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Obesity and Body Fat Distribution as Coronary Risk Factors and Supply of Proinflammatory Cytokines

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The role of obesity on coronary heart disease risk is not fully understood; some studies have found linear associations while others have reported J- or U-shaped associations or even no significant effects, which could be related to the use of different measures of obesity. The amount and type of body fat distribution (frequently assessed by waist circumference or waist-to-hip ratio) were found to be better predictors of cardiovascular morbidity and mortality than total body weight and overall obesity, often measured by body mass index. Visceral and subcutaneous fat (both included when waist circumference is measured) have been frequently associated to metabolic complications, but only a few studies have addressed the cardiovascular role of peripheral fat mass (fat located in upper and lower limbs), which might be less atherogenic than abdominal fat, due to a low fatty acid turn-over and a differential hormone production. Moreover, a gender-effect may be present, but further research is needed to confirm it. The same associations reported with cardiovascular risk have been found with low-grade chronic inflammation. Adipose tissue is a known source of pro-inflammatory cytokines, and measures of central obesity seem to be stronger and more consistent predictors of inflammation than overall obesity.
From this review, further metabolic studies to clarify how sex hormones may modulate the way in which fat is accumulated and stored and how it could influence the production of adipokines are warranted. Also, longitudinal research is needed to confirm the potential sex effect on the relation of peripheral fat with coronary risk (protective in women and adverse in men).
Key-words: obesity; body fat distribution; inflammation; cytokines; coronary heart disease

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Compelling evidence supports that obesity is related to a higher risk of coronary heart disease (CHD), type 2 diabetes and certain cancers, and to a shorter life expectancy (1-4), which attributes to this entity a considerable public heath interest. Furthermore, obesity is considered one of the leading global risks for worldwide CHD mortality (5).

The role of obesity on CHD risk is not completely understood. Different magnitude and associations' shape between obesity and CHD have been described; some studies have found linear associations while others have reported J- or U-shaped associations or even no significant effects (6-8), which could be related to the use of different measures of obesity.

Several studies have suggested that the amount and type of body fat distribution seem to be more important to cardiovascular risk than overall obesity *per se*, often assessed by body mass index (BMI). Under this context, waist circumference (WC) and waist-to-hip ratio (WHR) were found to be better predictors of cardiovascular morbidity and mortality than total body weight and BMI (7, 9-12). This could be because a higher BMI may reflect increased fatness, but also higher musculoskeletal mass; moreover BMI is not a good measure of visceral fat, considered as the key determinant of metabolic abnormalities (13-14). In fact, epidemiological studies have suggested that abdominal fat distribution is a significant predictor for CHD, independently of BMI (7,9-10,12).

According to the model proposed by Deprés and colleagues (15), individuals who have elevated abdominal fat are really divided into two subgroups: a visceral fat group and a subcutaneous trunk fat group, both of which can independently increase the CHD risk. Research has been suggested that the adipose tissue accumulated in the visceral region (intra-abdominal fat) seems to be associated to more metabolic complications or a more deleterious risk profile than that accumulated subcutaneously (13,15-19).

WC, reflecting both visceral and subcutaneous fat, has been extensively used to identify individuals at increased risk for obesity-associated risk factors, due to its well-documented positive association with cardiovascular diseases (4,14,20-22). At the same time, WHR is attracting growing interest, due to the favorable role recently

attributed to peripheral fat (fat located in upper and lower limbs) in the modulation of cardiovascular risk (12,23-24). Therefore, in a recent review (24) the need for capturing the separate effects of abdominal and peripheral adiposity was highlighted, and the authors suggested that WHR is a simple and inexpensive measure which could improve the assessment of the CHD risk.

Data on the specific role of peripheral fat mass on coronary risk are scant. A few studies have suggested that fat accumulated in peripheral depots, such as arms and legs, has less adverse metabolic effects on cardiovascular risk than other types of fat store (18,25-30). Tankó and colleagues showed that, in postmenopausal women, peripheral fat measured by dual-energy x-ray absorptiometry had a favorable long-term effect on systolic blood pressure, serum triglycerides and white blood cells, and was inversely associated with aortic calcification, a direct measure of atherosclerosis (25-26). In another study, measuring peripheral fat with the same method, the authors concluded that some degree of protection is conferred by this type of fat accumulation, which was inversely (*i.e.* favorably) associated with stiffness of the brachial and the carotido-femoral segment (29). Particularly in men, direct associations of peripheral fat with lipoprotein concentrations, blood pressure and insulin levels (31-32) have been reported. In a population-based case-control study conducted in the Portuguese population (33), a peripheral subcutaneous fat index (upper members) predicted a lower risk of acute myocardial infarction in women, but a higher risk in men. Further research should confirm this sex difference in the effect of peripheral fat on coronary risk.

Although the mechanisms underlying the development of obesity and its comorbidities are not well established, it has been recognized that these clusters of disorders are associated to chronic mild inflammation, in which the metabolism of fat tissue plays an important role (34-39). Adipose tissue secretes a multiplicity of factors, commonly named adipokines with different protein structures and functions, such as cytokines or related-proteins [leptin, tumor necrosis factor-α (TNF-α), intelukine-6 (IL-6)], chemoattractant proteins (monocyte chemotactic protein-1), proteins of the complement system (adipsin), proteins involved in the regulation of blood pressure, vascular haemostasis or angiogenesis (angiotensinogen, plasminogen activator inhibitor-1, vascular endothelial growth factor) and molecules involved in the glucose and lipid metabolisms (adiponectin, resistin, visfatin) (39).

