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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 hours), CRF (peak oxygen uptake, $\dot{V}O_{2peak}$), 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; β=-0.328, *P*<0.05) and alanine aminotransferase (ALT; β=-0.376, *P*<0.01) 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.

Keywords: 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 an 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 futher 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 surounding the associations and 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 $kg \cdot m^{-2}$) or obesity (BMI>30 $kg \cdot m^{-2}$) [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 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes 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 hour 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 ($\dot{V}O_{2peak}$) was assessed on an electronically braked Lode Excalibur Sport Cycle Ergometer (Groningen, The Netherlands). Initial power was 40W increasing in 10W 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-second averages. Achievement of $\dot{V}O_{2peak}$ was assumed with the presence of two or more of the following criteria: 1) volitional fatigue (>18 on BORG scale), 2) peak respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) ≥1.1, 3) achieving >85% of age predicted maximum heart rate (HR), and 4) failure of $\dot{V}O_2$ 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 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 five minutes 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) x 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 plus 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 were as follows; the lowest tertile (Low-CRF group): $\dot{V}O_{2peak} \leq 21.9$ mL·kg^{-1}·min^{-1} in men and $\dot{V}O_{2peak} \leq 17.2$ mL·kg^{-1}·min^{-1} in women; the medium tertile (Moderate-CRF group): $21.9 < \dot{V}O_{2peak} \leq 26.5$ mL·kg^{-1}·min^{-1} in men and $17.2 < \dot{V}O_{2peak} \leq 21.1$ mL·kg^{-1}·min^{-1} in women; the highest tertile (High-CRF group): $\dot{V}O_{2peak} > 26.5$ in men and $\dot{V}O_{2peak} > 21.1$ mL·kg^{-1}·min^{-1} in women. Statistical significance was set at $P<0.05$. All analyses were performed using Statistical Package for Social Sciences (IBM, Version 24).

Results

When split by sex (Table 1), men presented a higher ($P<0.05$) age, TBW, DBP, $\dot{V}O_{2peak}$, AST, ALT and TG, whilst women showed a higher ($P<0.05$) FM, TC, HDL-C and LDL-C concentrations. There were no significant sex differences in any other variables.

Table 1. Demographic and descriptive characteristics of the participants split by sex. Values are mean±SD or percentages (%) for categorical variables.

	All (N=214)	**Men (N=138)**	**Women (N=76)**	***P***
Age (years)	53.5±7.7	54.4±7.9	52.0±7.3	0.03*
BMI (Kg/m^2)	32.0±4.5	31.9±4.2	32.0±5.0	0.9
TBW (%)	48.4±6.5	50.7±4.6	44.3±7.2	<0.001***
FM (%)	34.3±8.5	30.8±7.7	40.8±5.7	<0.001***
SBP (mmHg)	136.2±12.8	136.8±12.2	135.2±14.0	0.4
DBP(mmHg)	78.4±8.3	79.7±7.6	76.1±8.9	0.003**
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	22.5±5.4	24.1±5.3	19.6±4.4	<0.001***
CRP (mg/L)	4.3±4.3	3.8±4.0	5.0±4.6	0.1
AST (U/L)	25.3±11.6	26.8±12.7	22.4±8.6	0.01*
ALT (U/L)	32.2±20.9	35.3±22.1	26.6±17.4	0.002**
AST/ALT	0.90±0.4	0.86±0.49	0.98±0.3	0.08
GGT (U/L)	39.1±43.3	43.0±48.4	29.5±25.2	0.1
TC (mmol/L)	5.3±0.9	5.2±1.0	5.6±0.9	0.007**
HDL-C (mmol/L)	1.2±0.3	1.2±0.2	1.4±0.3	<0.001***
LDL-C (mmol/L)	3.4±0.8	3.3±0.9	3.6±0.8	0.02*
TG (mmol/L)	1.6±0.9	1.7±1.0	1.3±0.6	0.003**

