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Overweight, Obesity and Abdominal Adiposity Effects in Inflammatory Proteins: C-reactive Protein and Fibrinogen

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Inflammatory acute phase proteins has been identified as a possible connection between overweight, adiposity, obesity and cardiovascular disease risk, mainly in what refers to C-reactive Protein (CRP) and fibrinogen. The present study aimed to identify correlations between anthropometric and body composition measurements with these inflammatory proteins. Sample included 70 individuals aged 30-60 years which had been submitted to anthropometric and body fat mass assessment while blood samples were collected for CRP and fibrinogen determination. Very strong associations has been found between anthropometric and body composition variables. Strong associations had been found between Waist Circumference (WC), Body Mass Index (BMI), Body Fat (BF) mass and C-reactive protein in females and between C-reactive protein, waist circumference and body mass index but only in the 30-39 age group. Body mass index and waist circumference were also strongly associated with C-reactive protein in females 40 to 49 years old. Fibrinogen has shown very strong associations with body mass index and fat mass in females 30 to 39 years old and strong in what concerns to waist circumference in the same age group. Considering the well known pejorative impact of obesity, especially abdominal adiposity in what concerns to cardiovascular disease, these data has reinforced the importance of monitor inflammatory acute phase proteins like C-reactive protein in pre-obese and obese patients.

Key words: Adiposity, abdominal adiposity, inflammation, cardiovascular disease risk, inflammatory markers

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INTRODUCTION

Obesity had been recognized as a disease in 1985 (Greenway and Smith, 2000) and it has been defined as a multifactorial etiology (Suleiman *et al*., 2009; Afridi and Khan, 2004) disease characterized by an exacerbated fat mass deposition in human body when comparing to references for the same age, height and gender. Additionally to being a esthetical problem, excessive weight and body fat mass had been associated with several health concerns (Conway and Rene, 2004; Lau *et al*., 2005). For several years, adipose tissue had been considered an inert tissue being exclusively associated with fat deposition functions (Visser *et al*., 1999; Kershaw and Flier, 2004; Fantuzzi, 2005). However, several studies conducted on the last decade observed an intense endocrine function with an important role in metabolism (Visser *et al*., 1999). Two types of adipose tissue can be found in mammals: White Adipose Tissue (WAT) which is the main component of body adipose tissue and Brown Adipose Tissue (BAT). Brown adipose tissue has mainly been associated with thermogenesis, being responsible for heat production and cold acclimation in mammals (Cannon and Nedergaard, 2004). It had been seen as a potential weapon against obesity considering results which revealed a preventive effect of uncoupling-protein 1 produced by BAT in overfeed rats obesity (Xue *et al*., 2007). However some controversies has remained in what refers to its role in energy homeostasis and weight gain prevention in human adults (Ravussin and Galgani, 2011; Lee *et al*., 2010). Studies suggested that WAT should not be seen as restricted to lipogenic and lipolytic activities (Lau *et al*., 2005). It was observed that this heterogeneous tissue is composed by several types of cells including pre-adipocytes, adipocytes, endothelial cells, fibroblasts and macrophages (Ahima and Flier, 2000; Balistreri *et al*., 2010; Weiss *et al*., 2011). Several data concluded that it is involved not only in metabolic processes but also immune, cardiovascular and endocrine activities considering that it produces a broad range of bioactive substances (Bastard *et al*., 2006; Balistreri *et al*., 2010). A systemic inflammatory process has been observed in obesity, which could be naturally explained by these polyvalent adipose tissue actions. In fact, some authors reported high correlations between increased adiposity and high levels of some acute phase inflammatory proteins like C-Reactive Protein and Fibrinogen (Festa *et al*., 2001; Nguyen *et al*., 2009; Berg and Scherer, 2005) while they had seem to decrease during weight loss (Al-Hamdan *et al*., 2009). C-Reactive Protein (CRP) was the first acute phase protein being described and it has been used as a marker to inflammatory and infectious diseases (Panichi *et al*., 2012; Sargolzai *et al*., 2008) but it had also been associated with high risk of cardiovascular disease even in healthy individuals (Patel *et al*., 2001; Nguyen *et al*., 2009). Adding up to this, high levels of Fibrinogen has also been reported in inflammatory processes. This protein, a fibrin precursor, has been recognized as a determinant element in plaque and erythrocyte aggregation especially in peripheral tissues which could result in tissue hypoxia and endothelial dysfunction. These blood flow impairments could be among the physiologic and pathologic causes of cardiovascular disease (Lowe, 2010). Considering these data, the present work intended to study the correlation between adiposity, CRP and Fibrinogen in apparently healthy individuals aiming to add up new data about the role of these markers on cardiovascular disease risk.

