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

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ABSTRACT

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

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Cardiorespiratory fitness; cardiovascular risk; dietary pattern; metabolically abnormal obese; sex differences

Introduction

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

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

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

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

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

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

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

Methods

Study participants

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

Measures

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

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

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

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

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

A blood sample (12.5mL) was collected from each participant in the Clinical Trials Unit of Tecnalia (HUA, Vitoria-Gasteiz) after an overnight fast to determine the biochemical profile including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose, insulin, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), and C-Reactive Protein (CRP) (13). Type 2 Diabetes mellitus was defined as a fasting glucose ≥126 mg/dL (16). HOMA-IR was used to evaluate insulin resistance [fasting serum insulin (μU/mL) × fasting plasma glucose (mg/dL)/405] (17).

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

Statistical analyses

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

Results

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

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

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

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

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

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

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

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

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

Table 2. Participants' peak exercise function.

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

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

*** P < 0.001.

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

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

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

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

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

*P < 0.05.

elevated ALT and GGT and lower AST/ALT ratio (P = 0.001, P = 0.030, and P = 0.018, respectively) compared to medium (ALT: P < 0.05, Δ = 50.8%, and GGT: P = 0.085, Δ = 41.2%) and high (ALT: P < 0.001, Δ = 118.8%, GGT: P = 0.035, Δ = 76.4% and AST/ALT ratio: P = 0.014, Δ = 27.3%) CRF level. No significant differences were observed in the rest of biochemical parameters among CRF levels.

Discussion

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

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

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

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

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

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

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

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

All population

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

There is increasing evidence that **sex differences** are important in pathophysiology treatment, and more relevant for noncommunicable diseases as HTN. With regard to body composition, the heterogeneity by sex in the relationship between hormones and body composition is well known. Thus, women present increased subcutaneous fat accumulation promoted by estrogen, and men feature a greater trunk and visceral and liver fat (36). The aforementioned was corroborated by the results of the present study in relation to a "better" body composition in men (*i.e*, higher FFM and lower FBM, Table 1) compared to women, but women showed a better metabolic profile (higher values in HDL-C and lower triglycerides and hepatic enzymes, Table 3) than men. However, taking into account the percentage of FBM, both sexes were obese according to cut off points for body fat percentage (*i.e.*, ≥25.0% for men and ≥35.0% for women) (37). Hence, men could present a higher CV or metabolic risk profile mainly due to the higher liver enzyme activities (*i.e.*, ALT, ALT, GGT, and AST/ALT ratio), and specifically with ALT values upper to healthy cutoff (<30 U/L), which is closely associated with non-alcoholic fatty liver disease (38). Furthermore, even though both sexes presented HDL-C and triglycerides values within the normal healthy range, the indirect vascular effect of estrogen in women may have had an influence on serum lipid concentrations with better values compared to men (Table 3), leading to a cardioprotective effect (39). Likewise, circulating estrogen in women may potentiate the vasodilatory effect of β-adrenergic activation by a nitric oxide mechanism causing vasodilation and favoring a lower resting DBP (P = 0.001) compared to men (Table 1) (40).

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

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

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

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

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

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

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Declaration of interest

The authors have nothing to disclose.

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