TC/HDL-C	4.5±1.5	4.6±1.6	4.2±1.1	0.05
Glucose (mmol/L)	5.7±1.4	5.6±1.2	5.8±1.6	0.4
Insulin (mU/L)	12.0±7.3	11.8±7.6	12.4±6.8	0.7
HOMA-IR	3.3 ±2.6	3.1±2.3	3.5±3.0	0.4
HbA1c (%)	6.0±0.9	5.9±0.9	6.0±0.9	0.7
Statin (%)	14	15.9	10.5	0.3
Hypoglycemic (%)	7	9.4	2.6	0.1
ACEI (%)	36.9	35.5	39.5	0.6
ARB (%)	43	44.2	40.8	0.6
Diuretic (%)	40.2	37.7	44.7	0.3
CCB (%)	15	18.1	9.2	0.1
BB (%)	7.5	7.2	7.9	0.9
Antiplatelet (%)	4.7	5.8	2.6	0.3
Smokers (%)	12.1	13	10.5	0.6

BMI: Body mass index. TBW: Total body water. FM: Fat mass. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. $\dot{V}O_{2peak}$: 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<0.05, **P<0.01, ***P<0.001

A series of linear regression analyses were conducted to assess the independent associations between $\dot{V}O_{2peak}$ and variables in the biochemical profile. As shown in Table 2, $\dot{V}O_{2peak}$ was negatively associated with CRP (P<0.001*)* unadjusted, however, but no significant associations in models 2 and 3 (P=0.084). $\dot{V}O_{2peak}$ was negatively associated with ALT both unadjusted (P=0.007*)* and following adjustment of covariates (P=0.005). Whilst AST was not significantly associated without adjustment, it was significantly associated when covariates were considered (P=0.026) 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 $\dot{V}O_{2peak}$ without adjustment (β=0.153) but not when adjustments in model 2 and 3 were made. $\dot{V}O_{2peak}$ was not significantly associated with GGT. No significant associations were found between $\dot{V}O_{2peak}$ and any of the lipid profile variables (TC, HDL-C, LDL-C, TG and TC/HDL-C). In addition, $\dot{V}O_{2peak}$ was not associated with HbA1c (Table 3).

Table 2. Linear regression models. Association between $\dot{V}O_{2peak}$ and CRP and hepatic enzymes. N=214.

Linear regression model	β Coefficient	LCI	UCI	*P*	Model R^2
$\dot{V}O_{2peak}$–CRP					
Unadjusted	**-0.377**	-0.568	-0.187	<0.001	0.142
Model 2	-0.296	-0.638	0.048	0.090	0.212
Model 3	-0.269	-0.575	0.037	0.084	0.258
$\dot{V}O_{2peak}$–AST					
Unadjusted	-0.051	0.196	-0.094	0.487	0.003
Model 2	**-0.329**	-0.616	-0.042	0.026	0.321
Model 3	**-0.328**	-0.616	-0.040	0.026	0.324
$\dot{V}O_{2peak}$–ALT					
Unadjusted	**-0.187**	-0.323	-0.051	0.007	0.035
Model 2	**-0.377**	-0.635	-0.119	0.005	0.452
Model 3	**-0.376**	-0.632	-0.120	0.005	0.466
$\dot{V}O_{2peak}$-AST/ALT					
Unadjusted	**0.153**	0.013	0.306	0.037	0.023
Model 2	0.131	-0.131	0.393	0.305	0.458
Model 3	0.128	-0.128	0.384	0.318	0.469
$\dot{V}O_{2peak}$–GGT					
Unadjusted	-0.128	-0.304	0.048	0.153	0.016
Model 2	-0.151	-0.548	0.246	0.441	0.644
Model 3	-0.115	-0.491	0.261	0.534	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. $\dot{V}O_{2peak}$: 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%).

Table 3. Linear regression models. Association between $\dot{V}O_{2peak}$ and lipid profile and insulin sensitivity. N=214.