MATERIALS AND METHODS

Ethics: The study design and procedures were previously approved by an ethical and scientific commissions and were all conducted according to Portuguese legislation as well as Declaration of Helsinki from World Medical Association. Data were obtained under informed consent.

Sample: Several apparently healthy individuals were chosen among a local public healthcare center situated in Cacém/Queluz, Portugal. From these, 70 individuals were chosen according to inclusion and exclusion criteria. The study took place from September to December 2011.

Inclusion criteria: The sample included all the patients attended at the medical consultation in the local healthcare unit were initially considered after accepting their participation in this study.

Exclusion criteria: From the initial sample several patients were excluded if:

- Were under 30 years old or more than 60 years old
- Suffered from an infectious or inflammatory disease
- Laboratory data had revealed CRP above 1.0 mg dL^{-1} (Pearson *et al*., 2003; Yeh and Willerson, 2003; Pepys and Hirschfield, 2003)
- Had presented Fibrinogen values below 156 mg dL^{-1} or above 400 mg dL^{-1} (laboratory reference values)
- Were using any kind of hormonal contraceptive measures (Pearson *et al*., 2003; Pepys and Hirschfield, 2003)

- Were smokers (Pearson *et al.*, 2003; O'Loughlin *et al.*, 2008)
- Reported an excessive alcoholic drink consumption: = 24 g day^{-1} in male and = 16 g day^{-1} in female (Foerster *et al.*, 2009)

Anthropometric measures and body composition data: After general data was collected (name, age), anthropometric assessment and body composition by BIA were conducted. Height was measured using a stadiometer with 1 mm precision and a maximum height of 2.10 m with the individuals on their foot, with no shoes, equally distributed weight between feet, heels together and natural pending arms aside of the body with open hands with palms close to lateral thigh region and head positioned according to Frankfort's plane (Ball *et al.*, 2010). Individuals were weighted minimally dressed in a portable digital scale with a 150 kg maximum capacity and +/-100 g error margin. Body mass index was calculated through the quotient between weight and square height. Body fat mass was determined using a TANITA BF-552 bioelectrical impedance scale. Waist Circumference (WC) with a flexible non-elastic tape while the individuals stood feet together with warms resting by their sides. Waist circumference was measured in the horizontal plane between the lowest rib end and the iliac crest. Different criteria was considered for each gender: (a) in waist circumference equal or above 94 cm in men and equal or above 80 cm in women present high cardiovascular risk (b) normal body fat mass range varies from 15 to 20% in men and 21 to 33% in women.

C-reactive protein and fibrinogen determination: Less than 10 mL of blood was collected through an arm venous puncture after assuring total aseptic conditions. C-reactive protein was determined by immunoturbidimetry (Jovicic *et al.*, 2006) and fibrinogen through Clauses modified method (Mackie *et al.*, 2002).

Statistical analysis: The statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version PASW Statistics 18. Initially a general descriptive analysis was done for all the anthropometric and body composition measures as well as CRP and fibrinogen values. Normality test Shapiro-Wilk revealed a normal distribution within the variables considered which allowed the application of parametric tests. ANOVA-one way variance analysis was chosen to compare means between men and women for all the parametric, body composition and biochemical parameters. All the statistical tests conducted were two-tailed and were statistically significant at the 0.05 significance level. In order to establish the associations between BMI, waist circumference, body fat mass, CRP and fibrinogen, a Pearson correlation analysis was conducted. This analysis was stratified according to gender and age stages (30-39, 40-49 and 50-60). This bivariate correlation analytic method measures the intensity and direction of the association between two quantitative variables.

The correlation coefficients can vary from -1 to 1 (Nikolic *et al.*, 2012):

- $r = 1$ perfect linear association
- $0.8<r<1$ very strong association
- $0.6<r<0.8$ strong association
- $0.4<r<0.6$ moderate association
- $0.2<r<0.4$ weak association
- $0<r<0.2$ very weak association

It is important to consider that this method does not indicate causality rather only measures the strength and direction of variable association.

