT (U/L)	39.1 ± 43.3	43.0 ± 48.4	29.5 ± 25.2	.1
TC (mmol/L)	5.3 ± 0.9	5.2 ± 1.0	5.6 ± 0.9	.007**
HDL-C (mmol/L)	1.2 ± 0.3	1.2 ± 0.2	1.4 ± 0.3	<.001***
LDL-C (mmol/L)	3.4 ± 0.8	3.3 ± 0.9	3.6 ± 0.8	.02*
TG (mmol/L)	1.6 ± 0.9	1.7 ± 1.0	1.3 ± 0.6	.003**
TC/HDL-C	4.5 ± 1.5	4.6 ± 1.6	4.2 ± 1.1	.05
Glucose (mmol/L)	5.7 ± 1.4	5.6 ± 1.2	5.8 ± 1.6	.4
Insulin (mU/L)	12.0 ± 7.3	11.8 ± 7.6	12.4 ± 6.8	.7
HOMA-IR	3.3 ± 2.6	3.1 ± 2.3	3.5 ± 3.0	.4
HbA1c (%)	6.0 ± 0.9	5.9 ± 0.9	6.0 ± 0.9	.7
Statin (%)	14	15.9	10.5	.3
Hypoglycemic (%)	7	9.4	2.6	.1
ACEI (%)	36.9	35.5	39.5	.6
ARB (%)	43	44.2	40.8	.6
Diuretic (%)	40.2	37.7	44.7	.3
CCB (%)	15	18.1	9.2	.1
BB (%)	7.5	7.2	7.9	.9
Antiplatelet (%)	4.7	5.8	2.6	.3
Smokers (%)	12.1	13	10.5	.6

BMI: body mass index; TBW: total body water; FM: fat mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; VO_{2peak}: peak oxygen consumption; CRP: C reactive protein; AST: aspartate aminotransferase; ALT: alanine transaminase; GGT: gamma-glutamyl transpeptidase; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; HOMA-IR: insulin resistance index; HbA1c: haemoglobin A1c; SD: standard deviation; ACEI: angiotensin-converting-enzyme inhibitors; ARB: angiotensin II receptor blockers; CCB: calcium channel blockers; BB: beta-blockers.
Significant difference between men (M) and women (W): *$p < .05$, **$p < .01$, ***$p < .001$.
Values are mean ± SD or percentages (%) for categorical variables.

reported Borg scale (6–20 scale) was recorded at the end of each stage. After completion of the test, participants remained on the bike 5 min of passive recovery with electrocardiogram and BP monitoring.

In a separate visit, a blood sample (12.5 mL) was collected from each participant at the Clinical Trials Unit of Tecnalia (HUA, Vitoria-Gasteiz) following an overnight fast. That sample was used to determine the biochemical profile which consisted of CRP, AST, ALT, gamma-glutamyl transpeptidase (GGT), total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), glucose, insulin and haemoglobin A1c (HbA1c). The AST/ALT and TC/HDL-C ratios were calculated, and insulin resistance index (HOMA-IR) was determined by [fasting serum insulin (μU/mL) × fasting plasma glucose (mg/dL)/405] [19].

Cut points of parameters

According to previous research, concentrations of CRP >3 mg/L indicated cardiometabolic abnormality [20]. According to prior study [12], abnormal values for the three hepatic enzymes were considered when >30 U/L for AST, >30 U/L for ALT, >50 U/L for GGT and <1 for AST/ALT ratio. With respect to the lipid profile, the Adult Treatment Panel III considers that the concentrations were not optimal when different parameters were TC >200 mg/dL (5.172 mmol/L), LDL-C >100 mg/dL (2.586 mmol/L), HDL-C <40 mg/dL (1.034 mmol/L), TG >200 mg/dL (2.258 mmol/L) and TC/HDL-C ratio >3.5 [5]. Based on the Diabetes Federation Statement [21], glucose was considered high when its concentration was greater than 100 mg/dL (5.55 mmol/L). The HOMA-IR ratio cut point was established at 3.8, insulin cut point at 16.7 mU/L and HbA1c at 6% [22,23].

Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous variables and percentage (%) for categorical variables. For sex comparisons, independent *t*-tests were used to check mean differences for continuous variables, and the chi-square tests were used to verify frequency differences for categorical variables. Linear regression was performed to assess the association of CRF (independent variable) with the biomarkers (dependent variables) with and without adjustment for covariates. The biomarkers CRP, AST, ALT, AST/ALT ratio and GGT were adjusted in model 2 for age, sex, FM, TBW, SBP, TC, HDL-C, TG, glucose, insulin, statin intake, hypoglycaemic intake, antihypertensive medication intake and smoking status. The lipid profile variables (i.e. CT, HDL, LDL TG and CT/HDL) were adjusted as in the previous model 2 excluding the adjustment for TC, HDL-C and TG. Finally, covariates in model 2 for glucose, insulin, HOMA-IR and % HbA1c were the same of the first explained model 2 excluding glucose and insulin. The adjustment of model 3 for all the aforementioned variables included all covariates of model 2 + BMI. Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated (with and without adjustment for covariates) using logistic regression models to evaluate the associations of CRF with the relevant biomarkers, taking into account the previously explained cut points. Participants were mathematically divided into CRF tertiles (i.e. low, moderate and high CRF) for logistic regression analysis. The range in each group was as follows: the lowest tertile (Low-CRF group): $VO_{2peak} \leq 21.9\ mL \cdot kg^{-1} \cdot min^{-1}$ in men and $VO_{2peak} \leq 17.2\ mL \cdot kg^{-1} \cdot min^{-1}$ in women; the medium tertile (Moderate-CRF group): $21.9 < VO_{2peak} \leq 26.5\ mL \cdot kg^{-1} \cdot min^{-1}$ in men and $17.2 < VO_{2peak} \leq 21.1\ mL \cdot kg^{-1} \cdot min^{-1}$ in women; the highest tertile (High-CRF group): $VO_{2peak} > 26.5$ in men and $VO_{2peak} > 21.1\ mL \cdot kg^{-1} \cdot min^{-1}$ in women. Statistical significance was set at $p < .05$. All analyses were performed using Statistical Package for Social Sciences (IBM, Version 24).

Table 2. Linear regression models.

Linear regression model	β Coefficient	LCI	UCI	*p*	Model R^2
VO_{2peak}–CRP					
Unadjusted	**−0.377**	−0.568	−0.187	<.001	0.142
Model 2	−0.296	−0.638	0.048	.090	0.212
Model 3	−0.269	−0.575	0.037	.084	0.258
VO_{2peak}–AST					
Unadjusted	−0.051	0.196	−0.094	.487	0.003
Model 2	**−0.329**	−0.616	−0.042	.026	0.321
Model 3	**−0.328**	−0.616	−0.040	.026	0.324
VO_{2peak}–ALT					
Unadjusted	**−0.187**	−0.323	−0.051	.007	0.035
Model 2	**−0.377**	−0.635	−0.119	.005	0.452
Model 3	**−0.376**	−0.632	−0.120	.005	0.466
VO_{2peak}–AST/ALT					
Unadjusted	**0.153**	0.013	0.306	.037	0.023
Model 2	0.131	−0.131	0.393	.305	0.458
Model 3	0.128	−0.128	0.384	.318	0.469
VO_{2peak}–GGT					
Unadjusted	−0.128	−0.304	0.048	.153	0.016
Model 2	−0.151	−0.548	0.246	.441	0.644
Model 3	−0.115	−0.491	0.261	.534	0.701

Model 2 covariates: age, sex, fat mass, total body water, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, insulin, statin intake, hypoglycemic intake, antihypertensive medication intake, smoking status. Model 3: model 2 + body mass index. VO_{2peak}: peak oxygen consumption; CRP: C reactive protein; AST: aspartate aminotransferase; ALT: alanine transaminase; GGT: gamma-glutamyl transpeptidase; LCI: lower confidence interval (95%); UCI: upper confidence interval (95%).
Association between VO_{2peak} and CRP and hepatic enzymes. $N = 214$.
All values below $p < 0.05$ are in bold. *p* column shows the corresponding values.

Results

When split by sex (Table 1), men presented a higher ($p < .05$) age, TBW, DBP, VO_{2peak}, AST, ALT and TG, whilst women showed a higher ($p < .05$) FM, TC, HDL-C and LDL-C concentrations. There were no significant sex differences in any other variables.

A series of linear regression analyses were conducted to assess the independent associations between VO_{2peak} and variables in the biochemical profile. As shown in Table 2, VO_{2peak} was negatively associated with CRP ($p < .001$) unadjusted, however, but no significant associations in models 2 and 3 ($p = .084$). VO_{2peak} was negatively associated with ALT both unadjusted ($p = .007$) and following

Table 3. Linear regression models.

Linear regression model	β Coefficient	LCI	UCI	*p*	Model R^2
VO_{2peak}–TC					
Unadjusted	−0.002	−0.162	0.158	.981	0.000
Model 2	0.129	−0.171	0.429	.394	0.164
Model 3	0.123	−0.177	0.423	.413	0.184
VO_{2peak}–HDL-C					
Unadjusted	−0.050	−0.188	0.088	.473	0.002
Model 2	0.180	−0.102	0.462	.209	0.262
Model 3	0.173	−0.108	0.454	.223	0.282
VO_{2peak}–LDL-C					
Unadjusted	0.054	−0.087	0.195	.452	0.003
Model 2	0.235	−0.064	0.534	.121	0.271
Model 3	0.226	−0.074	0.526	.137	0.279
VO_{2peak}–TG					
Unadjusted	0.022	−0.179	0.093	.748	0.000
Model 2	0.063	−0.237	0.363	.677	0.193
Model 3	0.066	−0.232	0.364	.661	0.197
VO_{2peak}–TC/HDL					
Unadjusted	0.040	−0.096	0.176	.563	0.002
Model 2	−0.131	−0.427	0.165	.377	0.201
Model 3	−0.131	−0.427	0.165	.382	0.201
VO_{2peak}–Glucose					
Unadjusted	**−0.163**	−0.297	−0.029	.017	0.027
Model 2	−0.088	−0.239	0.063	.253	0.221
Model 3	−0.057	−0.215	0.101	.478	0.229
VO_{2peak}–Insulin					
Unadjusted	**−0.244**	−0.454	−0.035	.023	0.059
Model 2	−0.247	−0.503	0.009	.059	0.389
Model 3	−0.198	−0.438	0.042	.104	0.486
VO_{2peak}–HOMA-IR					
Unadjusted	**−0.288**	−0.494	−0.082	.007	0.083
Model 2	−0.258	−0.527	0.011	.060	0.332
Model 3	−0.208	−0.463	0.045	.106	0.428
VO_{2peak}–% HbA1c					
Unadjusted	−0.149	−0.354	0.062	.166	0.022
Model 2	−0.080	−0.302	0.142	.486	0.438
Model 3	−0.042	−0.246	0.168	.703	0.501

Model 2 covariates for TC, HDL-C, LDL-C, TG and TC/HDL-C: age, sex, fat mass, total body water, systolic blood pressure, glucose, insulin, statin intake, hypoglycemic intake, antihypertensive medication intake, smoking status. Model 3 for TC, HDL-C, LDL-C, TG and TC/HDL-C: model 2 + body mass index. Model 2 covariates for glucose, insulin, HOMA-IR and % HbA1c: age, sex, fat mass, total body water, systolic blood pressure, TC, HDL-C, TG, statin intake, hypoglycemic intake, antihypertensive medication intake, smoking status. Model 3 for glucose, insulin, HOMA-IR and % HbA1c: model 2 + body mass index. VO_{2peak}: peak oxygen consumption; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; HOMA-IR: insulin resistance index; HbA1c: haemoglobin A1c; LCI: lower confidence interval (95%); UCI: upper confidence interval (95%).
Association between VO_{2peak} and lipid profile and insulin sensitivity. $N = 214$. All values below $p < 0.05$ are in bold. *p* column shows the corresponding values.

adjustment of covariates ($p = .005$). Whilst AST was not significantly associated without adjustment, it was significantly associated when covariates were considered ($p = .026$) in the model β Coefficients of model 3 for AST and ALT were −0.328 and −0.376, respectively. The AST/ALT ratio was related to VO_{2peak} without adjustment ($\beta = 0.153$) but not when adjustments in model 2 and 3 were made. VO_{2peak} was not significantly associated with GGT. No significant associations were found between VO_{2peak} and any of the lipid profile variables (TC, HDL-C, LDL-C, TG and TC/HDL-C). In addition, VO_{2peak} was not associated with HbA1c (Table 3). However, when the regression was conducted without any adjustment, a negative relationship was found between VO_{2peak} and glucose, insulin and HOMA-IR ($\beta = -0.163$, $\beta = -0.244$ and $\beta = -0.288$, respectively). But, the association was not significant following adjustment ($p > .05$).