Linear regression model	β Coefficient	LCI	UCI	*P*	Model R^2
$\dot{V}O_{2peak}$-TC					
Unadjusted	-0.002	-0.162	0.158	0.981	0.000
Model 2	0.129	-0.171	0.429	0.394	0.164
Model 3	0.123	-0.177	0.423	0.413	0.184
$\dot{V}O_{2peak}$–HDL-C					
Unadjusted	-0.050	-0.188	0.088	0.473	0.002
Model 2	0.180	-0.102	0.462	0.209	0.262
Model 3	0.173	-0.108	0.454	0.223	0.282

$\dot{V}O_{2peak}$–LDL-C					
Unadjusted	0.054	-0.087	0.195	0.452	0.003
Model 2	0.235	-0.064	0.534	0.121	0.271
Model 3	0.226	-0.074	0.526	0.137	0.279
$\dot{V}O_{2peak}$-TG					
Unadjusted	0.022	-0.179	0.093	0.748	0.000
Model 2	0.063	-0.237	0.363	0.677	0.193
Model 3	0.066	-0.232	0.364	0.661	0.197
$\dot{V}O_{2peak}$-TC/HDL					
Unadjusted	0.040	-0.096	0.176	0.563	0.002
Model 2	-0.131	-0.427	0.165	0.377	0.201
Model 3	-0.131	-0.427	0.165	0.382	0.201
$\dot{V}O_{2peak}$-Glucose					
Unadjusted	**-0.163**	-0.297	-0.029	0.017	0.027
Model 2	-0.088	-0.239	0.063	0.253	0.221
Model 3	-0.057	-0.215	0.101	0.478	0.229
$\dot{V}O_{2peak}$-Insulin					
Unadjusted	**-0.244**	-0.454	-0.035	0.023	0.059
Model 2	-0.247	-0.503	0.009	0.059	0.389
Model 3	-0.198	-0.438	0.042	0.104	0.486
$\dot{V}O_{2peak}$-HOMA-IR					
Unadjusted	**-0.288**	-0.494	-0.082	0.007	0.083
Model 2	-0.258	-0.527	0.011	0.060	0.332
Model 3	-0.208	-0.463	0.045	0.106	0.428
$\dot{V}O_{2peak}$-% HbA1c					
Unadjusted	-0.149	-0.354	0.062	0.166	0.022
Model 2	-0.080	-0.302	0.142	0.486	0.438
Model 3	-0.042	-0.246	0.168	0.703	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. $\dot{V}O_{2peak}$: 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%).

However, when the regression was conducted without any adjustment, a negative relationship was found between $\dot{V}O_{2peak}$ and glucose, insulin and HOMA-IR (β=-0.163, β=-0.244 and β=-0.288, respectively). But the association was not significant following adjustment (*P*>0.05*)*.

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*<0.064). 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*>0.05) was found following adjustment for covariates (Table 4).

Table 4. Logistic regression models. Association between $\dot{V}O_{2peak}$ and CRP and hepatic enzymes. N=214.

	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	0.297	1.158	0.274	4.894	0.842	1.119	0.267	4.678	0.878
High CRF	**0.128**	0.037	0.443	0.001	**0.173**	0.031	0.965	0.045	0.194	0.034	1.102	0.064
Elevated AST												
Moderate CRF	**0.416**	0.176	0.982	0.045	**0.022**	0.002	0.288	0.004	**0.023**	0.002	0.288	0.004
High CRF	**0.186**	0.059	0.587	0.004	**0.040**	0.003	0.619	0.021	**0.041**	0.003	0.641	0.023
Elevated ALT												
Moderate CRF	**0.456**	0.231	0.900	0.024	**0.145**	0.032	0.650	0.012	**0.127**	0.026	0.62	0.011
High CRF	**0.221**	0.103	0.474	<0.001	**0.121**	0.019	0.768	0.025	**0.109**	0.016	0.75	0.024
Low AST/ALT												
Moderate CRF	1.836	0.769	4.385	0.171	0.336	0.041	2.769	0.310	0.310	0.035	2.718	0.290
High CRF	2.627	1.091	6.327	0.153	0.229	0.019	2.712	0.243	0.225	0.019	2.678	0.238
Elevated GGT												
Moderate CRF	**0.293**	0.095	0.901	0.032	0.009	0.000	4.216	0.133	0.009	0.000	4.978	0.145
High CRF	**0.202**	0.053	0.768	0.019	25.965	0.060	11299.629	0.293	25.832	0.062	10691.539	0.290

