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Original Article

Effects of Body Mass Index on the Lipid Profile and Biomarkers of Inflammation and a Fibrinolytic and Prothrombotic State

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***Aim*: Both an overweight status and obesity are associated with high cardiovascular morbidity and mortality. The aim of this study was to examine the effects of obesity on different underlying mechanisms, i.e. inflammation, fibrinolysis and a prothrombotic state, in a young high-risk population in the Mediterranean area.**

***Methods*: The study population included 237 subjects (median age: 44 years). We recorded the presence of cardiovascular risk factors and premature ischaemic heart disease and performed weight stratification using the body mass index (BMI) according to the established World Health Organization (WHO) criteria. We also measured the serum/plasma lipid, fibrinogen, D-dimer, von Willebrand factor, tissue plasminogen activator antigen (t-PA), plasminogen activator inhibitor-1 antigen (PAI-1) and high-sensitivity C-reactive protein (CRP-hs) levels in samples of peripheral blood.**

***Results*: The subjects with premature ischaemic heart disease and hypertension had higher BMI values ($p<0.01$), and the subjects with an increased weight showed an unadjusted detrimental lipid profile, with a proinflammatory, prothrombotic state and abnormal fibrinolytic parameters. According to a multivariate analysis, the HDL-cholesterol ($r^2=0.176$; $p<0.001$), t-PA antigen ($r^2=0.235$; $p<0.001$), PAI-1 antigen ($r^2=0.164$; $p<0.001$) and CRP-hs ($r^2=0.096$; $p=0.019$) levels were significantly related to the weight stratification.**

***Conclusions*: A high BMI is a common finding in young populations at high risk of cardiovascular disease. In the current study, the patients with an increased BMI demonstrated an unhealthy lipid profile, as well as a proinflammatory and prothrombotic state and abnormal fibrinolytic parameters.**

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Key words: Obesity, Inflammation, Fibrinolysis, Lipid profile, Prothrombotic state

Introduction

The World Health Organization (WHO) defines an overweight status and obesity as abnormal or excessive fat accumulation that presents as a risk factor to health[1)]. Excessive adiposity has been reported to be associated with increased morbidity and cardiovascular mortality directly or in part due to other conditions related to obesity, such as diabetes mellitus, hypertension and dyslipidemia[2, 3)]. Furthermore, obesity has been recognized to be an independent cardiovascular risk factor[4)], and the incidence of conditions associated with obesity is currently increasing dramatically among the populations of middle-income countries, particularly in the urban setting, and is now considered pandemic in developed countries[5, 6)].

Obesity confers a major cardiovascular risk, promoting a proinflammatory and prothrombotic state

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related to insulin resistance[7]. Improvements in biochemical techniques have renewed interest in the study of different biomarkers and their role in the development of cardiovascular disease. For example, the high-sensitivity C-reactive protein (CRP-hs) level is widely used as systemic biomarker for diagnosing acute and chronic inflammation and is considered a therapeutic target in patients receiving cardiovascular therapy[8]. Haemostatic and endothelial damage markers and fibrinolytic factors have also been shown to be associated with the development of cardiovascular disease and subsequently proposed to be markers of atherosclerotic damage[9].

Atherosclerosis is the fundamental underlying disease substrate of cardiovascular disease. Intravascular thrombogenesis, the main pathogenic mechanism of coronary artery disease, is influenced by the complex interplay of procoagulant, anticoagulant, fibrinolytic, endothelial damage/dysfunction and inflammatory processes[10].

Aim

The aim of this study was to examine the effects of obesity on different underlying mechanisms assessed according to different established biomarkers, i.e. inflammation (CRP-hs), fibrinolysis (tissue plasminogen activator [t-PA antigen] and its inhibitor [PAI-1 antigen]), endothelial damage/dysfunction (von Willebrand factor [vWF]) and a prothrombotic state (fibrinogen and fibrin D-dimer), in a young high-risk Mediterranean population.

Methods

Consecutive patients were recruited from primary care physicians of our referred tertiary hospital area. All subjects were young with at least two cardiovascular risk factors. In addition, patients were recruited from the secondary care setting after experiencing premature acute myocardial infarction (presenting with prior myocardial infarction at a young age, that is, age ≤45 years). Our study cohort consisted of 237 subjects (92% men, 44 (40-48) years), of whom 142 (59.9%) suffered from myocardial infarction at a young age. The exclusion criteria were prosthetic heart valves, a pacemaker or automated internal defibrillator, current oral anticoagulant use, inflammatory or infectious disease, recent surgery (<3 months), malignancy, severe hepatic/renal disease, HIV, severe haematological disorders or refusal of consent.