For some independent variables, logistic regression analysis confirmed the linear regression models. As shown in Table 4, high CRF group was 87% less likely to have elevated CRP when unadjusted. The association was significant in model 2 (high CRF group was 83% less likely to have elevated CRP), however, in model 3, only a trend toward significance was shown ($p < .064$). Otherwise, moderate and high CRF groups were less likely to have elevated AST (98% and 96%, respectively) and elevated ALT (87% and 89%, respectively) in model 3. GGT was associated with CRF groups in unadjusted analysis (i.e. 71% and 80% less likely to have elevated GGT in moderate and high CRF groups, respectively). However, no significant association ($p > .05$) was found following adjustment for covariates (Table 4). Logistic regression did not show a significant association between CRF groups and elevated TC, HDL-C, LDL-C and TG (Table 5). The high CRF group was 62% less likely to have an elevated TC/HDL-C ratio when compared to the low CRF group, but there was no significant association following adjustment. For glucose, associations were found in moderate and high CRF groups when unadjusted and following adjustment for covariates in model 2 ($p = .014$ and $p = .046$ for moderate and high CRF groups, respectively). In model 3, the moderate CRF group was 64% less likely to have elevated glucose compared to the low CRF group ($p = .016$), but there was no significance in high CRF group ($p = .096$). HOMA-IR showed a significant association with the high CRF group in the unadjusted model ($p = .037$) and in model 2 ($p = .043$). However, but there was no significance in model 3 ($p = .062$). Using logistic regression insulin and HbA1c did not show any significant associations with the CRF groups (Table 5).

Discussion

Although population from this study has been previously categorized by sex and CRF level [24], to our knowledge, this is the first study to determine the relationship between CRF and biochemical profile in overweight/obese adults diagnosed with HTN. The main findings of the study were: (1) CRF was independently and inversely associated with concentrations of AST and ALT; these relationships were confirmed by linear and logistic regression analysis. (2) CRP, AST/ALT ratio, GGT, TC/HDL-C ratio, glucose, insulin and HOMA-IR were associated, but not independently, with CRF in unadjusted linear and/or logistic regression models. In addition, glucose was independently associated with logistic regression analysis, with the moderate CRF group. As such, they were less likely to have elevated glucose compared to the low CRF group. A trend was observed in the high CRF group, but this was not significant.

Previously, higher levels of CRF and physical activity were inversely associated with hepatic enzymes [12,25]. In agreement with the current study, previous literature has reported an inverse association between CRF and both AST and ALT, which was independent of body composition

Table 4. Logistic regression models.

	Unadjusted				Model 2				Model 3			
	OR	LCI	UCI	*p*	OR	LCI	UCI	*p*	OR	LCI	UCI	*p*
Elevated CRP												
Moderate CRF	0.588	0.217	1.594	.297	1.158	0.274	4.894	.842	1.119	0.267	4.678	.878
High CRF	**0.128**	0.037	0.443	.001	**0.173**	0.031	0.965	.045	0.194	0.034	1.102	.064
Elevated AST												
Moderate CRF	**0.416**	0.176	0.982	.045	**0.022**	0.002	0.288	.004	**0.023**	0.002	0.288	.004
High CRF	**0.186**	0.059	0.587	.004	**0.040**	0.003	0.619	.021	**0.041**	0.003	0.641	.023
Elevated ALT												
Moderate CRF	**0.456**	0.231	0.900	.024	**0.145**	0.032	0.650	.012	**0.127**	0.026	0.62	.011
High CRF	**0.221**	0.103	0.474	<.001	**0.121**	0.019	0.768	.025	**0.109**	0.016	0.75	.024
Low AST/ALT												
Moderate CRF	1.836	0.769	4.385	.171	0.336	0.041	2.769	.310	0.310	0.035	2.718	.290
High CRF	2.627	1.091	6.327	.153	0.229	0.019	2.712	.243	0.225	0.019	2.678	.238
Elevated GGT												
Moderate CRF	**0.293**	0.095	0.901	.032	0.009	0.000	4.216	.133	0.009	0.000	4.978	.145
High CRF	**0.202**	0.053	0.768	.019	25.965	0.060	11299.629	.293	25.832	0.062	10691.539	.290

These odds ratios are referring for that in the low CRF group. Model 2 covariates: age, sex, fat mass, total body water, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, insulin, statin intake, hypoglycemic intake, antihypertensive medication intake, smoking status. Model 3: model 2 + body mass index. CRP: C reactive protein; AST: aspartate aminotransferase; ALT: alanine transaminase; GGT: gamma-glutamyl transpeptidase; OR: odds ratio; LCI: lower confidence interval (95%); UCI: upper confidence interval (95%).
Association between VO_{2peak} and CRP and hepatic enzymes. $N = 214$.
All values below $p < 0.05$ are in bold. P column shows the corresponding values.

Table 5. Logistic regression models.

	Unadjusted				Model 2				Model 3			
	OR	LCI	UCI	*p*	OR	LCI	UCI	*p*	OR	LCI	UCI	*p*
Elevated TC												
Moderate CRF	1.027	0.535	1.970	.936	0.315	0.070	1.423	.133	0.317	0.071	1.419	.133
High CRF	1.528	0.780	2.995	.217	2.224	0.373	13.260	.380	2.207	0.373	13.067	.383
Low HDL-C												
Moderate CRF	0.867	0.394	1.905	.722	2.521	0.459	13.837	.287	2.243	0.402	12.503	.357
High CRF	0.636	0.273	1.479	.293	0.557	0.067	4.602	.587	0.511	0.060	4.358	.539
Elevated LDL-C												
Moderate CRF	0.546	0.218	1.367	.196	0.349	0.026	4.666	.454	0.358	0.027	4.818	.439
High CRF	1.200	0.419	3.439	.734	1.605	0.056	46.155	.873	1.606	0.057	45.426	.781
Elevated TG												
Moderate CRF	1.182	0.491	2.847	.710	0.711	0.115	4.378	.713	0.496	0.072	3.434	.478
High CRF	0.626	0.227	1.723	.364	1.347	0.141	12.885	.796	1.073	0.105	11.016	.952
Elevated TC/HDL												
Moderate CRF	0.589	0.260	1.335	.205	0.286	0.045	1.837	.187	0.278	0.042	1.815	.181
High CRF	**0.383**	0.172	0.851	.018	0.384	0.052	2.852	.350	0.381	0.051	2.847	.347
Elevated Glucose												
Moderate CRF	0.529	0.273	1.025	.059	**0.357**	0.158	0.809	.014	**0.364**	0.160	0.827	.016
High CRF	**0.388**	0.194	0.777	.008	**0.408**	0.170	0.983	.046	0.457	0.182	1.148	.096
Elevated Insulin												
Moderate CRF	1.842	0.552	6.140	6.140	1.992	0.397	9.990	.402	2.383	0.420	13.529	.327
High CRF	0.126	0.014	1.172	.069	0.058	0.001	2.300	.129	0.070	0.002	2.563	.148
Elevated HOMA-IR												
Moderate CRF	1.161	0.378	3.567	.795	0.605	0.116	3.167	.552	0.632	0.106	3.771	.614
High CRF	**0.165**	0.030	0.898	.037	**0.088**	0.008	0.931	.043	0.109	0.011	1.118	.062
Elevated % HbA1c												
Moderate CRF	1.006	0.323	3.134	.992	1.566	0.362	6.774	.548	1.797	0.353	9.150	.481
High CRF	0.366	0.092	1.453	.153	0.359	0.050	2.595	.310	0.464	0.058	3.694	.469

These odds ratios are referring for that in the low CRF group. Model 2 covariates for TC, HDL-C, LDL-C, TG and TC/HDL-C: age, sex, fat mass, total body water, systolic blood pressure, glucose, insulin, statin intake, hypoglycemic intake, antihypertensive medication intake, smoking status. Model 3 for TC, HDL-C, LDL-C, TG and TC/HDL-C: model 2 + body mass index. Model 2 covariates for glucose, insulin, HOMA-IR and % HbA1c: age, sex, fat mass, total body water, systolic blood pressure, TC, HDL-C, TG, statin intake, hypoglycemic intake, antihypertensive medication intake, smoking status. Model 3 for glucose, insulin, HOMA-IR and % HbA1c: model 2 + body mass index. TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; HOMA-IR: insulin resistance index; HbA1c: haemoglobin A1c; OR: odds ratio; LCI: lower confidence interval (95%); UCI: upper confidence interval (95%).
Association between VO_{2peak} and lipid profile and insulin sensitivity. $N = 214$.
All values below $p < 0.05$ are in bold. *p* column shows the corresponding values.

[12,25]. When unadjusted, GGT and AST/ALT ratio showed a favorable association with CRF, but it was dependent of other covariates. Other research has described similar findings [26], indicating that body composition mediated CRF and its relationship with GGT and AST/ALT. It is known that hepatic enzymes are found not only in the liver but also in cardiac and muscle cells. However, while ALT and GGT mainly exist in the hepatic cells and, therefore, are related to liver and abdominal fat, AST is also present in cardiac and muscle cells. Thus, low CRF arising from the

lack of regular aerobic exercise has adverse effects on the hepatic enzymes and muscle oxidative capacity, concentrations of AST, ALT (i.e. in the present study high CRF group was 96% and 85% less likely to have elevated concentrations in model 3, respectively) and GGT (i.e. high CRF group was 80% less likely to have raised concentration in model 1) [12]. These results may be associated with the presence of non-alcoholic fatty liver disease [27].

Previous studies which did not look at overweight/obese populations with HTN have suggested that a high CRF may attenuate the risk of incidence in HTN in individuals with high concentrations of inflammatory markers, such as CRP [28]. Thus, better CRF was strongly associated with reduced CRP concentrations even after adjustment for BMI and FM [11,29]. In addition, a better body composition has previously been associated with lower CRP concentrations [30], and higher CRF with an enhanced body composition [31]. Findings from the current study may support the notion that CRF is negatively associated with CRP, even though the adjusted analysis only showed a trend toward significance. Thus, it may be that there is an underlying mechanism that explains the relationship although it is still not well understood [29]. Circulating concentrations of some inflammatory markers, in particular, CRP, raises the risk of development and progression of atherosclerosis, and as a consequence are reliable predictors of CV events [32]. Although it is beyond the scope of this article, previous studies have presented the potential pathways: (1) hepatic CRP production is stimulated by interleukin-6 and, to a lesser extent, by interleukin-1 and tumor necrosis factor-α, which are stimulated from the visceral adipose tissue [11]; (2) regular physical activity and acute exercise have shown to decrease resting concentrations of interleukin-6 and tumor necrosis factor-α and, thus, potentially, CRP [11,29]; (3) increased sympathetic stimulation is related to inflammation. Therefore, reductions in inflammatory markers occur with an enhanced fitness and concomitant better autonomic nervous system activity through exercise-induced cholinergic anti-inflammatory pathways [33].

No associations were found between CRF and any markers of lipid profile in the current study with the exception of TC/HDL-C ratio. Those participants with high CRF had reduced chance of having a high TC/HDL-C ratio (62% less likely); though, the association disappeared when adjusted. The TC/HDL-C ratio is an essential cumulative index of the presence of an atherogenic dyslipidemic profile related to insulin resistance [34]. Lack of exercise or low CRF is linked with a greater endothelial dysfunction (i.e. reduced vasodilation along with greater proinflammatory and prothrombic markers), HTN, and an increased TC/HDL-C [35]. However, exercise has been shown to remodel the vessels positively [35]. Likewise, previous studies found an association between CRF and lipid profile, directly with HDL-C, and inversely with TG and TC/HDL-C ratio [9,36], whereas LDL-C appears not to be linked with CRF. A recent longitudinal study has shown that anthropometric parameters, such as BMI and waist circumference, were more associated with blood lipids than CRF was [36]. Thus, a better anthropometric profile could improve the blood lipid profile, whereas CRF may have limited influence [36]. However, more research is needed to confirm the lack of association shown in overweight/obese participants with HTN.

Indicators of glucose tolerance and insulin resistance (specifically, glucose, insulin, and HOMA-IR) were inversely linked with CRF in the current study (Tables 3 and 5), but HbA1c did not show any association with CRF. Previously, the association between CRF, glucose tolerance and insulin resistance has been apparent, and it appears to be independent of body composition [37,38]. In the present study, the glucose concentration also shows an independent association in logistic regression analysis with the moderate CRF group (i.e. resulting in less likely to have elevated glucose than the low CRF group). However, not all studies showed independence from body composition [10], and as such more research is needed to clarify the potential associations between these parameters, particularly in an overweight/obese population with HTN. Even so, according to previous research, it seems clear that an increased CRF in obese adults has positive effects on insulin sensitivity [38].

Because of the associations among CRF, biochemical profile, CV risk and mortality [4,8,32], the results of the current study build on evidence of highlighting the usefulness of CRF as a potential screening tool in the public health setting. Early identification of low CRF would mean early detection of people with higher odds of developing CVD and mortality [8,13]. The present study highlights the importance that CRF has in maintaining a healthy biochemical profile.

The authors feel that to interpret findings from the current study, it is essential to consider the strengths and limitations. The design of the study allowed for a good cross-sectional presentation. Although the aim of the study was not to establish mechanisms behind the relationships, we were able to identify several associations in a small ($n = 214$) but specific population with overweight/obesity and HTN. However, possible confounding factors could have influenced the relationships, such as physical activity or diet, and even though the analysis was adjusted with medications, it is difficult to assess their influence on the results. Despite this, using the objective measure of CRF and the inclusion of body composition as a covariate in the analyses, we have significantly enhanced the existing body of research in this at-risk population.