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%).

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=0.014 and P=0.046 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=0.016), but there was no significance in high CRF group (P=0.096). HOMA-IR showed a significant association with the high CRF group in the unadjusted model (P=0.037) and in model 2 (P=0.043). However, but there was no significance in model 3 (P=0.062). Using logistic regression insulin and HbA1c did not show any significant associations with the CRF groups (Table 5).

Table 5. Logistic regression models. Association between $\dot{V}O_{2peak}$ and lipid profile and insulin sensitivity. N=214.

	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	0.936	0.315	0.070	1.423	0.133	0.317	0.071	1.419	0.133
High CRF	1.528	0.780	2.995	0.217	2.224	0.373	13.260	0.380	2.207	0.373	13.067	0.383
Low HDL-C												
Moderate CRF	0.867	0.394	1.905	0.722	2.521	0.459	13.837	0.287	2.243	0.402	12.503	0.357
High CRF	0.636	0.273	1.479	0.293	0.557	0.067	4.602	0.587	0.511	0.060	4.358	0.539
Elevated LDL-C												
Moderate CRF	0.546	0.218	1.367	0.196	0.349	0.026	4.666	0.454	0.358	0.027	4.818	0.439
High CRF	1.200	0.419	3.439	0.734	1.605	0.056	46.155	0.873	1.606	0.057	45.426	0.781
Elevated TG												
Moderate CRF	1.182	0.491	2.847	0.710	0.711	0.115	4.378	0.713	0.496	0.072	3.434	0.478
High CRF	0.626	0.227	1.723	0.364	1.347	0.141	12.885	0.796	1.073	0.105	11.016	0.952
Elevated TC/HDL												
Moderate CRF	0.589	0.260	1.335	0.205	0.286	0.045	1.837	0.187	0.278	0.042	1.815	0.181
High CRF	**0.383**	0.172	0.851	0.018	0.384	0.052	2.852	0.350	0.381	0.051	2.847	0.347
Elevated Glucose												
Moderate CRF	0.529	0.273	1.025	0.059	**0.357**	0.158	0.809	0.014	**0.364**	0.160	0.827	0.016
High CRF	**0.388**	0.194	0.777	0.008	**0.408**	0.170	0.983	0.046	0.457	0.182	1.148	0.096
Elevated Insulin												
Moderate CRF	1.842	0.552	6.140	6.140	1.992	0.397	9.990	0.402	2.383	0.420	13.529	0.327
High CRF	0.126	0.014	1.172	0.069	0.058	0.001	2.300	0.129	0.070	0.002	2.563	0.148
Elevated HOMA-IR												
Moderate CRF	1.161	0.378	3.567	0.795	0.605	0.116	3.167	0.552	0.632	0.106	3.771	0.614
High CRF	**0.165**	0.030	0.898	0.037	**0.088**	0.008	0.931	0.043	0.109	0.011	1.118	0.062
Elevated % HbA1c												
Moderate CRF	1.006	0.323	3.134	0.992	1.566	0.362	6.774	0.548	1.797	0.353	9.150	0.481
High CRF	0.366	0.092	1.453	0.153	0.359	0.050	2.595	0.310	0.464	0.058	3.694	0.469

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%).

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 in 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 [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 paper, 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], while 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, while 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].

Due to 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, while 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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