RESULTS

Sample general characteristics: The final sample considered was composed of 70 individuals, 48 were female (68.5%) and 22 were male (31.4%). The youngest was 30 years old and the oldest 60 years old. The reported age average was 46.77±8.00. Table 1 summarizes age group distribution among both sexes. Because there were only two individuals 60 years old, they were placed in the 50-60 years old.

Anthropometric and body composition assessment: According to general obesity and overweight classification criteria (Sharma and Kushner, 2009), 64% of the sample has shown an excessive weight, from these 21% were obese. When separating men and women, 55% of the men were pre-obese and 23% were obese while in women 35% were pre-obese and 23% obese. Individuals have also shown average high waist circumference values, 63.54% of men had presented values above 94 cm and 89.59% of women had waists larger than 80 cm. Not all women with high WC values were pre-obese or obese, 30% have shown normal weight despite their increased abdominal adiposity. Bioelectrical impedance analysis has

Table 1: Sample distribution according to age groups

	Men (n = 22)		Women (n = 48)	
Age group	N	%	N	%
30-39	7	32	7	14
40-49	8	36	20	42
50-59	6	27	17	26
60-69	1	5	1	2

Table 2: Distribution of increased waist circumference and body fat mass values among the sample

	Waist circumference (a)		Body fat mass (b)	
Gender	Normal range (%)	Above (%)	Normal range (%)	Above (%)
Women	10.42	89.58	45.83	54.71
Men	36.36	63.54	13.64	86.36

Table 3: Comparison of general sample characteristics according to gender

Parameters	Men (n = 22)	Women (n = 48)
Age (years)	45.00±9	48.00±8
Body mass index (kg m^{-2})	28.00±4	27.00±4
Waist circumference (cm)	99.00±10	94.00±11
Body fat mass (%)	26.00±6	35.00±7
C-reactive protein (mg dL^{-1})	0.11±0.13	0.26±0.3
Fibrinogen (mg dL^{-1})	293.00±48	326.00±50

Values are as Mean±SD

Table 4: Comparison of the several anthropometric and biochemical parameters within the several age groups and between gender

Age group	BMI (kg m^{-2})	Waist circumference (cm)	Body fat mass (%)	CRP (mg dL^{-1})	Fibrinogen (mg dL^{-1})
Men					
30-39	27.92±4.41	96.29±12.51	24.30±8.07	0.076±8.071	225.57±24.54
40-49	28.82±3.04	101.29±7.45	27.24±5.35	0.148±0.203	294.13±50.94
50-60	27.93±4.28	98.57±10.86	25.74±2.16	0.116±0.082	330.29±32.43
Women					
30-39	29.09±6.12	95.14±11.63	35.99±11.49	0.45±0.52	339.14±83.70
40-49	25.32±3.95	92.05±10.69	32.19±5.69	0.17±0.27	320.50±65.46
50-60	27.64±3.88	95.57±12.31	36.58±6.53	0.267±0.237	338.57±46.89

Values are as Mean±SD, BMI: Body mass index, CRP: C-reactive protein

also shown high body fat mass values, 54.71% of the women were above 33% body fat mass and 86.36% of the men were above 20% body fat mass (Table 2). Table 3 presents a brief comparison of anthropometric and body composition measurements as well as CRP and Fibrinogen values between sexes. It shows clearly that the reported average values of BMI, WC and body fat mass are elevated. Body fat mass and fibrinogen differed significantly between men and women ($p<0.05$), CRP and fibrinogen were higher in women but without statistical significance ($p>0.05$). It is important to note that 13% of women were pre-obese and have shown simultaneously high WC and CRP values. Around 9% of females had high fibrinogen values together with pre-obesity and elevated WC. The same was less frequent in male individuals, only 5% of the men were overweight together with WC and CRP values.

Anthropometric measures, body fat mass, CRP and fibrinogen among age groups: Comparing anthropometric measures, body composition and biochemical parameters, some differences can be found within the several age groups like presented in Table 4. In men, BMI, WC, body fat mass and CRP are higher when they are 40 to 49 years old, while the same happens in female 30 to 39 years old. In fact, body fat mass and fibrinogen differences significantly within age groups and between sexes ($p<0.05$).