Conclusion

The current study suggests that CRF is associated with the biochemical profile in an overweight/obese population with HTN. An inverse and independent association was observed between CRF and AST and ALT, whereas the influence of CRF is limited by other covariates in the association with CRP, AST/ALT ratio, GGT, TC/HDL-C ratio, glucose, insulin and HOMA-IR. As such, a healthy lifestyle intervention should be adopted by this population to improve CRF and consequently their biochemical profile. Future work should

look to determine the effects of conducting regular physical activity and exercise to enhance CRF and biochemical profile.

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Disclosure

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9.2. Anexo 2: *"Long-Term Effects in the EXERDIET-HTA Study: Supervised Exercise Training vs. Physical Activity Advice"*

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Long-term Effects in the EXERDIET-HTA Study: Supervised Exercise Training *vs.* Physical Activity Advice

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ABSTRACT

Purpose: To determine whether improvements in cardiorespiratory fitness (CRF), blood pressure (BP) and body composition previously seen after a 16-week exercise intervention (POST) with hypocaloric diet are maintained following six months (6M) of unsupervised exercise time. **Methods**: Overweight/obese, physically inactive participants with primary hypertension (HTN) (n = 190) were randomly assigned into an attention control group (physical activity recommendations) or one of three supervised exercise groups. After POST, all participants received diet and physical activity advice for the following 6M but no supervision. All anthropometric and physiological measurements were taken pre and post the 16-week supervised intervention period, as well as after 6M of no supervision. **Results**: After 6M: 1) body mass (BM) (Δ = 2.5%) and waist circumference (Δ = 1.8%) were higher ($P < .005$) than POST, but lower ($P < .005$) than pre-intervention (BM, Δ = −5.1%; waist circumference, Δ = −4.7%), with high-volume and high-intensity interval training group revealing a higher BM reduction (Δ = −6.4 kg) compared to control group (Δ = −3.5 kg); 2) BP variables were higher ($P < .001$) compared to POST with no change from pre-intervention; and 3) CRF was higher compared to pre-intervention (Δ = 17.1%, $P < .001$) but lower than POST (Δ = −5.7%, $P < .001$). **Conclusions**: When an overweight/obese population with HTN attains significant improvements in cardiometabolic health POST intervention with diet restriction, there is a significant reduction following 6M when exercise and diet supervision is removed, and only recommendations were applied. These results suggest the need for a regular, systematic and supervised diet and exercise programs to avoid subsequent declines in cardiometabolic health.

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Obesity; blood pressure; cardiorespiratory fitness; body composition

The prevalence of primary hypertension (HTN) and overweight/obesity is considered an important public health issue in developed countries (Jensen et al., 2014; Mancia et al., 2013). Overall, 39% of adults were overweight in 2016, and 13% were obese (World Health Organization, 2018). Worryingly both HTN and overweight/obesity are two of the most common causes of premature death, yet they are modifiable cardiovascular risk factors (Authors/Task Force Members et al., 2016; Mancia et al., 2013). Consequently, lowering both blood pressure (BP) and body mass (BM) would likely result in substantial improvements in cardiometabolic health (Authors/Task Force Members et al., 2016).

All international guidelines recommend appropriate lifestyle changes for the prevention and treatment of HTN and obesity (Jensen et al., 2014; Mancia et al., 2013). Interventions combining both exercise and diet have been shown to be effective for reducing BM, BP and increasing cardiorespiratory fitness (CRF) (Landsberg et al., 2013; Mancia et al., 2013). Recently, CRF (measured by peak oxygen uptake [$\dot{V}O_{2peak}$]) has been recognized as an independent predictor of all-cause, and disease-specific mortality in a variety of different populations (Harber et al., 2017). As such CRF has an inverse relationship with cardiovascular disease risk factors such as dyslipidemia, obesity, diabetes mellitus, and HTN (Bakker, Sui, Brellenthin, & Lee, 2018; Myers et al., 2015). Consequently, people with HTN are advised to perform at least 30 min of moderate-intensity dynamic aerobic exercise 5–7 days per week (Mancia et al., 2013). However, alternative exercise options are available, including interval training which has previously shown to be a time-efficient method for improving CRF in a population with HTN (Gorostegi-Anduaga et al., 2018b; Pescatello, MacDonald, Lamberti, & Johnson, 2015). In order for interval training to be effective, the exercise program should be designed in a

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systematic and individualized manner by an exercise specialist, and Frequency, Intensity, Time and Type should be considered (*i.e.*, FITT principle) (Pescatello et al., 2015). Previous data from the EXERDIET-HTA study found that all groups (*i.e.*, diet and supervised aerobic exercise *vs.* diet and physical activity advice only), significantly improved body composition, BP and CRF following a 16-week intervention program, regardless exercise supervision, and independent of the FITT principle *(i.e.*, different volumes and exercise intensities). However, it was shown that the supervised exercise groups (*i.e.*, high volume and moderate-intensity continuous training [HV-MICT], HV and high-intensity interval training [HV-HIIT], and low volume-HIIT [LV-HIIT]) had significantly greater improvements in BM and CRF compared to a group which only had physical activity advice (Gorostegi-Anduaga et al., 2018a).

Whilst short-term diet and physical activity interventions are important for the reduction of BM and improvement of cardiometabolic health, the main goal is a lifestyle based on long-standing behavioral patterns (*i.e.*, Dietary Approaches to Stop Hypertension [DASH] diet, and regular physical exercise) (Authors/Task Force Members et al., 2016; Mancia et al., 2013). No known longitudinal study has investigated the long-term effects of supervised training cessation or the persistence of changes in overweight/obese and hypertensive adults, who are receiving only diet and physical activity advice after an intervention period. Further, previous literature provides discordant data with respect to the type of exercise, periods of training, supervised training cessation, and population studied. Thus, while some investigations found that the exercise training induced-improvements were maintained after supervised training cessation period (Mora-Rodriguez et al., 2014; Tokmakidis et al., 2014), other found significant reductions (Moker, Bateman, Kraus, & Pescatello, 2014; Volaklis, Douda, Kokkinos, & Tokmakidis, 2006). Given this discourse, the results cannot be applied to an overweight/obese population with HTN.

Therefore, the aim of this study was to determine whether the improvements in CRF, BP and body composition previously seen during both a 16-week supervised exercise training intervention and a physical activity advice intervention with hypocaloric diet are maintained following six months (6M) of unsupervised time.

Methods

Research design

Data from the current study are from the EXERDIET-HTA study (multi-arm parallel, a randomized, single-blind controlled experimental trial, www.clinicaltrials.gov, number NCT02283047). This longitudinal data were collected between September 2013 and January 2018. While the current study will describe the methods, more specific details regarding the design, selection criteria and procedures associated with the EXERDIET-HTA study have been previously published (Maldonado-Martín et al., 2016). The Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) and Clinical Investigation of Araba University Hospital (2015–030) approved the study design, protocols, and informed consent.

Participants

Two-hundred and 24 non-Hispanic white participants took part in the EXERDIET-HTA study, conducted in Vitoria-Gasteiz (Basque Country, Spain). Fifteen participants left the study during the intervention, and 19 more did not attend the 6M assessment. Therefore, 190 participants (n = 126 men and n = 64 women, 54.3 ± 7.3 yrs.) completed all three visits and are included in all analysis. A schematic representing the study design is presented in Figure 1. Participants were non-physically active, overweight or obese, with primary HTN. Hypertension was defined as systolic BP (SBP) of 140–179 mmHg and/or diastolic BP (DBP) of 90–109 mmHg, and/or under antihypertensive pharmacological treatment (Mancia et al., 2013). To ensure participants were non-physically active, the International Physical Activity Questionnaire (IPAQ) was used. For all other inclusion and exclusion criteria, please refer to the previously published study protocol (Maldonado-Martín et al., 2016).

Measurements

Anthropometry and body composition

Measurements were taken in accordance with guidelines from the International Society for the Advancement of Kinanthropometry. Stature, total BM, BM index (BMI), waist and hip circumferences, waist-to-hip ratio (WHR), fat-free mass (FFM), total body water and fat body mass (FBM) were recorded using a Tanita bio-impedance device (BF 350, Tokyo, Japan).

Blood pressure

An ambulatory BP monitoring (ABPM) recorder (6100-Welch Allyn, New York, USA) was used during a 24-hr period. In accordance with the European guidelines (Mancia et al., 2013), measures were taken at 30 min intervals during the daytime and 60 min during night time. Participants self-disclosed their typical bedtime and wake up time, and this was used to define the

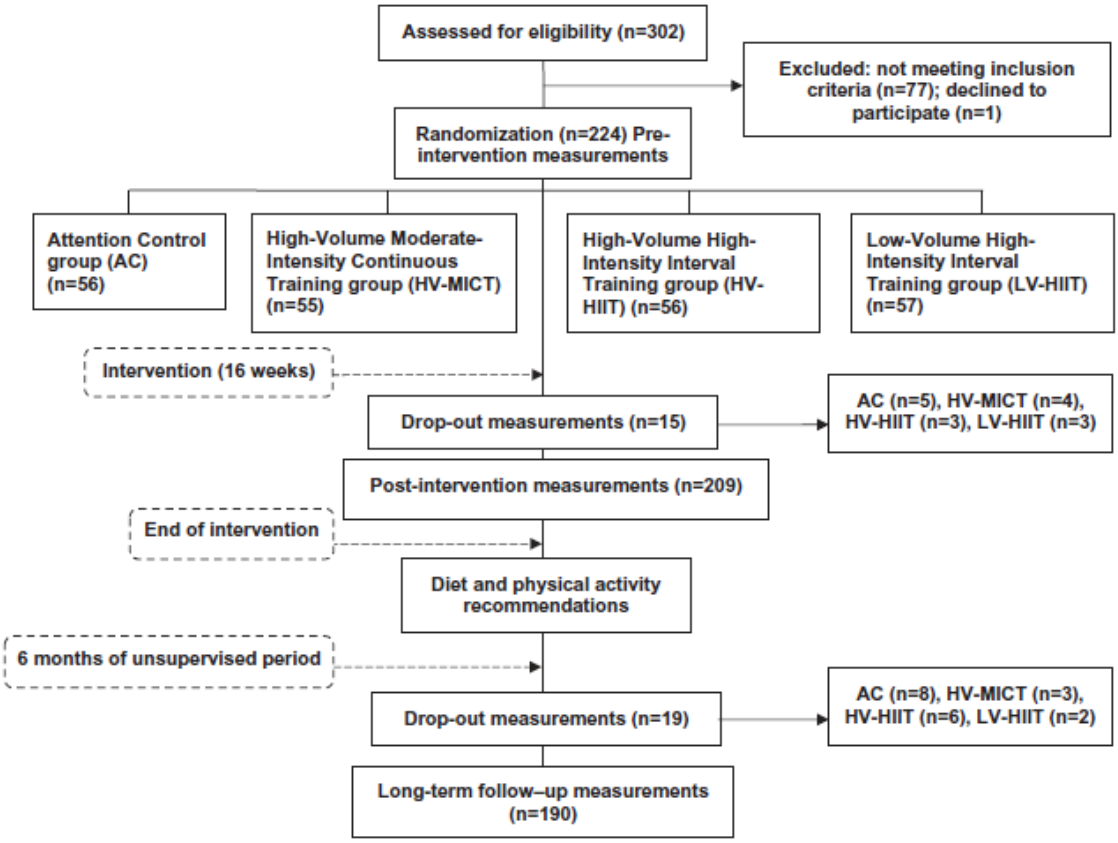

Figure 1. Flow diagram of the EXERDIET-HTA study from recruitment to the 6-month follow-up unsupervised period.

automated 30 min and 60 min day/night time intervals (Maldonado-Martín et al., 2016). Mean BP (MBP) was calculated as [DBP+0.333x(SBP-DBP)].

Cardiorespiratory fitness

Cardiorespiratory fitness ($\dot{V}O_{2peak}$) was assessed using an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). The testing protocol maintained 70 rpm throughout and started at 40 W with gradual increments of 10 W every minute until volitional exhaustion occurred. For safety reasons, an electrocardiogram was used throughout the test. Expired gas analysis was collected using an Ergo CardMedi-soft S.S (Belgium Ref. USM001 V1.0) that was calibrated prior to each test. The test was considered "true" in the presence of two or more of the following criteria: 1) volitional fatigue (>18 on BORG scale), 2) peak respiratory exchange ratio of ≥1.1, 3) achieving >85% of age-predicted maximum heart rate, and 4) a plateau in oxygen uptake and/or heart rate (Mezzani et al., 2012). Blood pressure was measured every 2 min both during and following the cardiopulmonary exercise test. During the recovery period, participants remained on the bike for 5 min to monitor the electrocardiogram and BP. All other measurements have been previously published (Maldonado-Martín et al., 2016).