We recorded the presence of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or receiving antihypertensive agents according to the Seventh Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure)[11], hyperlipidemia (according to the Third Report of the National Cholesterol Education Program Adult Treatment Panel Ⅲ)[12], diabetes mellitus (defined according to the American Diabetes Association)[13], the smoking status (current smokers, ex-smokers and non-smokers), physical inactivity and a first-degree family history of premature coronary artery disease (before 55 years of age in men or 65 years of age in women)[14] as conventional coronary risk factors. Physical inactivity is recognized to be an important risk factor for multiple causes of death as well as chronic morbidity and disability. This parameter is divided in two categories according to the WHO: level 1 exposure (inactive), defined as engaging in no or very little physical activity at work, home, for transport or in the subject's discretionary time; and level 2 exposure (insufficiently active), defined as engaging in some physical activity, but less than 150 minutes of moderate intensity physical activity or 60 minutes of vigorous intensity physical activity a week accumulated across the work, home, transport and discretionary domains[15].

A common measurement of increased weight is the body mass index (BMI). The BMI associates a person's weight with their height (Kg/m^2), being the same for both sexes and all ages in adults. In order to analyse variables associated with increased weight, we performed weight stratification using the BMI according to the established WHO criteria: normal, BMI ≤25; overweight, 25 < BMI < 30; and obese, BMI ≥30[1].

Laboratory Measurements

Venous blood was collected without trauma or stasis in the morning by specialized staff with the patient fasting for more than nine hours. The blood samples were centrifuged for 15 minutes at 3,500 g within 20 minutes after collection, and the isolated serum and plasma samples were immediately frozen and stored at −80℃ until the batched analysis. Blood sampling was performed at least three months after acute myocardial infarction and in the stable phase of the disease, as some of the assessed biomarkers are acute-phase reactants, which may modify the results.

In order to determine the lipid profiles, colorimetric assays were used to measure the total cholesterol, HDL-cholesterol and triglyceride levels (all employing Roche/Hitachi Products). The plasma LDL-cholesterol levels were estimated using the equation of Friedewald *et al.*[16]. The fibrinogen levels were deter-

mined according to the method of Clauss[17] using an STA coagulation analyser (Diagnostica STAGO, Paris, France). The D-dimer, plasma vWF antigen, t-PA antigen and PAI-1 antigen levels were measured according to the ELISA technique (Diagnostica STAGO, Paris, France). The CRP-hs levels were measured in the serum samples and analysed using a sandwich enzyme immunoassay (IMMAGE®, Beckman), according to the manufacturer's instructions. All analyses were performed according to the manufacturers' specifications, and quality control was within the recommended range of precision for each test, with inter- and intra-assay coefficients of variation of $<10\%$. The present study was approved by the ethics committee of Hospital General Universitario de Alicante (Alicante, Spain), and all patients provided their informed consent.

Statistical Analysis

The distribution of continuous variables was analysed using the Kolmogorov-Smirnov test. Parametric variables are expressed as the mean ± SD and non-parametric variables as the median (IQR, interquartile range), with comparisons made according to the unpaired Student's *t*-test or Mann Whitney test, as appropriate. Categorical variables are presented as absolute and relative frequencies, and associations between these variables were tested using the chi-square test. Associations between quantitative variables (biomarkers) and the weight stratification were evaluated using an ANOVA or the Kruskal-Wallis test, if appropriate. Correlations between two quantitative variables were investigated based on the Pearson coefficient (or Spearman coefficient, if appropriate). Multivariate analyses (linear regression, Enter method) were performed to assess the effects of different variables (age, sex, cardiovascular risk factors, presence of premature cardiovascular disease and, specifically, the weight stratification) on the analysed biomarkers. A p value of less than 0.05 was considered to be significant. The statistical analyses were carried out using the *Statistical Package for the Social Sciences* (SPSS), version 17.0 for Windows software program (Chicago, Illinois, USA).

Results

The clinical characteristics and medications of the study population are summarized in **Table 1**. The median age was 44 (40-48) years and the vast majority of subjects were men (92%). Of the study cohort, 24.9% showed a normal BMI, 53.6% were overweight and 21.5% were obese. The subjects with premature ischaemic heart disease ($p<0.001$) and hypertension ($p=0.004$) had higher BMI values, whereas the differences in BMI among smokers ($p=0.090$) and diabetics ($p=0.056$) did not reach a level of statistical significance.