Table 5: Anthropometric parameters comparison among individuals with high CRP values in both genders

	Men		Women	
Parameters	CRP<0.3 mg dL^{-1}	CRP≥0.3 mg dL^{-1}	CRP<0.3 mg dL^{-1}	CRP≥0.3 mg dL^{-1}
Age (years)	45.32±9.36	43.00±6.27	47.49±6.97	47.85±9.16
BMI (kg m^{-2})	28.44±3.91	27.06±2.74	25.73±3.91	30.00±4.36
Waist circumference (cm)	98.84±10.62	98.00±8.72	91.09±11.23	102.00±7.82
Body fat mass (%)	25.75±5.36	26.90±8.21	32.55±6.69	40.24±5.71
CRP (mg dL^{-1})	0.07±0.05	0.49±0.10	0.09±0.09	0.67±0.28
Fibrinogen (mg dL^{-1})	290.89±44.50	309.00±74.64	314.74±49.09	355.54±41.36

Values are as Mean±SD, BMI: Body mass index, CRP: C-reactive protein

Anthropometric and body composition characterization according to CRP values: Significant statistical differences ($p<0.05$) were found between BMI, WC, body fat mass and fibrinogen when comparing individuals with and without increased CRP values. As presented in Table 5 average values suggest that men with increased CRP are pre-obese, with an average BMI of 27.06±2.74 kg m^{-2} and women are obese, the average BMI reported was 30.00±4.36 kg m^{-2}. Females had shown a higher abdominal adiposity with an average waist circumference 102.00±7.82 cm compared to 98±8.72 cm in men, higher body fat mass percentage (40.24±5.71 versus 26.90±8.21) and higher CRP values (0.67±0.28 versus 0.49±0.10). The same had happened with Fibrinogen (355.54±41.36 versus 309.00±74.64).

Association between BMI, WC, body fat and biochemical parameters: Pearson correlation analysis was conducted separately in both sexes and within the several age groups. Table 6 and 7 present correlation coefficients for men and women, respectively. Very strong associations were generally found within anthropometric and body composition variables in all age groups and both sexes. In men (Table 6), strong associations were found between BMI and CRP (0.614) as well as between WC and PCR (0.640) but only in age group 30 to 39 years old while null or negative associations were found in other age groups. In what concerns to females (Table 7) strong and very strong associations were found between CRP, BMI, WC and body fat (0.781; 0.848; 0.783). In the 40-49 age group,

Table 6: Pearson correlation coefficients comparison among the different variables in men

Age group	Variable	BMI	WC	BF	FB	CRP
30-39	BMI	1	0.978	0.974	-0.413	0.614
	WC	0.978	1	0.932	-0.442	0.640
	BF	0.974	0.932	1	-0.367	0.482
	FB	-0.413	-0.442	-0.367	1	0.482
	CRP	0.614	0.640	0.482	-0.564	1
40-49	BMI	1	0.914	0.715	-0.078	0.060
	WC	0.914	1	0.683	-0.015	0.319
	BF	0.715	0.683	1	0.101	0.481
	FB	0.060	0.319	0.101	1	0.360
	CRP	-0.078	-0.015	0.481	0.386	1
50-59	BMI	1	0.989	0.929	0.073	-0.143
	WC	0.989	1	0.918	0.024	-0.168
	BF	0.929	0.918	1	0.114	0.011
	FB	0.073	0.024	0.114	1	0.010
	CRP	-0.143	-0.168	0.011	0.010	1

BMI: Body mass index, WC: Waist circumference, BF: Body fat, CRP: C-reactive protein, FB: Fibrinogen

Table 7: Pearson correlation coefficients comparison among the different variables in women

Age group	Variable	BMI	WC	BF	FB	CRP
30-39	BMI	1	0.885	0.960	0.834	0.781
	WC	0.885	1	0.898	0.725	0.848
	BF	0.960	0.898	1	0.839	0.783
	FB	0.834	0.725	0.839	1	0.669
	CRP	0.781	0.848	0.783	0.669	1
40-49	BMI	1	0.838	0.740	0.286	0.656
	WC	0.838	1	0.879	0.454	0.627
	BF	0.740	0.879	1	0.257	0.483
	FB	0.286	0.454	0.257	1	0.617
	CRP	0.656	0.627	0.483	0.617	1
50-60	BMI	1	0.933	0.838	0.456	0.173
	WC	0.933	1	0.854	0.425	0.196
	BF	0.838	0.854	1	0.465	0.373
	FB	0.173	0.196	0.373	1	0.047
	CRP	0.456	0.425	0.465	0.047	1

BMI: Body mass index, WC: Waist circumference, BF: Body fat, CRP: C-reactive protein, FB: Fibrinogen

strong associations were also found for CRP, BMI and WC (0.656 and 0.627). Body fat mass was moderately associated with CRP (0.483). Only moderate associations were also found in the oldest age group. No significant associations were found between fibrinogen, anthropometric and body composition variables in men (Table 6) but the same did not happened in women (Table 7). In age group 30-39 years very strong associations were found between BMI, body fat and fibrinogen (0.834 and 0.839) while between WC and fibrinogen (0.725) the association was only moderate.