Intervention

After baseline measurements, participants were randomly allocated in one of the four intervention groups stratified by sex, systolic BP (SBP), BMI, and age using a time-blocked computerized randomization program. The four groups were attention control group (AC, participants were given physical activity advice only) and three supervised exercise groups: HV-MICT, HV-HIIT, and LV-HIIT, which trained two non-consecutive days under supervision by exercise specialists for a 16-week period. In addition, all participants received a hypocaloric diet. The advice for the AC group was to participate in at least 30 min of moderate-intensity aerobic exercise (walking, jogging, cycling or swimming) 5–7 days per week blended with some dynamic resistance exercises (Maldonado-Martín et al., 2016). All

the protocols for each group, including procedures and diet intervention have been previously published (Gorostegi-Anduaga et al., 2018b; Maldonado-Martín et al., 2016).

Six months post-intervention follow-up

After the 16-week intervention (POST), all participants received diet and physical activity advice for the following 6M. Participants had no further supervised intervention or attention from any of the research staff. Participants were also provided heart rate data for their current moderate and high exercise intensity domains to enable them to self-monitor. All the aforementioned anthropometric and physiological measurements for the study were taken before, POST, and 6M following the end of the intervention (Figure 1).

Statistical analysis

Descriptive statistics were calculated for all variables and presented as mean±SD unless otherwise stated. To determine normality, a Kolgomorov-Smirnov test was performed on all variables, and those with a skewed distribution were log-transformed prior to any analysis. Repeated measures analysis of variance (ANOVA) was used to test the change in body composition, BP and CRF variables over time. Bonferroni post-hoc test was used to determine the level of significance when a significant main effect was found. From the repeated measures ANOVA, eta-squared (η^2) was reported as a measure of effect size (ES). Analysis of covariance (ANCOVA) was performed to test the differences among groups in the delta score (differences between pre- *vs.* post-intervention and post-intervention *vs.* 6M follow-up); adjusting the analysis for age, sex and changes in BM (except for BM and BMI, that were adjusted by age and sex). Helmert contrast was used to compare the AC group *vs.* supervised exercise groups, and Bonferroni post-hoc test was used to determine the level of significance between groups when a significant main effect was found. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 24.0. For all analysis, the alpha level of significance was set at $P < .05$.

Results

Baseline data (Gorostegi-Anduaga et al., 2018b) and the effects of the 16-week intervention (Gorostegi-Anduaga et al., 2018a) from the EXERDIET-HTA study have been previously published.

Table 1 presents body composition, BP, and CRF data at baseline (pre-intervention), POST and after the 6M post-intervention period (long-term follow-up).

Repeated measures ANOVA and Bonferroni post-hoc analysis on all participants (irrespective of intervention group) found that BM ($P < .001$, difference%, $\Delta = -5.1\%$, ES = 0.57), BMI ($P < .001$, $\Delta = -5.1\%$, ES = 0.57), and waist circumference ($P < .001$, $\Delta = -4.7\%$, ES = 0.45) at 6M follow-up were all significantly reduced from pre-intervention. In addition, FFM ($P < .001$, $\Delta = 3.0\%$, ES = 0.25) at 6M follow-up was significantly higher than the pre-intervention. However, at 6M follow-up, BM ($P < .001$, $\Delta = 2.5\%$), BMI ($P < .001$, $\Delta = 2.7\%$) and waist circumference ($P < .001$, $\Delta = 1.8\%$) were significantly higher than immediately POST, and FFM ($P < .001$, $\Delta = -2.2\%$) was significantly lower at immediately POST compared to 6M follow-up (Table 1 and Figure 2(d)). The ANCOVA analysis revealed there were significant between-group differences in BM ($P = .034$) and BMI ($P = .049$). Post-hoc analysis revealed a higher BM reduction in the HV-HIIT group (pre-intervention *vs.* 6M follow-up, $\Delta = -6.4$ kg, 95% confidence interval, CI = −8.1–4.7 kg) compared to AC ($\Delta = -3.5$ kg, 95% CI = −4.9–2.0 kg) group (Table 1 and Figure 2(a)). No other significant between-group differences were detected in changes between pre-intervention *vs.* 6M follow-up and POST *vs.* 6M follow-up measures.

Repeated measures ANOVA and Bonferroni post-hoc analysis found that there was no significant change from pre-intervention to 6M follow-up for SBP, DBP, and MBP ($P > .05$) in all participants irrespective of the intervention group. However, SBP ($\Delta = 4.6\%$, ES = 0.14), DBP ($\Delta = 4.6\%$, ES = 0.17) and MBP ($\Delta = 4.6\%$, ES = 0.17) were higher ($P < .001$) at 6M follow-up compared to immediately POST (Table 1 and Figure 2(d)). According to CRF, $\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) and MET were higher at 6M follow-up compared to pre-intervention ($\Delta = 17.1\%$, $P < .001$, ES = 0.35) and lower than immediately POST ($\Delta = -5.7\%$, $P < .001$, Table 1 and Figure 2(d)). Helmert contrast revealed there were significant between-group differences (pre-intervention *vs.* 6M follow-up, AC *vs.* exercise groups) in DBP ($P = .042$) and MBP ($P = .042$), with AC group having the smallest decline in DBP and MBP compared to exercise groups at 6M follow-up when compared with pre-intervention. Further, Bonferroni post-hoc analysis showed pre-intervention *vs.* 6M follow-up differences ($P = .037$) between AC ($\Delta = -2.4$ mmHg, 95% CI = −5.3–0.6 mmHg) and HV-MICT in DBP ($\Delta = 1.0$ mmHg, 95% CI = −1.9–3.9 mmHg) resulting in the change lower for the AC group. No other significant between-group

Table 1. Changes in mean ± SD body composition, blood pressure and cardiorespiratory fitness at pre-intervention (PRE), immediately post-intervention (POST), and 6 months following supervised exercise cessation (6M).

	All (n = 190)	Effect Size (η^2)	AC (n = 43)	HV-MICT (n = 48)	HV-HIIT (n = 47)	LV-HIIT (n = 52)	Time x group	*P* AC *vs.* EG PRE-6M	*P* groups PRE-6M	*P* AC *vs.* EG POST-6M	*P* groups POST-6M
Body mass (kg)											
PRE	90.7 ± 15.2	0.571	87.8 ± 13.3	93.2 ± 16.8	90.2 ± 16.9	91.2 ± 13.6	**0.029**	0.078	**0.034**$^{\#}$	0.953	0.297
POST	83.9 ± 14.2		82.2 ± 13.4	85.6 ± 15.6	82.4 ± 15.3	85.1 ± 12.7					
6M	86.0 ± 15.0*		84.3 ± 13.8*	88.2 ± 16.8*	83.4 ± 16.1*	87.4 ± 12.9*					
BMI (kg/m^2)											
PRE	31.6 ± 4.0	0.572	30.9 ± 3.6	32.4 ± 4.6	31.1 ± 3.8	31.8 ± 4.1	**0.029**	0.083	**0.049**	0.839	0.287
POST	29.2 ± 3.9		28.9 ± 3.9	29.8 ± 4.1	28.5 ± 3.7	29.7 ± 3.9					
6M	30.0 ± 4.0*		29.7 ± 4.0*	30.6 ± 4.3*	29.0 ± 3.9*	30.5 ± 3.8*					
Waist (cm)											
PRE	102.6 ± 10.9	0.445	101.6 ± 10.2	104.9 ± 12.1	101.3 ± 12.1	102.5 ± 9.2	0.290	0.275	0.844	0.949	0.865
POST	96.1 ± 10.5		96.3 ± 10.3	97.8 ± 10.9	94.0 ± 12.1	96.1 ± 10.5					
6M	97.8 ± 11.0*		97.9 ± 10.2^{x}	99.6 ± 12.3^{x}	95.1 ± 11.9^{x}	98.4 ± 9.2*					
FFM (%)											
PRE	66.2 ± 7.8	0.252	66.6 ± 7.8	64.5 ± 8.3	67.3 ± 6.8	66.6 ± 8.0	0.202	0.978	0.554	0.454	0.455
POST	69.7 ± 8.1		69.2 ± 8.3	68.4 ± 8.1	71.4 ± 7.4	69.8 ± 8.4					
6M	68.2 ± 8.5*		68.1 ± 8.1^{x}	67.1 ± 8.0*	70.3 ± 7.4*	67.5 ± 10.0					
SBP (mmHg)											
PRE	135.1 ± 12.4	0.144	138.6 ± 13.2	133.5 ± 12.0	131.9 ± 11.0	136.0 ± 12.6	0.124	0.067	0.138	0.091	0.067
POST	128.0 ± 11.1		132.3 ± 14.0	125.6 ± 8.6	128.1 ± 10.1	126.6 ± 10.5					
6M	133.9 ± 12.5$^{\$}$		135.2 ± 12.3	134.5 ± 12.8$^{\$}$	130.9 ± 10.2	134.8 ± 13.9$^{\$}$					
DBP (mmHg)											
PRE	78.0 ± 7.8	0.172	79.9 ± 7.7	75.2 ± 8.0	78.7 ± 7.1	78.4 ± 7.9	0.155	**0.042**	**0.037**$^{\blacktriangledown}$	0.256	0.114
POST	73.7 ± 7.4		75.3 ± 8.1	71.6 ± 6.9	73.6 ± 7.4	73.6 ± 7.6					
6M	77.1 ± 8.0$^{\$}$		77.6 ± 7.2	76.2 ± 9.1$^{\$}$	76.4 ± 7.2	78.1 ± 8.3$^{\$}$					
MBP (mmHg)											
PRE	97.0 ± 8.4	0.172	99.5 ± 8.8	94.6 ± 8.2	96.4 ± 7.6	97.6 ± 8.6	0.157	**0.042**	0.074	0.136	0.066
POST	91.8 ± 7.8		94.3 ± 9.2	89.6 ± 6.4	92.5 ± 7.2	91.3 ± 7.8					
6M	96.0 ± 8.6$^{\$}$		96.8 ± 8.1	95.6 ± 9.4$^{\$}$	94.6 ± 7.6	97.0 ± 9.3$^{\$}$					
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})											
PRE	22.8 ± 5.5	0.353	24.6 ± 6.6	21.8 ± 5.1	22.5 ± 5.0	22.8 ± 5.3	**0.010**	0.191	0.426	0.098	0.299
POST	28.3 ± 7.5		27.4 ± 8.2	27.0 ± 6.9	29.8 ± 6.7	28.3 ± 6.7					
6M	26.7 ± 7.3*		27.0 ± 6.9^{x}	25.2 ± 6.2*	27.5 ± 7.8*	27.2 ± 8.0^{x}					
MET											
PRE	6.5 ± 1.6	0.353	7.0 ± 1.9	6.2 ± 1.4	6.4 ± 1.4	6.5 ± 1.6	**0.018**	0.212	0.549	0.100	0.332
POST	8.1 ± 2.2		7.8 ± 2.4	7.7 ± 2.0	8.5 ± 2.3	8.2 ± 1.9					
6M	7.6 ± 2.1*		7.7 ± 2.0^{x}	7.2 ± 1.8*	7.9 ± 2.2*	7.7 ± 2.3^{x}					

AC: attention control group; HV: high volume; LV: low volume; MICT: moderate-intensity continuous training group; HIIT: high-intensity interval training group; EG: Exercise groups; BMI: body mass index; Waist: Waist circumference; FFM: fat-free mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; $\dot{V}O_{2peak}$: peak oxygen uptake; MET: metabolic equivalent of task.
*$P < 0.005$ between POST-6M and PRE-6M. $^{x}P < 0.005$ between PRE-6M. $^{\$}P < 0.005$ between POST-6M. $^{\#}P < 0.005$ AC and HV-HIIT. $^{\blacktriangledown}P < 0.005$ between AC and HV-MICT.

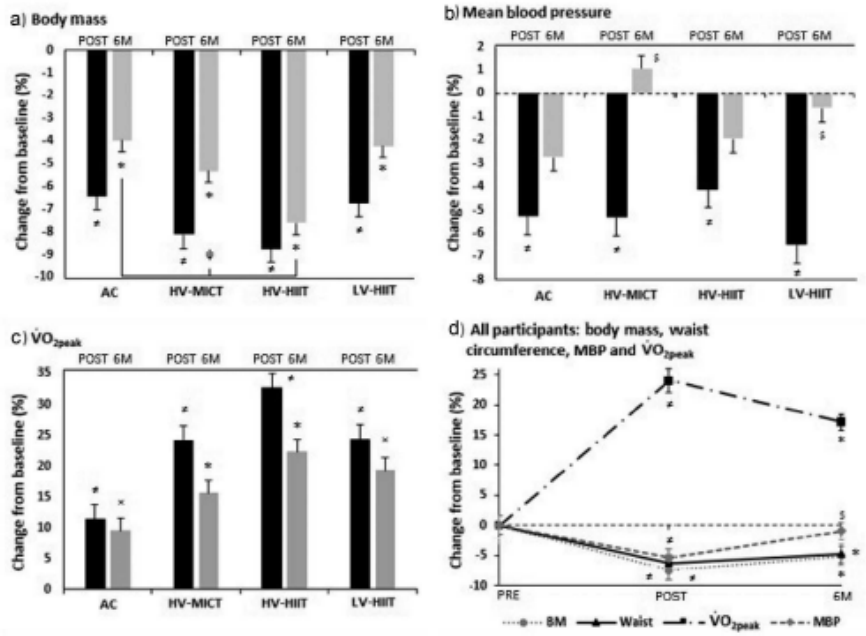

Figure 2. Percentage change from pre-intervention in percentages of body mass (BM), (a), mean blood pressure (MBP), (b) and peak oxygen uptake ($\dot{V}O_{2peak}$), (c) displayed as group. Change from baseline of the whole sample in percentages of body mass, MBP, waist circumference (Waist) and $\dot{V}O_{2peak}$ (d). PRE: pre-intervention measurements. POST: post-intervention measurements. 6M: long-term six months follow-up measurements. AC: attention control group; HV: high volume; LV: low volume; MICT: moderate-intensity continuous training group; HIIT: high-intensity interval training group. *Note.* $^{\neq}$ $P < .005$ between POST-PRE. * $P < .005$ between 6M-POST and 6M-PRE. $^{\times}$ $P < .005$ between 6M-PRE. $ $P < .005$ between 6M-POST. $^{\varphi}$ $P < .005$ AC and HV-HIIT in change between PRE-6M.

differences were observed in any other variables (Table 1 and Figure 2(b,c)).