The role of adipose tissue in the development of local or systemic inflammation is demanded by its heterogeneity at the cellular level. The cell content of white adipose tissue – the one considered as a major endocrine organ, with an important role in the regulation of energy intake and metabolism - is extremely heterogeneous: mature adipocytes represent no more than half of the total cell content; the remaining cell components are pre-adipocytes, fibroblast, endothelial cells and macrophages (40). During adipose tissue growth, there is an increase in the size and number of mature adipocytes differentiated from progenitor cells (*e.g.* preadipocytes). During this fat mass expansion, macrophages from peripheral blood seem to infiltrate within adipose tissue (40-41). The molecular mechanisms responsible for it are not yet completely understood; it seems that some adipokynes such as monocyte chemotactic protein-1 and leptin can favour the diapedesis of macrophages from circulation to adipose tissue (42). Infiltrated macrophages in the adipose tissue seem to be responsible for almost the total amount of TNF-α and a significant part of IL-6 produced (40).

There is evidence that adipocytes have distinct intrinsic characteristics (*e.g.* fatty acid-binding proteins and enzymes of fat metabolism), which contribute to the heterogeneity in free fatty acids handling by the different fat depots (43). It has been suggested that visceral adipocytes have higher lipolytic activity, which leads to an overexposure of the liver to free fatty acids, resulting in insulin resistance and hyperinsulinaemia. Moreover, omental adipose tissue, which is a subfraction of visceral adipose tissue, secretes more IL-6 than subcutaneous adipose tissue (44).

On the other hand, peripheral adipose tissue seems to have a high lipoprotein lipase activity and a low fatty acid turnover; it takes up, more frequently, free fatty acids from circulation and stores them, protecting the liver from high free fatty acids exposure (45). Peripheral adipose tissue seems also to secrete higher quantities of adiponectin (46). Adiponectin may affect insulin sensitivity by acting on muscle fatty acid oxidation and hormone-sensitivity lipase. Also, by stimulating nitric oxide production and the reduction in the expression of adhesion molecules in endothelial cells, adiponectin could be responsible for some anti-hypertensive and anti-atherogenic effects (47).

A higher release of free fatty acids and glycerol from adipocytes has been described in obese than in lean individuals, probably promoting insulin resistance and type 2 diabetes through the blocking of the insulin signal transduction (48). Moreover, several procoagulant proteins such as plasminogen activator inhibitor type 1 and tissue factor show higher expression in adipose tissue of obese in comparison to lean individuals (49). This over-expression could explain, at some extent, the high atherogenic risk associated with obesity.

An improvement in the circulating proinflammatory profile appears to be attained with weight loss (50). Although knowledge on the interplay of inflammation with obesity is not fully understood, the available evidence suggests that dietary interventions will become a major element of future approaches to prevent and treat obesity, its related metabolic complications, the metabolic syndrome and, at last, cardiovascular diseases (39).

Similarly to what happens with CHD risk, measures of central obesity seem to be stronger and more consistent predictors of inflammation than general obesity (51-53). Panagiotakos, et al. (51) have found that subjects with central fat, compared to participants with normal body fat distribution, exhibited 53% significantly higher high-sensitivity C-reactive protein (hs-CRP) levels, 30% higher TNF-*α* levels, 17% higher white blood cell count and

42% higher IL-6 levels. The authors also concluded that the models that included WC or WHR as independent variables had higher explanatory ability than the models that included BMI. Also, in a large triethnic population of the Insulin Resistance Atherosclerosis Study (52), WC significantly explained 14.5% of the variability of circulating hs-CRP levels and BMI only 0.4%.

Although the consistence of the results described, it has been claimed that is relatively difficult to differentiate between the effect of abdominal obesity and total body fat due to the high correlation between measures of obesity, which could constitute a limitation of this type of studies. To overcome this, the use of principal component analysis to create uncorrelated components of body fat could be a useful approach to assess the independent effect of fat depots on health outcomes. Previous studies conducted by our research group (33,54) identified two patterns based on the same classical anthropometric measures - BMI and WC, by principal component analysis, showing that they are not independent from each other and can aggregate in different ways. While the general pattern of body fat distribution showed a high correlation with BMI and WC, the central pattern was characterized by high WC, but low BMI, supporting that it is relatively difficult to distinguish between the effects of abdominal and total body fat using simple anthropometric measures.

Overall, there is an increasing understanding of the metabolic effects of abdominal fat, both visceral and subcutaneous (51-53,55), but much less information is available on the relative contribution of peripheral fat to inflammation (25,51). As previously described, a study in postmenopausal women showed that peripheral fat was indirectly associated with white blood cells (25). Panagiotakos and colleagues (51) correlated hip circumference with levels of CRP, IL-6, TNF-α and white blood cells. In a previous study in the Portuguese population (54), a high proportion of peripheral subcutaneous fat (upper members), measured by a skinfold composite index, seems to be inversely associated with hs-CRP, but only in women.

Gender-related differences seem to be a major gap under this field. Some studies have described stronger associations between measures of obesity and inflammatory markers in women than in men (56-57). The observed sex differences might be related to different ranges of variation in levels of body fat (men have a larger proportion of visceral fat, while women have higher levels and variability of total and subcutaneous peripheral fat) (58-60), and to regional differences in secretion of cytokines and adiponectin by the different fat depots (44,46,61). Furthermore, sex hormones and the use of oral contraceptives and hormone replacement therapy could influence the inflammatory marker levels in women (62-64).

Further metabolic studies to clarify how sex hormones may modulate the way in which fat is accumulated and stored and how it could influence the production of adipokines are warranted (65). Also, longitudinal research is needed to confirm this potential sex effect on the relation of peripheral fat with coronary risk (protective in women and adverse in men).

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