Table 1. Clinical characteristics of the patients at baseline and current therapies at study entry

Number patients	237
Age, years [median(interquartile range)]	44 (40-48)
Male sex (%)	218 (92.0%)
Height, cm; median (interquartile range)	171 (167-175)
Weight, Kg (mean ± SD)	80.0 (72.0-89.0)
BMI, kg/m^2; median (interquartile range)	26.0 (24.8-29.0)
Normal (%)	59 (24.9%)
Overweight (%)	127 (53.6%)
Obese (%)	51 (21.5%)
Past medical history (%)	
Smoking habit	
Non-smoker	66 (27.8%)
Smoker	83 (35.0%)
Ex-smoker	88 (37.1%)
Hyperlipidemia	163 (68.8%)
Family history	80 (33.7%)
Hypertension	69 (29.1%)
Physical inactivity	78 (32.9%)
Diabetes	26 (11.0%)
Premature ischemic heart disease	142 (59.9%)
Drug therapies (%)	
Antiplatelets	132 (55.7%)
Statins	117 (49.3%)
β-blockers	84 (35.4%)
ACEI and ARA II	43 (18.1%)
Calcium channel blockers	26 (11.0%)
Nitrates	21 (8.8%)
Fibrates	9 (3.8%)
Diuretics	7 (3.0%)

BMI: body mass index. ACEI: angiotensin-converting enzyme inhibitor. ARA II: angiotensin II receptor antagonist.

The results of the unadjusted analysis of the biomarkers and weight stratification are presented in **Table 2**. The patients with an increased weight (BMI above 25 kg/m^2), primarily the obese subgroup (BMI above 30 kg/m^2), exhibited abnormal lipid profiles (especially low HDL-cholesterol), with evidence of a proinflammatory and prothrombotic state. In addition, abnormal fibrinolysis was observed in this group, as reflected by higher levels of CRP-hs, fibrinogen, t-PA antigen and PAI-1 antigen (all $p<0.05$).

There were significant correlations between BMI and various biomarkers (**Table 3**). Notably, BMI was negatively correlated with HDL-cholesterol ($r=-0.27$,

Table 2. Unadjusted levels of lipids and prothrombotic, fibrinolytic and inflammatory markers according to the weight stratification

Marker	Whole cohort	Reference control cohort*	Normal BMI ≤ 25
Total cholesterol (mg/dL)	197.4 ± 48.7	193.1 ± 24.0	204.5 ± 43.0
HDL-cholesterol (mg/dL)	34.0 ± 11.9	48 (42-55)	40.8 ± 13.5
LDL-cholesterol (mg/dL)	129.0 (103.0-154.0)	125 ± 27.1	130.0 (112.0-157.0)
Triglycerides (mg/dL)	132.0 (91.0-194.5)	100.4 ± 35.1	115.0 (86.0-151.2)
tPA antigen (ng/mL)	13.5 ± 4.3	9.3 ± 5.4	11.6 ± 4.7
PAI-1 antigen (ng/mL)	65.4 (34.4-102.0)	43.0 ± 26.0	43.4 (19.2-100.0)
Fibrinogen (mg/dL)	325.9 ± 77.1		316.1 ± 65.1
D-dimer (ng/mL)	290.0 (229.2-379.0)		274.0 (219.0-356.0)
von Willebrand factor (%)	109.3 ± 32.5		112.6 ± 28.5
CRP-hs (mg/dL)	0.170 (0.090-0.317)	0.100 (0.030-0.350)	0.127 (0.062-0.292)

Marker	Overweight 25 < BMI < 30	Obese BMI ≥ 30	*p* value**
Total cholesterol (mg/dL)	198.0 ± 54.0	195.3 ± 41.5	0.628
HDL-cholesterol (mg/dL)	32.8 ± 10.3	30.5 ± 10.8	≤ 0.001
LDL-cholesterol (mg/dL)	127.5 (103.0-156.7)	133.0 (101.0-154.5)	0.882
Triglycerides (mg/dL)	131.5 (89.2-181.2)	156.0 (109.5-230.5)	0.053
tPA antigen (ng/mL)	13.9 ± 4.4	14.8 ± 3.1	< 0.001
PAI-1 antigen (ng/mL)	69.1 (34.3-96.9)	94.4 (58.8-102.1)	0.003
Fibrinogen (mg/dL)	319.0 ± 80.7	356.6 ± 84.0	0.013
D-dimer (ng/mL)	289.0 (231.0-398.7)	310.0 (240.7-432.2)	0.293
von Willebrand factor (%)	108.5 ± 33.3	112.0 ± 33.0	0.679
CRP-hs (mg/dL)	0.149 (0.080-0.290)	0.290 (0.169-0.583)	< 0.001

HDL-cholesterol: high-density lipoprotein-cholesterol; LDL-cholesterol: low-density lipoprotein-cholesterol; tPA: tissue plasminogen activator. PAI-1: plasminogen activator inhibitor. CRP-hs high-sensitivity C-reactive protein.
Control cohort*: Data for the control cohort were obtained from a previous article, reference [48].
**: Comparisons were performed within the whole cohort among the BMI groups.