Discussion

The effects of different aerobic exercise programs conducted twice a week in conjunction with a hypocaloric DASH diet have been previously analyzed (Gorostegi-Anduaga et al., 2018a). The authors reported that the intervention was an optimal non-pharmacological tool in the management of risk factors in overweight/obese, non-physically active individuals with HTN. Thus, after the 16 weeks intervention, body composition, BP, and CRF significantly improved in all groups (*i.e.*, supervised exercise, and physical activity advice). In addition, the study revealed between-group differences; the supervised exercise group was better than the AC group for reducing BM and improving CRF. However, there were no between-group differences in BP (Gorostegi-Anduaga et al., 2018a).

In the present study, the focus was to analyze the effects of withdrawing exercise supervision for 6M post following the 16-week intervention period. In addition, a secondary aim was to determine any potential differences between the 16-week intervention groups (supervised exercise training *vs.* physical activity advice). The main findings of the current study were: 1) the intervention induced-benefits in body composition and CRF were not maintained after 6M of physical activity advice, but they were still significantly better than those seen pre-interventions. However, the significant improvement in BP returned to baseline following 6M supervision cessation; 2) although a favorable effect by HV-HIIT exercise-induced in BM compared to AC group was found after 6M follow-up, there were no other significant between-group differences following the removal of exercise and diet supervision.

Long-term detraining syndrome or exercise training cessation is a clinical state arising when individuals involved in a systematic, supervised, designed exercise program suddenly stop their regular physical activity for more than 4 weeks. As such, the physiological consequences of an insufficient training stimulus to maintain training-induced adaptations will be presented (Mujika & Padilla, 2000a, 2000b). In the current study, the removal of supervised exercise training followed by 6M of only physical activity advice resulted in a worsening of the positive adaptations, which were previously achieved

during the supervised 16-week intervention in the all groups (supervised exercise, and physical activity advice only group). After this withdrawal, both body composition (*i.e.*, BM, Δ = 2.5%; BMI, Δ = 2.7%; waist circumference, Δ = 1.8%; and FFM, Δ = −2.2%) and CRF (Δ = −5.7%) significantly worsened. However, it should be noted that they remained significantly better than the values seen at baseline (Table 1). Our findings are in line with previous studies with other "at risk" populations (*i.e.*, coronary artery disease patients, overweight polycystic ovary syndrome, and women with parental HTN, adults with metabolic syndrome, healthy men, and women with Type II Diabetes), using different types of exercise, duration of intervention, and detraining periods (*i.e.*, 4 weeks to 4 months) (Mora-Rodriguez et al., 2014; Orio et al., 2008; St-Amand et al., 2012; Theodorou et al., 2016; Tokmakidis, Spassis, & Volaklis, 2008; Tokmakidis et al., 2014; Volaklis et al., 2006).

Another interesting finding of the present investigation was that HV-HIIT caused a greater reduction (6M follow-up *vs.* pre-intervention, $P = .034$) in BM (Δ = −6.4 kg) compared to AC group (Δ = −3.5 kg) after 6M of no supervision (Table 1, Figure 2(a)). As such, our data help to confirm that enhanced energy expenditure elicited by HV and moderate-to-high intensity exercise training, is related to long-term BM loss maintenance (Donnelly et al., 2009). Previous studies have supported this and have shown that HIIT is an effective stimulus for reducing body fat in those individuals with obesity (Batacan, Duncan, Dalbo, Tucker, & Fenning, 2017; Ouerghi et al., 2017). The possible mechanisms behind HIIT-induced fat loss include 1) a more elevated catecholamine response, and 2) an increased excess post-exercise oxygen consumption leading to an increase in fat oxidation (Boutcher, 2011; LaForgia, Withers, & Gore, 2006). With respect to our study, it is important to note that the removal of supervised exercise training for 6 M, did not lead to a complete loss of CRF assessed by $\dot{V}O_{2peak}$ (Δ = 18% comparing follow-up *vs.* pre-intervention) in any of the intervention groups as shown in Figure 2. In addition, it is well known that each 1-MET increment in CRF is associated with a ~ 13–15% lower risk of all-cause and cardiovascular mortality (Harber et al., 2017). Thus, comparing 6M follow-up to pre-intervention data only the supervised exercise groups in the intervention period preserved >1MET compared to baseline (AC = 0.7, HV-MICT = 1, HV-HIIT = 1.5, LV-HIIT = 1.2) (Table 1). Although adherence with the 16-week exercise intervention was very high in the supervised-exercise groups, 6M later only 51% of all participants were engaged in physical activity >2 times per week and implementing the recommendations (unpublished data from the EXERDIET-HTA study). This suggests that supervised exercise is needed to potentially achieve optimal results.

In accordance with previous research (Abdelaal & Mohamad, 2015) after removing exercise supervision for 6M, BP returned to pre-intervention values, but it was significantly higher compared to POST, as shown in Table 1. This finding is of importance given that BP is a robust and sensitive clinical marker associated with changes in BM (Neter, Stam, Kok, Grobbee, & Geleijnse, 2003) due to an increase in visceral adiposity (in the present study, at follow-up BM Δ = 2.5%; and waist circumference Δ = 1.8% compared to post-intervention, $P < .005$). It is possible that a range of physiological factors and biological pathways, such as physical compression of the kidneys by fat, over activation of the renin-angiotensin-aldosterone system, and increased sympathetic nervous system activity, will be involved in the increased BP response seen in the current study (Hall, do Carmo, da Silva, Wang, & Hall, 2015). Even though there is enough evidence reporting the efficacy of the DASH diet, BM loss, and exercise in lowering BP (Blumenthal et al., 2010; Gorostegi-Anduaga et al., 2018a), the adherence to DASH diet seems difficult to follow by individuals with HTN, and even lower DASH accordance is shown in those with obesity (Kim & Andrade, 2016). Therefore, in this population, an optimal training FITT and supervised exercise together with close dietetic supervision are needed to particularly optimize the BP-lowering capacities of exercise and diet (Hinderliter et al., 2014; Pescatello et al., 2015).

The authors feel that to interpret findings from the current study; it is essential to consider both the strengths and limitations. The main aim of the study was to assess the effects of supervised exercise cessation 6M following a 16-week supervised exercise and dietary intervention. Whilst the design of the study is appropriate, the lack of exercise supervision could have led to inter-individual differences, which could be masked with quantitative data techniques. Future studies should look to use mixed-methods to help interpret the reasons behind the reported changes. Although efforts were done to assess all post-intervention participants, 19 individuals do not perform the 6M follow-up tests (nine from the AC group), that may have affected the between-group differences in BP values favoring AC group and the lack of differences with exercise supervised groups in body composition and CRF. Further, dietary intake was self-reported through questionnaires at pre-intervention, but it was not assessed at follow-up, which hinders the knowledge regarding the adherence to DASH diet.

In conclusion, when overweight/obese individuals with HTN attain significant improvements in cardiometabolic health following 16-week supervised-exercise intervention with diet restriction, there is a significant

reduction following 6M when the exercise and diet supervision is removed, and only recommendations were applied. These results suggest the need for a regular, systematic and supervised diet and exercise programs to avoid subsequent declines in cardiometabolic health. Future research needs to determine whether long-term exercise and diet supervision can maintain improvements in cardiometabolic health.

What does this article add?

The recommended lifestyle measures for reducing BP and BM management include regular physical exercise (*i.e.*, at least 30 min of moderate-intensity dynamic aerobic exercise on 5–7 days per week, and also aerobic interval training). In order to be effective, the exercise has to be designed in a systematic and individualized manner in terms of the frequency, intensity, time, and type (FITT principle). However, there is a lack of evidence regarding the impact of well-designed but only advised *vs.* adequately powered and supervised exercise. Although these effects have been evaluated in other populations, the present study is a well-designed, high-quality randomized clinical trial, and the first to examine the exercise intervention effects, based on FITT recommendations for people with overweight/obesity and HTN, and to evaluate the long-term effects of supervised training cessation, who are receiving only diet and physical activity advice after an intervention period.

To our knowledge, the consensus in the FITT of the recommended exercise prescription and design for this population will not present optimum health-related results if the exercise program is not closely supervised by exercise professionals. Supervision and not only physical activity advice is necessary to monitor all the acute responses and chronic adaptations to training and when appropriate, to modify the FITT exercise design, accordingly.

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9.3. Anexo 3: "*A Metabolically Healthy Profile Is a Transient Stage When Exercise and Diet Are Not Supervised: Long-Term Effects in the EXERDIET-HTA Study*"

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Article

A Metabolically Healthy Profile Is a Transient Stage When Exercise and Diet Are Not Supervised: Long-Term Effects in the EXERDIET-HTA Study

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Abstract: Metabolically unhealthy obesity (MUO) is a regular state in people with primary hypertension (HTN), obesity, and who are physically inactive. To achieve and maintain a metabolically healthy overweight/obese (MHO) state should be a main treatment goal. The aims of the study were (1) to determine differences in metabolic profiles of overweight/obese, physically inactive individuals with HTN following a 16-week (POST) supervised aerobic exercise training (SupExT) intervention with an attentional control (AC) group, and (2) to determine whether the changes observed were maintained following six months (6 M) of unsupervised time. Participants (n = 219) were randomly assigned into AC or SupExT groups. All participants underwent a hypocaloric diet. At POST, all participants received diet and physical activity advice for the following 6 M, with no supervision. All measurements were assessed pre-intervention (PRE), POST, and after 6 M. From PRE to POST, MUO participants became MHO with improved ($p < 0.05$) total cholesterol (TC, $\Delta = -12.1$ mg/dL), alanine aminotransferase ($\Delta = -8.3$ U/L), glucose ($\Delta = -5.5$ mg/dL), C-reactive protein ($\Delta = -1.4$ mg/dL), systolic blood pressure (SBP), and cardiorespiratory fitness (CRF) compared to unhealthy optimal cut-off values. However, after 6 M, TC, glucose, and SBP returned to unhealthy values ($p < 0.05$). In a non-physically active population with obesity and HTN, a 16-week SupExT and diet intervention significantly improves cardiometabolic profile from MUO to MHO. However, after 6 M of no supervision, participants returned to MUO. The findings of this study highlight the need for regular, systematic, and supervised diet and exercise programs to avoid subsequent declines in cardiometabolic health.

Keywords: obesity; hypertension; inactivity; supervised exercise

1. Introduction

Obesity is a complex and chronic non-communicable disease with a disparity in the way it is classified [1]. The combination of obesity, physical inactivity, and primary hypertension (HTN) is widely recognized as a pre-eminent cause of cardiovascular risk and metabolic complications [2,3], and is termed 'metabolically unhealthy obesity' (MUO) [4,5]. Therefore, to become metabolically healthy overweight/obese (MHO) (i.e., overweight/obesity in the absence of a clearly defined cardiometabolic disorder and/or high level of cardiorespiratory fitness (CRF)) [6,7] should be one of the main priorities in the treatment of this population. A previous systematic review and meta-analysis found that MHO individuals had significantly higher levels of physical activity and CRF, and spent less time in sedentary behaviour than MUO, suggesting that a healthier metabolic profile could be partially due to a healthier lifestyle [5].

Major international guidelines recommend non-pharmacological, tailored, and long-term lifestyle changes for the prevention and treatment of HTN and obesity in this population [8–10]. Previously, interventions with engagement in regular physical activity, exercise, and a healthy diet in overweight/obese individuals with HTN reported significantly reduced blood pressure (BP) [10,11], and improved body composition [8,11], CRF [11,12], and biochemical profile [12,13]. In addition, it was suggested that physical activity and diet recommendations were not enough to improve biochemical profile alone and that supervision was needed [14]. As such, education programs (including healthy diet and physical exercise) should be regular, systematic, and supervised by specialists. This is particularly important since previously it has been found that declines in cardiometabolic health occur after finishing a time-limited exercise program in different populations [15–17].