DISCUSSION

The present study has found some significant associations between adiposity, especially abdominal adiposity, overweight and inflammatory acute phase proteins like CRP and Fibrinogen. Overweight was particularly frequent as well as high WC values which indicate increased abdominal adiposity, this was especially concerning in female subjects. These results have revealed a quite considerable high cardiovascular disease risk in the most productive age groups (30-39 years).Women had shown higher CRP values which are in accordance with previous studies (Visser *et al*., 1999; Snodgrass *et al*., 2007; Khera *et al*., 2009). The Pearson correlation analysis indicated high correlation coefficients between BMI, WC and CRP, these results are in accordance with data reported by Khera *et al*. (2009). In KORA study (Thorand *et al*., 2006) women had higher IL-6 values which may suggest that adipose tissue has higher metabolic active in women. It is important to note that IL-6 promotes liver CRP production (Moshage *et al*., 1988; Mohammed-Ali *et al*., 1997). Additionally, WC was higher in females and higher values of this anthropometric measurement has been associated with cardiovascular risk. Abdominal adiposity is associated with a unfavourable metabolic profile: insulin resistance, dyslipidemia and systemic inflammation which may account for higher cardiovascular risk (Berg and Scherer, 2005; Calle and Kaaks, 2004; Snijder *et al*., 2006; Mahajan *et al*., 2010) and it could also affect the severity of other diseases like asthma (Morsi, 2009). Dyslipidemia and obesity, especially with abdominal increased adiposity in women has also been considered relevant breast cancer risk factors (Owiredu *et al*., 2009; Barnett *et al*., 2002). These results also revealed a very strong association between WC and CRP, even stronger than the reported for BMI and CRP. BMI had been considered for years one important adiposity measure but it is essentially only associated with increased weight (Aslam *et al*., 2010). Its association with cardiovascular risk is higher when considering other measurements like WC (Lee *et al*., 2008) that can be increased even in normal weight individuals. Body fat mass was also strongly associated with CRP in women aged 30 to 39 years old and only moderate in the other age groups. Higher body fat values could also be associated with increased inflammation (Koster *et al*., 2010). Fibrinogen did not revealed so significant associations with anthropometric and body composition variables. In female from the first age stage, very strong associations were found between Fibrinogen with BMI and body fat and a strong association was reported between fibrinogen and WC. Several studies confirmed this controversy. Tousoulis *et al*. (2011) concluded that Fibrinogen has only a marginal effect as cardiovascular risk factor itself despite others suggesting that it is an important predictor for these diseases (Berg and Scherer, 2005; Festa *et al*., 2001; Heinrich *et al*., 1994; Peverill *et al*., 2007). Some controversies remain about the role of fibrinogen as cardiovascular risk factor. In the present study in spite of there were not reported increased fibrinogen values, there were some strong correlations between this biochemical marker and other cardiovascular risk factors like obesity, abdominal adiposity and body fat mass in female subjects.

CONCLUSIONS

The present study revealed higher associations between acute phase inflammatory proteins like CRP and increased abdominal adiposity, overweight and obesity which all had been considered important cardiovascular risk factors. This was especially concerning in women, especially because it is affecting one potentially very productive age group (30-39 years). Obesity itself is an important risk factor, as well as overweight, due to metabolic consequences of exacerbated adiposity. This study adds up the possible effect of this adiposity in inflammatory markers that had also been recognized as cardiovascular risk factors, especially CRP and Fibrinogen. These results reinforce the importance of monitoring not only CRP and Fibrinogen values in obese and pre-obese individuals but also simple anthropometric measurements like WC even in pre-obese that have itself an increased cardiovascular risk. This study had suffered logistic limitations which shortened the sample size, considering the results obtained. Further studies could be specifically centred in female individuals and analyze added biochemical markers that could also be considered cardiovascular and metabolic risk factors like insulinemia and glycaemia.

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