$p<0.001$) and positively correlated with triglycerides ($r=0.18$; $p=0.008$), CRP-hs ($r=0.31$; $p<0.001$), t-PA antigen ($r=0.27$; $p<0.001$), PAI-1 antigen ($r=0.25$; $p<0.001$) and fibrinogen ($r=0.15$; $p=0.027$).

The subgroup of patients with premature coronary disease demonstrated significantly higher levels of triglycerides [150.1 mg/dL (107.0-201.0) vs 109.5 mg/dL (76.7-155.2)]; $p=0.001$], fibrinogen [336.1 mg/dL (247.7-424.3) vs 310.2 mg/dL (362.5-257.9); $p=0.006$], fibrin D-dimer [301.5 ng/mL (437.5-235.0) vs 273.1 ng/mL (340.5-216.2); $p=0.006$] and vWF [113.1% (144.3-81.7) vs 103.7% (137.2-70.2); $p=0.032$] and lower levels of HDL-cholesterol [31.9 ± 9.5 mg/dL vs 37.1 ± 14.5 mg/dL; $p=0.003$].

In the multivariate analyses (**Table 4**), the HDL-cholesterol levels were predicted by the proposed model ($r^2=0.176$; $p<0.001$) and found to be independently associated with the weight stratification ($p=0.002$). Among fibrinolytic parameters, the t-PA ($r^2=0.235$; $p<0.001$) and PAI-1 antigen ($r^2=0.164$; $p<0.001$) levels were also significantly predicted by the models and identified to be independently associated with the weight stratification ($p=0.002$ and $p<0.001$, respectively). Furthermore, the CRP-hs levels were predicted by the model ($r^2=0.096$; $p=0.019$) and shown to be independently associated with the weight stratification ($p=0.006$). In contrast, neither the fibrinogen ($r^2=0.089$; $p=0.028$) nor triglyceride ($r^2=0.163$; $p<0.001$) levels were independently associated with the weight stratification ($p=0.131$ and $p=0.326$, respectively).

Discussion

The present study demonstrated a high prevalence of an overweight status or obesity in a young Mediterranean population at high risk for cardiovascular disease. This finding is related to the effects of premature coronary heart disease (CHD) and other cardiovascular risk factors. In addition, the patients with an increased weight exhibited unhealthy lipid profiles, as well as a proinflammatory and prothrombotic state and abnormal fibrinolytic parameters.

Obesity is an independent CHD risk factor in

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Table 3. Bivariant correlations between BMI and the biomarkers

Biomarker	*r* value	*p* value
Triglycerides	0.182	0.008
HDL-Cholesterol	−0.266	<0.001
CRP-hs	0.314	<0.001
t-PA antigen	0.265	<0.001
PAI-1 antigen	0.252	<0.001
Fibrinogen	0.153	0.027

tPA: tissue plasminogen activator. PAI-1: plasminogen activator inhibitor. CRP-hs: high-sensitivity C-reactive protein.

Table 4. Adjusted levels of lipids and prothrombotic, fibrinolytic and inflammatory markers

Marker	r^2 value	p^* value	p^{**} value
HDL-cholesterol	0.176	0.001	0.002
t-PA antigen	0.235	0.001	0.002
PAI-1 antigen	0.164	0.001	<0.001
CRP-hs	0.096	0.019	0.006
Fibrinogen	0.089	0.028	0.131
Triglycerides	0.163	<0.001	0.326

p^* value of the model. p^{**} regarding the weight stratification.

adults[18-21]. Prospective studies suggest that obesity is a CHD risk factor, even after adjusting for other risk factors[11, 14, 22]. Conversely, weight loss is associated with a reduction in cardiovascular risks[23]. In our young Mediterranean high-risk population, the patients with a history of prior myocardial infarction had significantly higher BMI values.