Previous data from the EXERDIET-HTA investigation found that all study groups improved body composition, BP, and CRF following a 16-week intervention program [11]. However, there was a significant reduction in the improvements found after the 6-month (6 M) follow up, when the exercise and diet supervision were removed and only recommendations were applied [14]. Nevertheless, no known study has analysed the changes in metabolic profile in an overweight/obese population with HTN. Accordingly, the aims of the study were (1) to determine differences in metabolic profiles of overweight/obese, physically inactive individuals with HTN following a 16-week supervised aerobic exercise training (SupExT) intervention with an attentional control (AC) group, both with a hypocaloric diet, and (2) to analyse whether the changes observed during supervision were maintained following 6 M of unsupervised time.

2. Methods

2.1. Research Design

The EXERDIET-HTA study is a randomised controlled trial (ClinicalTrials.gov ID: NCT02283047) that compares the immediate (POST) and 6 M-effects of different 16-week SupExT programmes (performed 2 days/week) combined with a dietary intervention in physically inactive, overweight/obese individuals with HTN. The Clinical Investigation of Araba University Hospital (2015-030) and the Ethics Committee of The University of the Basque Country (UPV/EHU, CEISH/279/2014) approved the study design, protocols, and informed consent. More details regarding the design, selection criteria, and procedures of the EXERDIET-HTA study have been explained in previous publications [11,14,18].

2.2. Participants

The EXERDIET-HTA study was conducted in Vitoria-Gasteiz (Basque Country, Spain). Non-Hispanic white adult participants (n = 219) took part in the study, but 23 participants left the study during the intervention and 19 participants did not attend the 6 M follow-up visit. These participants did not differ in any way from the main sample. As such, 177 participants (n = 114 men and n = 63 women, 51.6 ± 8.9 years) were included in the analysis. Figure 1 represents the participants and design of the EXERDIET-HTA study from recruitment to 6 M post intervention. The main inclusion criteria

were being physically inactive and having overweight/obesity with primary HTN. The International Physical Activity Questionnaire (IPAQ) determined physical activity behaviour [19], and participants were below the *"Global Recommendations on Physical Activity for Health"* set by the World Health Organization [20]. Body mass index (BMI) had to be above 25 $kg \cdot m^2$ [8]. Primary HTN was defined as systolic BP (SBP) of 140–179 mmHg and/or diastolic BP (DBP) of 90–109 mmHg, and/or under antihypertensive pharmacological treatment [21]. For all other inclusion and exclusion criteria, please refer to the previously published study protocol [18].

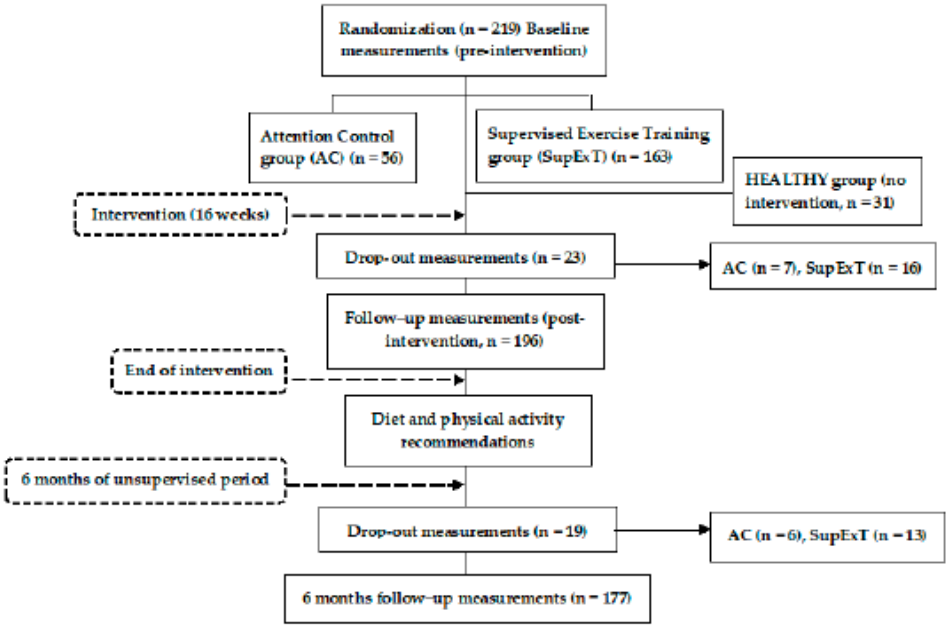

Figure 1. Flow diagram of the EXERDIET-HTA study from recruitment to the 6-month unsupervised period.

In addition to the EXERDIET-HTA study participants, another group was created to allow for comparison to a normal body mass healthy population (hereinafter termed: HEALTHY). The HEALTHY (n = 31, 40.0 ± 9.0 years, 58% women) group did not participate in any intervention. Only baseline measures were assessed for comparison to the EXERDIET-HTA study participants. Inclusion for HEALTHY criteria were age (25–55 years) and exclusion criteria were being pregnant, currently breastfeeding, taking regular medication, or having any known medical condition.

2.3. Measurements

Anthropometric, clinical, and physiological measurements were taken at baseline (PRE), immediately after the 16-week intervention (POST), and at 6 M follow-up (Figure 1) by trained investigators and specialists. Each assessment included anthropometry (body mass, stature, BMI, waist circumference, and body composition), 24 h ambulatory BP monitoring, determination of peak oxygen uptake ($\dot{V}O_{2peak}$) to asses CRF, and collection of fasting blood samples (12.5 mL) at the Clinical Trials Unit of Tecnalia (HUA, Vitoria-Gasteiz). The fasting blood samples were used to determine the metabolic profile which consisted of: C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), glucose, insulin, and haemoglobin A1c (HbA1c). HOmeostatic Model Assessment-Insulin resistance

index (HOMA-IR) was determined by: fasting serum insulin (μU/mL) × fasting plasma glucose (mg/dL)/405 [22]. For more details of the assessments, please refer to the study protocol [18] and previous cardiometabolic profiling manuscript [14].

The cut-off points of parameters related to cardiometabolic abnormalities were: concentrations of CRP > 3 mg/L [23]. Hepatic enzymes when AST > 30 U/L, ALT > 30 U/L, GGT > 50 U/L [24]. With respect to the lipid profile, when TC > 200 mg/dL (52 mmol/L), LDL-C > 100 mg/dL (26 mmol/L), HDL-C < 40 mg/dL (10.4 mmol/L), TG > 200 mg/dL (2.28 mmol/L), and TC/HDL-C ratio > 3.5 [25]. Based on the Diabetes Federation Statement [26], glucose > 100 mg/dL (5.55 mmol/L). The HOMA-IR ratio cut point was established at 3.8, insulin cut point at 16.7 mU/L, and HbA1c at 6% [27,28]. A CRF ($\dot{V}O_{2max}$ in mL·kg^{-1}·min^{-1}) reference value lower than the 50th percentile was used as the cut-off point, according to the FRIEND Registry [29]. The definition of the MUO and the MHO phenotypes were obtained based on the joint combination of obesity markers (i.e., BMI) and cardiometabolic abnormalities, taking into account the following definitions: the National Cholesterol Education Program-Adults Treatment Panel III, Wildman, Wildman Modified and Ortega [4,5,30].

2.4. Intervention and 6-Month Post-Intervention Follow-up

After baseline measurements, participants were randomly allocated into one of the intervention groups stratified by sex, SBP, BMI, and age using a time-blocked computerised randomisation program. All participants underwent a hypocaloric DASH diet (Dietary Approaches to Stop Hypertension) [13]. Habitual food consumption and nutrient intake were evaluated using three questionnaires: Dietary History, Food Frequency Questionnaire, and 24 h Recall Questionnaire. Every 2 weeks, participants were weighed and received encouragement and advice alongside nutritional counselling in order to aid compliance. The four intervention groups were AC group (AC, participants were given physical activity advice only), and three SupExT groups: high-volume and moderate-intensity continuous training, high-volume and high-intensity interval training, and low-volume and high-intensity interval training. These groups trained on 2 non-consecutive days under supervision by exercise specialists for 16-weeks. The advice for the AC group was to participate in at least 30 min of moderate-intensity aerobic exercise (walking, jogging, cycling, or swimming) for 5–7 days per week blended with some dynamic resistance exercises [18].

In a preliminary analysis of the data used in this article, SupExT groups had no significant differences ($p > 0.05$) among them in the target variables (biochemical profile variables) over time (i.e., PRE versus POST, POST versus 6 M, and PRE versus 6 M). Therefore, for the purposes of this article, the three SupExT groups were put together in one group and thus comparative analyses were performed between groups (AC versus SupExT).

After POST assessment, all participants received physical activity and diet advice for the following 6 M. Participants had no further supervised intervention or attention from any of the research staff. All participants received exercise intensity domains (i.e., individual heart rate values at moderate- and high-intensity ranges) to self-monitor. All the protocols for each group, including procedures and diet intervention, have been previously published [11,18].

2.5. Statistical Analysis

Descriptive statistics were calculated for all variables and presented as mean ± standard deviation (SD) or percentage. To determine normality, a Kolmogorov–Smirnov test was performed on all variables, and those with a skewed distribution were log-transformed prior to any analysis. For comparisons between HEALTHY and the EXERDIET-HTA study population, independent *t*-tests were used to assess mean differences for continuous variables, and the chi-square test was performed to verify frequency differences for categorical variables. One-way repeated measures analysis of variance (ANOVA) was used to test the change in biochemical profile variables over time, when the differences presented significance, the Bonferroni post hoc test was applied. From the repeated measures ANOVA, partial eta-squared (η_p^2) was reported as a measure of effect size (ES). Two-way repeated measures ANOVA

was used to evaluate the interaction effects (time × group) in biochemical profile variables. Analysis of covariance (ANCOVA) was performed to test the differences between groups for the delta score (Δ, differences between PRE versus POST, POST versus 6 M follow-up, and PRE versus 6 M follow-up), adjusting the analysis for age, sex, medication intake, and changes in body mass. Cochran's Q test was executed to analyse the change in medication intake and smoking status. Chi-square test was used to test the differences between groups for the change in medication intake and smoking status (differences between PRE versus POST, POST versus 6 M follow-up, and PRE versus 6 M follow-up) over time. As previously described in the study protocol [18], the required sample size was determined for the primary outcome variable (SBP) of the EXERDIET-HTA study. It was identified that adequate power (0.95) to evaluate differences in our design consisting of four experimental groups would be achieved with 164 people (41 each group, $\alpha = 0.05$, ES f = 0.4). Data were analysed according to the intention-to-treat principle. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 24.0 (IBM Corp., Armonk, NY, USA). For all analysis, the alpha level of significance was set at $p < 0.05$.

3. Results

Table 1 presents baseline anthropometric, BP, CRF, biochemical profile, medication intake, and smoking status data of the EXERDIET-HTA study population compared to the HEALTHY group. The EXERDIET-HTA study population had significantly higher ($p < 0.05$) age, BM, BMI, waist circumference, SBP, DBP, mean BP (MBP), CRP, AST, ALT, GGT, TC, LDL-C, TG, TC/HDL-C, glucose, insulin, HOMA-IR, and HbA1C compared to the HEALTHY group. Nevertheless, the EXERDIET-HTA group had significantly lower fat-free mass, $\dot{V}O_{2peak}$, and HDL-C than the HEALTHY group. There was no difference in smoking status between groups. As previously described [31], the participants from the EXERDIET-HTA study were considered MUO with the following parameters showing concentrations and values with cut-off points outside of those considered healthy: LDL-C, TC, TC/HDL-C, ALT, glucose, BP, CRP, and low CRF.

Table 1. Baseline results of the study population compared to a HEALTHY (normal body mass healthy population) group.

Variables	HEALTHY ($n = 31$)	EXERDIET-HTA ($n = 219$)	P PHEALTHY-EXERDIET-HTA
Age (years)	40.0 ± 9.0	53.3 ± 7.6	<0.001
Body mass (kg)	66.1 ± 10.5	92.4 ± 15.1	<0.001
BMI (kg/m^2)	22.7 ± 2.2	32.4 ± 4.2	<0.001
Waist circumference (cm)	74.7 ± 8.0	103.5 ± 11.2	<0.001
FFM (%)	79.1 ± 6.2	65.0 ± 7.7	<0.001
SBP (mmHg)	114.0 ± 6.6	136.0 ± 11.8	<0.001
DBP (mmHg)	68.1 ± 7.2	78.0 ± 8.3	<0.001
MBP (mmHg)	83.4 ± 5.9	97.4 ± 8.5	<0.001
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	48.0 ± 8.2	22.4 ± 5.4	<0.001
CRP (mg/L)	0.8 ± 0.7	4.1 ± 3.9	<0.001
AST (U/L)	21.9 ± 3.6	25.1 ± 9.4	0.001
ALT (U/L)	18.1 ± 5.9	33.3 ± 21.2	<0.001
GGT (U/L)	16.7 ± 8.3	40.1 ± 41.9	<0.001
TC (mg/dL)	180.9 ± 35.8	206.5 ± 38.3	0.001
HDL-C (mg/dL)	63.0 ± 10.8	47.2 ± 11.0	<0.001
LDL-C (mg/dL)	104.8 ± 30.3	132.0 ± 34.1	<0.001
TG (mg/dL)	70.6 ± 21.3	139.6 ± 78.9	<0.001
TC/HDL-C	2.9 ± 0.5	4.6 ± 1.5	<0.001
Glucose (mg/dL)	83.1 ± 9.3	101.9 ± 24.4	<0.001
Insulin (mU/L)	3.9 ± 1.3	12.3 ± 7.3	<0.001
HOMA-IR	0.8 ± 0.4	3.3 ± 2.4	<0.001
HbA1c (%)	5.5 ± 0.3	5.9 ± 0.8	0.019

Table 1. *Cont.*

Variables	HEALTHY (n = 31)	EXERDIET-HTA (n = 219)	p PHEALTHY-EXERDIET-HTA
Medication Intake and Smoking Status			
Statin (%)	0.0	14.2	0.024
Hypoglycaemic (%)	0.0	7.8	0.105
ACEI (%)	0.0	38.4	<0.001
ARB (%)	0.0	39.3	<0.001
Diuretic (%)	0.0	38.8	<0.001
CCB (%)	0.0	14.2	0.024
BB (%)	0.0	6.8	0.129
Antiplatelet (%)	0.0	3.7	0.275
Smokers (%)	15.6	11.0	0.533

BMI: Body mass index. FFM: Fat-free mass SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MBP: Mean blood pressure. VO_{2peak}: Peak oxygen consumption. CRP: C-reactive protein. AST: Aspartate aminotransferase. ALT: Alanine transaminase. GGT: Gamma-glutamyl transpeptidase. TC: Total cholesterol. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol. TG: Triglycerides. HOMA-IR: HOmeostatic Model Assessment-Insulin resistance index. HbA1c: haemoglobin A1c. ACEI: Angiotensin-converting-enzyme inhibitors. ARB: Angiotensin II receptor blockers. CCB: Calcium channel blockers. BB: Beta-blockers.

3.1. PRE versus POST Changes

Table 2 presents metabolic profile data at PRE, POST, and after 6 M follow-up. Analysing the change in group from PRE to POST, a one-way repeated measures ANOVA found that the SupExT group reduced concentrations of CRP (mean difference, Δ = −1.5 mg/L, 95% confidence interval (CI) = −2.4, −0.5 mg/L), ALT (Δ = −9.1 U/L, 95% CI = −14.3, −3.8 U/L), GGT (Δ = −9.1 U/L, 95% CI = −12.1, −5.4 U/L), TC (Δ = −13.9 mg/dL, 95% CI = −20.4, −7.4 mg/dL), LDL-C (Δ = −9.5 mg/dL, 95% CI = −15.5, −3.4 mg/dL), TG (Δ = −20.9 mg/dL, 95% CI = −30.3, −11.6 Mg/dL), TC/HDL-C (Δ = −0.3, 95% CI = −0.5, −0.1), glucose (Δ = −6.7 mg/dL, 95% CI = −12.0, −1.5 mg/dL), insulin (Δ = −2.2 mU/L, 95% CI = −3.9, −0.4 mU/L), HOMA-IR (Δ = −0.9, 95% CI = −1.5, −0.3), and HbA1C (Δ = −0.2%, 95% CI = −0.4, −0.1%). The AC group had reduced concentrations of CRP (Δ = −1.0, 95% CI = −1.8, −0.1), while there was no change in any other biochemical variable. Although the analysis by group found that the SupExT group had a greater reduction than the AC group, there was no interaction of time by group for PRE versus POST. Considering biochemical profile at POST, and the results previously presented for BMI, BP, and CRF [11], at POST, participants in the present study were considered MHO (i.e., overweight with healthy values of TC, TG, HDL-C, TC/HDL-C, glucose, insulin, HOMA, CRP, lower BP, and higher CRF compared to PRE).

Table 2. Changes in metabolic panel at pre-intervention (PRE), immediately post-intervention (POST), and 6 months post supervised exercise cessation (6 M).

Variables	All (n = 177)	Effect Size (η_p^2)	AC (n = 43)	ExT (n = 134)	Time × Group	p Groups PRE-POST	p Groups POST-6 M	p Groups PRE-6 M
CRP (mg/L)								
PRE	4.0 ± 3.9 *	0.113	3.2 ± 3.2 *	4.1 ± 4.0 *	0.595	0.677	0.937	0.361
POST	2.6 ± 2.6		2.2 ± 2.1	2.7 ± 2.7				
6 M	2.9 ± 3.0 $^{\varphi}$		2.7 ± 2.5	3.0 ± 3.1 $^{\varphi}$				
AST (U/L)								
PRE	24.7 ± 8.6 *	0.060	25.2 ± 5.8	24.6 ± 9.2	0.465	0.684	0.380	0.657
POST	22.6 ± 8.5 $^{\$}$		21.3 ± 5.0	22.9 ± 9.2 $^{\$}$				
6 M	25.0 ± 11.3		23.9 ± 6.2	25.3 ± 12.3				
ALT (U/L)								
PRE	33.4 ± 20.8 *	0.112	29.4 ± 12.8	34.4 ± 22.3 *	0.529	0.090	0.103	0.923
POST	25.1 ± 15.4		24.2 ± 14.7	25.3 ± 15.7				
6 M	27.9 ± 20.4		27.3 ± 13.6	28.1 ± 21.9 $^{\varphi}$				
GGT (U/L)								
PRE	36.1 ± 24.1 *	0.155	36.2 ± 24.8	36.1 ± 24.1 *	0.230	0.914	0.152	0.459
POST	27.4 ± 18.4 $^{\$}$		28.9 ± 27.6 $^{\$}$	27.0 ± 15.5 $^{\$}$				
6 M	31.8 ± 20.6		37.1 ± 33.5	30.4 ± 15.9 $^{\varphi}$				
TC (mg/dL)								
PRE	209.2 ± 36.3 *	0.103	207.3 ± 35.7	209.7 ± 36.6 *	0.281	0.102	0.330	0.195
POST	197.1 ± 35.4 $^{\$}$		202.1 ± 35.9 $^{\$}$	195.8 ± 35.2 $^{\$}$				
6 M	207.8 ± 36.1		211.0 ± 39.7	206.9 ± 35.2				
HDL-C (mg/dL)								
PRE	48.6 ± 11.0	0.090	47.7 ± 8.0	48.8 ± 11.7	0.419	0.177	0.421	0.615
POST	48.5 ± 11.2 $^{\$}$		47.1 ± 7.9	48.9 ± 12.0 $^{\$}$				
6 M	51.0 ± 12.7 $^{\varphi}$		48.8 ± 8.6	51.6 ± 13.6 $^{\varphi}$				
LDL-C (mg/dL)								
PRE	135.2 ± 33.5 *	0.056	133.8 ± 35.4	135.6 ± 33.1 *	0.228	0.566	0.889	0.121
POST	127.3 ± 31.6 $^{\$}$		131.2 ± 33.4 $^{\$}$	126.2 ± 31.1 $^{\$}$				
6 M	134.8 ± 31.5		140.4 ± 36.0	133.3 ± 30.1				
TG (mg/dL)								
PRE	125.2 ± 49.8 *	0.092	121.1 ± 38.2	126.3 ± 52.6 *	0.081	0.790	0.111	0.420
POST	108.2 ± 44.3		118.5 ± 45.4	105.4 ± 43.8				
6 M	109.8 ± 43.2 $^{\varphi}$		108.9 ± 41.8	110.0 ± 43.7 $^{\varphi}$				

Table 2. *Cont.*

Variables	All	Effect	AC	ExT	Time × Group	*p* Groups PRE-POST	*p* Groups POST-6 M	*p* Groups PRE-6 M
	(*n* = 177)	Size (η_p^2)	(*n* = 43)	(*n* = 134)				
TC/HDL-C								
PRE	4.6 ± 1.6 *	0.050	4.5 ± 1.1	4.5 ± 1.2 *	0.130	0.723	0.588	0.609
POST	4.3 ± 1.2		4.4 ± 1.2	4.2 ± 1.2				
6 M	4.4 ± 1.2 $^{\varphi}$		4.5 ± 1.1	4.2 ± 1.0 $^{\varphi}$				
Glucose (mg/dL)								
PRE	102.3 ± 25.7 *	0.043	96.9 ± 12.6	104.0 ± 28.3 *	0.392	0.098	0.137	0.765
POST	96.8 ± 22.5 $^{\$}$		95.2 ± 11.4	97.2 ± 24.9 $^{\$}$				
6 M	101.1 ± 29.7		97.1 ± 16.0	102.3 ± 32.7				
Insulin (mU/L)								
PRE	11.5 ± 6.1 *	0.077	10.6 ± 5.5	11.8 ± 6.3 *	0.492	0.576	0.679	0.827
POST	9.6 ± 6.0		9.5 ± 5.0	9.6 ± 6.3				
6 M	10.3 ± 5.9		9.3 ± 5.3	10.6 ± 6.1				
HOMA-IR								
PRE	3.1 ± 2.3 *	0.094	2.5 ± 1.3	3.3 ± 2.5 *	0.250	0.183	0.882	0.836
POST	2.3 ± 1.7 $^{\$}$		2.2 ± 1.1	2.4 ± 1.8 $^{\$}$				
6 M	2.8 ± 2.3		2.2 ± 1.5	3.0 ± 2.5				
HbA1c (%)								
PRE	5.9 ± 0.9 *	0.056	5.7 ± 0.3	6.0 ± 1.0 *	0.279	0.207	0.225	0.890
POST	5.7 ± 0.7 $^{\$}$		5.6 ± 0.3	5.8 ± 0.7 $^{\$}$				
6 M	5.9 ± 1.0		5.6 ± 0.4	5.9 ± 1.1				

AC: attention control group. ExT: Exercise training group. CRP: C-reactive protein. AST: Aspartate aminotransferase. ALT: Alanine transaminase. GGT: Gamma-glutamyl transpeptidase. TC: Total cholesterol. HDL-C: High density lipoprotein cholesterol. LDL-C: Low density lipoprotein cholesterol. TG: Triglycerides. HOMA-IR: HOmeostatic Model Assessment-Insulin resistance index. HbA1c: Haemoglobin A1c. * $p < 0.005$ intra-group PRE versus POST. $^{\$}$ $p < 0.005$ intra-group POST versus 6 M. $^{\varphi}$ $p < 0.005$ intra-group PRE versus 6 M.

3.2. POST versus 6-Month Follow-up Changes

A one-way repeated measures ANOVA found that between POST and 6 M follow-up in the SupExT group, AST (Δ = 2.4 U/L, 95% CI = 0.1, 4.7 U/L), GGT (Δ = 3.5 U/L, 95% CI = 0.1, 6.9 U/L), TC (Δ = 11.1 mg/dL, 95% CI = 4.4, 17.8 mg/dL), HDL-C (Δ = 2.8 mg/dL, 95% CI = 1.1, 4.4 mg/dL), LDL-C (Δ = 7.1 mg/dL, 95% CI = 1.2, 13.0 mg/dL), glucose (Δ = 5.0 mg/dL, 95% CI = 0.6, 9.4 mg/dL), HOMA-IR (Δ = 0.6, 95% CI = 0.1, 1.1), and HbA1C (Δ = 0.2%, 95% CI = 0.1, 0.3%) concentrations all significantly increased. There were no significant changes in all other biochemical markers. In the AC group, GGT (Δ = 8.2 U/L, 95% CI = 0.2, 16.2 U/L), TC (Δ = 8.9 mg/dL, 95% CI = 0.8, 17.0 mg/dL), and LDL-C (Δ = 9.2 mg/dL, 95% CI = 0.6, 17.7 mg/dL) were significantly raised from POST to 6 M follow-up. However, the two-way repeated measures ANOVA did not show an interaction of time by group for POST versus 6 M follow-up. Considering biochemical profile at 6 M follow-up, participants were again classified as MUO due to the following cardiometabolic abnormalities: obesity, higher values of TC, LDL-C, glucose, BP, and lower CRF compared to POST [14].

3.3. PRE versus 6-Month Follow-up Changes

Analysing the change from PRE to 6 M follow-up for the groups, a one-way repeated measures ANOVA found that, at 6 M follow-up, the SupExT group significantly reduced concentrations of CRP (Δ = −1.2 mg/L, 95% CI = −2.2, −0.2 mg/L), ALT (Δ = −6.3 U/L, 95% CI = −12.6, −0.1 U/L), GGT (Δ = −5.6 U/L, 95% CI = −11.1, −0.3 U/L), TG (Δ = −16.3 mg/dL, 95% CI = −26.4, −6.2 mg/dL), and TC/HDL-C (Δ = −0.3, 95% CI = −0.5, −0.1), and raised values in HDL-C (Δ = 2.8 mg/dL, 95% CI = 1.3, 4.4 mg/dL). No significant changes were found in any variable in the AC group. As changes occurred between PRE versus POST and POST versus 6 M follow up, no interaction of time by group was found for changes in PRE versus 6 M follow-up.