Obesity is associated with changes in lipoprotein metabolism, promoting the development of a deleterious lipid profile, with lower HDL-cholesterol levels[2]. Of note, a low HDL-cholesterol level (<35 mg/dL) has been recognized to be both an independent risk factor for CHD and independent parameter included in the complex definition of metabolic syndrome. With the recent advances in biochemical techniques, the usefulness of biomarkers for monitoring cardiovascular diseases has been demonstrated in several studies[2, 24-26]. In the present study, a low HDL-cholesterol level was found to be independently and inversely associated with increased weight and BMI values. As confirmed in the present study, premature coronary disease is characterized by an unfavourable lipid profile[27], with lower HDL-cholesterol and higher triglyceride levels.

Inflammation contributes to the pathogenesis of CHD, including the initiation, development and establishment of atherosclerotic lesions and onset of acute atherothrombotic events. The CRP-hs level is a valuable well-recognized inflammatory biomarker of vascular damage[28]. Despite evidence relating CRP-hs and CHD, the role of this protein in the development of a pathological state has not been completely established. Chronic elevation of the CRP-hs level is evident in individuals with cardiovascular disease risk factors, such as diabetes, smoking, obesity, hypertension and dyslipidemia[29-31]. In the current study, a significant and independent correlation was observed between the CRP-hs level and BMI, and the HDL-cholesterol and CRP-hs levels were shown to be significantly and independently associated with an increased weight. Hence, we hypothesize that the activity of lipid tissue is associated with low-grade subclinical inflammation.

On the other hand, haemostatic factors are also related to inflammatory markers. For example, the fibrinogen level is strongly and independently related to the cardiovascular risk[32, 33]. Fibrinogen directly increases the risk of cardiovascular disease via its effects on abnormal coagulation and blood rheology, platelet aggregation, the endothelial function, fibrin formation and thrombogenic effect[33-36]. The Framingham Study described significant linear relationships across fibrinogen tertiles ($p<0.001$) for age, BMI, smoking, diabetes mellitus, total cholesterol, HDL-cholesterol and triglycerides in both genders[37]. Similarly, the fibrinogen level was shown to be associated with the body weight stratification in the present study, and the patients with premature coronary disease showed significantly higher levels of fibrinogen, as observed in other studies[35, 38, 39]. Fibrinogen and its degradation products have been demonstrated to stimulate smooth muscle cell proliferation and migration, both of which represent essential mechanisms for atherogenesis.

A close association between the tPA/PAI-1 level and the onset of insulin resistance syndrome (BMI, triglycerides and HDL-cholesterol) has been reported[40]. According to our results, both the t-PA and PAI-1 levels are independently associated with body weight stratification and positively correlate with BMI. Collectively, subjects with high metabolic risks due to insulin resistance demonstrate dysfunction of the fibrinolytic system[40, 41]. In addition, several functional studies have shown that abnormal levels of tPA and PAI-1 are unequivocally associated with fibrinolytic dysfunction. Our group previously described a hypofibrinolytic state in both rheumatic and non-rheumatic AF patients, with elevated PAI-1 antigen and t-PA/

PAI-1 complex levels[42]. Moreover, we and others have shown that the levels of t-PA, PAI-1 and D-dimer are decreased after coagulation, thus indicating a hypofibrinolytic state[43, 44]. Furthermore, a study of lone AF found raised levels of plasma t-PA and PAI-1 antigens to be associated with fibrinolytic dysfunction[45]. Taken together, these observations highlight the importance of the tPA and PAI-1 levels as abnormal fibrinolytic biomarkers.

Limitations

This study is limited by the cross-sectional analysis and defined Mediterranean population. However, we targeted young patients (age ≤45) at high cardiovascular risk. Furthermore, the effects of some drugs taken by the patients at the time of blood sampling may have altered the levels of some of the biomarkers[38, 46, 47].

Conclusion

A high BMI is a common finding in young populations with a high risk of cardiovascular disease. The weight stratification (particularly an increased weight) is significantly associated with several abnormalities in biomarkers of the lipid profile (HDL-cholesterol), proinflammatory state (CRP-hs), prothrombotic state (fibrinogen) and/or abnormal fibrinolysis (t-PA and PAI-1), which may contribute to increased cardiovascular mortality. Taken together, these results indicate that a high BMI affects several pathways associated with an elevated risk of cardiovascular disease.

Abbreviations

WHO: World Health Organization, BMI: body mass index, CHD: coronary heart disease, CRP-hs: high-sensitivity C-reactive protein, PAI-1: plasminogen activator inhibitor, t-PA: tissue plasminogen activator, vWF: von Willebrand factor, HDL-cholesterol: high-density lipoprotein-cholesterol, ELISA: Enzyme-Linked ImmunoSorbent Assay

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Conflicts of Interest

None.

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