3.4. Medication Intake

Regarding medication intake, 89% of SupExT participants and 88% of AC participants were taking at least one medication at PRE. In SupExT, this percentage was significantly reduced in POST (83%, $p < 0.05$) and in 6 M follow-up (79%, $p < 0.001$). Although there was a reduction between POST and 6 M follow-up, the differences were not significant. In AC, 85.7% of participants were taking medication at POST, but the reduction was not significant from PRE ($p > 0.05$). There was no change from POST to 6 M follow-up (85.7%). From SupExT participants, 25.2% reduced the dose of their medication from PRE to POST, and 5.5% from POST to 6 M. Meanwhile, for the AC, 10.0% reduced the dose of their medication from PRE to POST, with no change from POST to 6 M follow-up. In particular, changes in SupExT medication intake were observed for statins (PRE 16.6%, POST 13.8%, 6 M follow-up 13.1%), Angiotensin-converting-enzyme inhibitors (ACEIs) (PRE 34.5%, POST 30.3%, 6 M follow-up 27.6%), and diuretics (PRE 42.1%, POST 37.9%, 6 M follow-up 36.6%). In AC, changes were only observed in ACEIs (PRE 49.0%, POST 42.9%, 6 M follow-up 42.9%). No significant change was observed in other medications. Although the separate analysis by group found more changes in SupExT than in the AC, the chi-square test revealed that there were no significant between-group differences in medication reduction. The percentage of smokers remained the same at PRE, POST, and 6 M follow-up in both groups.

4. Discussion

The current study demonstrated that a 16-week SupExT intervention with hypocaloric diet significantly improved cardiometabolic profiles from MUO to MHO. However, this was a transient stage as after 6 M of no supervision, participants' biochemical profiles and CRF had returned to MUO.

There is now increasing evidence that obese individuals with a healthy lifestyle pattern could have a similar cardiovascular risk as healthy individuals with no obesity, since adherence to exercise and healthy diet together lead to beneficial changes in body composition and cardiometabolic profile [32].

The present study showed that the MUO profile in the EXERDIET-HTA group (i.e., obesity, HTN, fasting glucose > 100 mg/dL, LDL-C > 100 mg/dL, TC > 200 mg/dL, ALT > 30 U/L, systemic inflammation with CRP > 3 mg/L, and low CRF, 22.4 ± 5.4 mL·kg^{-1}·min^{-1}, Figure 2) was significantly worse than the HEALTHY non-obese group (Table 1). These results confirm that obesity and physical inactivity are the major contributing factors to dyslipidaemia manifested by elevated LDL-C and TG [33], inducing chronic inflammation and activation of the renin angiotensin system, and exacerbating, consequently, the sympathetic activation and BP [3].

The changes observed after conducting the 16-week exercise and diet intervention revealed that the significantly better body composition and CRF (results published in previous papers) [11,14] may be associated with a metabolic protective effect which improves insulin sensitivity, lipid panel, and BP (Table 2, Figure 2). Thus, the whole sample significantly decreased their CRP (Δ = −1.4 mg/L) concentrations (i.e., inflammatory marker associated with cardiovascular disease) which could be explained by multiple mechanisms, including a decrease in cytokine production by adipose tissue, skeletal muscles, endothelial and blood mononuclear cells, improved insulin sensitivity and endothelial function, and possibly an antioxidant effect [34]. Interestingly, after the 16-week intervention, only the SupExT group showed significant and beneficial changes in all variables, except HDL-C (Table 2). Thus, lower concentrations of hepatic enzymes ALT (Δ = −9.1 U/L) and GGT (Δ = −9.1 U/L) were shown, which in elevated concentrations are both highly related to liver and abdominal fat, and predictors of the MUO phenotype, the diagnosis of non-alcoholic fatty liver disease, type 2 diabetes, and subclinical atherosclerosis [35]. Previously, exercise and hypocaloric diet interventions have been shown to improve hepatic lipid composition via different pathways [36]. Thus, some studies suggest that exercise could modulate liver fat by directly altering hepatic lipid oxidation and lipogenesis [37], and that the improvement may be driven by adiponectin and insulin sensitivity [38]. As such, this may in part explain some of the beneficial changes seen in Table 2 after the 16-week intervention, including: lower concentrations of glucose (Δ = −6.8 mmol/L), insulin (Δ = −2.2 mU/L), HOMA-IR (Δ = −0.9 %), and HbA1C (Δ = −0.2 %). These markers have previously been shown to be some of the chronic exercise adaptations seen in skeletal muscle after the upregulation of muscle GLUT4 protein, increased enzyme capacities, and muscle capillarisation [39]. Similar to previous studies investigating the beneficial effects of SupExT [33,40], the current study found that lipid profile improved with lower concentrations of TC (Δ = −13.9 mmol/L), LDL-C (Δ = −9.4 mmol/L), TG (Δ = −20.9 mmol/L), and TC/HDL-C (Δ = −0.3) at POST. Conversely, in the current study, HDL-C concentrations (upper normal values at baseline) did not change after the exercise intervention. In other studies, which included just SupExT with no diet intervention, it was common to find elevated concentrations of HDL-C [15,33,41,42]. One possible explanation for this could be the incorporation of the DASH diet in the current study. The DASH diet has been previously revealed to lower HDL-C concentrations, along with TC, LDL-C [43,44], and TG [45]. The effect of the hypocaloric DASH diet in the intervention must be considered, since it has been indicated that it is also effective at changing the biochemical profile, i.e., lowering concentrations of CRP, AST, ALT, insulin, and HOMA-IR [45–47]. Further, the benefits produced by SupExT are notable in CRF and body composition data (published data for the same EXERDIET-HTA sample show greater benefits in SupExT compared to AC) [11,14]. Given the strong association of CRF with metabolic risk [48], there appears to be a strong rationale for including the CRF level in the prognosis of MHO to improve the stratification in individuals with obesity [5], empowering the fat-but-fit paradigm and SupExT [49].

Although the aforementioned results show the benefits that aerobic exercise could add to the hypocaloric DASH diet with respect to the biochemical profile (i.e., lower concentrations of glucose, insulin, HOMA-IR, LDL-C, TC, TG, ALT, GGT, CRP), in the present study, when the ANCOVA analysis was performed, no differences in the delta score ($p > 0.05$) were found between AC and SupExT for any variables. However, considering that AC had fewer participants ($n = 43$) than SupExT ($n = 134$), this lack of significance may have been due to power and thus, more research is needed to confirm or deny this.

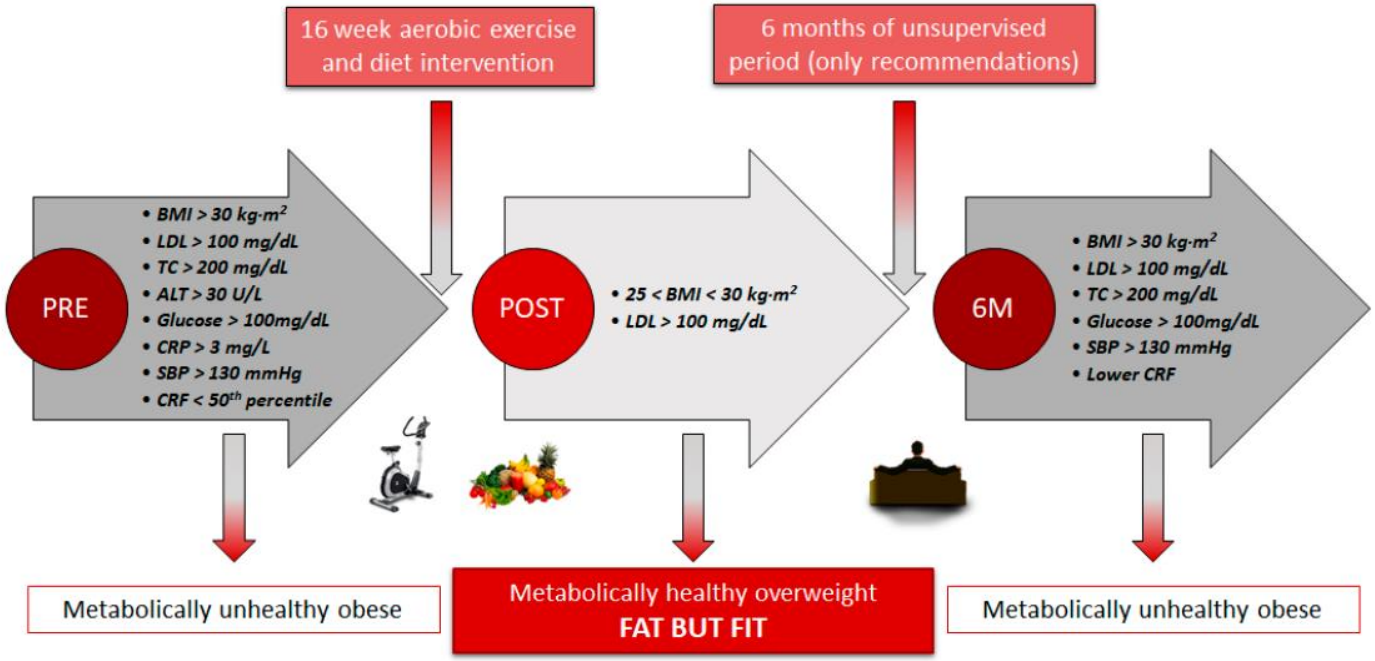

Figure 2. Participants' profile from metabolically unhealthy obese to metabolically healthy overweight and back. BMI: Body mass index. LDL: Low-density lipoprotein cholesterol. TC: Total cholesterol. ALT: Alanine aminotransferase. CRP: C-reactive protein. SBP: Systolic blood pressure. CRF: Cardiorespiratory fitness.

Based on findings from the current study and that previously presented by the research team [11,14], the 16-week intervention was effective in changing the metabolic profile from MUO to MHO according to the following criteria (Figure 2) [7]: from obesity to overweight lowering body fat, with TC, ALT, glucose, and CRP moving from unhealthy to optimal cut-off values, reflecting the absence of metabolic abnormalities and lower levels of systemic inflammatory mediators, and CRF from "percentile under 50" to "percentile upper 50" for VO_{2peak} classification [29]. Further, participants reduced their BP values (−5.4% reduction in MBP), and more than 7% of the participants stopped taking the medication and 25% reduced their doses under medical supervision [11,14].

Although there was a significant improvement in the metabolic profile after the 16-week intervention in the current study, there was subsequently a significant decline after 6 M when supervision was removed (Table 2, Figure 2). The MHO panel at POST was unable to be maintained after 6 M and participants regressed to MUO (Figure 2). The decrease in the lipidic, glycaemic, and haemodynamic profiles found after 6 M of no supervision in the present study is consistent with other studies which used different populations and with alternate types of exercise, duration of intervention, and non-supervised time [36,41,42,50]. These negative effects may be secondary to detraining-induced gains in body fat, favouring a more inflammatory status, and decreased CRF, as observed in participants. Previous studies have shown the pathophysiology of obesity related HTN [2]. Thus, an increase in the waist-to-hip ratio, parallel to a higher level of insulin, leptin, and the renin-angiotensin-aldosterone system seems to stimulate the sympathetic nervous system and concomitant increases in BP [2]. Further, it has already been established that a lower CRF, promoted by detraining, enhances the risk of suffering from metabolic syndrome and detrimental effects to the cardiovascular system, such as lack of regulation in BP, heart rate variability, myocardial oxygen demand, endothelial function, and systemic inflammation, in conjunction with inefficient fat storage [7]. Hence, it seems clear that the physical activity level differs between MHO and MUO in adults [1,5].

This suggests that supervision or alternative strategies of exercise provision are required given the need for MHO profile not to be a transient condition toward metabolic deterioration and consequently, a higher risk of developing cardiovascular disease [51,52]. Thus, in the present study, although the adherence with the 16-week intervention was very high in the SupExT, 6 M later, only 51% of all participants were engaged in physical activity (>2 times per week) and implementing the recommendations (unpublished data from the EXERDIET-HTA study). However, it is interesting to note that HDL-C concentrations were better at 6 M follow-up than in PRE (Δ = 2.4 mmol/L) and POST (Δ = 2.5 mmol/L). This may be due to the effects of a non-supervised diet being a prominent factor in HDL-C change, as previously discussed with the DASH diet [43,44].

In order to interpret findings from the current study, it is essential to consider both the strengths and limitations. Since pre-intervention measurements, 23 individuals did not finish the intervention and 19 participants did not attend the 6 M follow-up measurements, making the sample smaller, which may have affected the between-group differences. Further, although medication intake and smoking status was noted, it is difficult to assess the possible influence this had on the results. Dietary intake was self-reported through questionnaires at PRE and POST, but it was not assessed at 6 M follow-up, precluding knowledge about the adherence to the DASH diet.

Future areas for research could determine whether exercise and diet supervision can maintain the achieved improvements in cardiometabolic health, by comparing 6 M with supervision and without supervision. Further, it would be interesting to understand the reasons for the deterioration of cardiometabolic health when the supervision is removed. Lastly, analysing the physical activity and diet during the unsupervised period may provide information about the time course of these changes.

5. Conclusions

In conclusion, a 16-week SupExT and diet intervention was effective for improving cardiometabolic panel from MUO to MHO in a non-physically active population with obesity and HTN. However, this was a transient stage as after 6 M follow-up, participants returned to MUO. The findings of

this study highlight the need for regular, systematic, and supervised diet and SupExT programs to avoid subsequent declines in cardiometabolic health in people who are physically inactive with overweight/obesity and HTN.

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