THE INFLAMMATORY PROFILE ASSOCIATED WITH ABDOMINAL OBESITY

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Over the last 20 years, the study of adipose tissue distribution with imaging techniques has contributed to improve our understanding of the link between obesity and the development of metabolic complications. It is now well recognized that abdominal obesity is the most prevalent form of the metabolic syndrome which is associated with a cluster of atherogenic metabolic abnormalities including an inflammatory profile. In this regard, the adipose tissue is much more than an organ specialized in the mobilization of energy stored in the form of triglycerides, it is also an endocrine organ which secretes a wide variety of bioactive substances called adipokines such as inflammatory markers (adipocytokines). Recently it has been suggested that there is an overexpression of proinflammatory markers by the adipose tissue in the context of obesity which is explained by macrophage infiltration [1]. The dysregulation of adipocytokine production and secretion in the context of abdominal obesity could be the link with the development of metabolic and cardiovascular disease (Figure 1). More and more studies suggest that inflammatory markers such as tumour necrosis factor (TNF)-α and interleukin (IL)-6 may play a role in the development of metabolic complications associated with obesity such as insulin resistance. It has been proposed that TNF-α acts locally at the site of adipose tissue through autocrine/paracrine mechanisms having effects on insulin resistance and inducing IL-6, whereas IL-6 rather appears to be released systemically by the adipose tissue acting more as an endocrine signal that induces the hepatic acute-phase response or insulin resistance in the liver [2]. Although it is still debated how adipose TNF-α and IL-6 expression may cause insulin resistance, both have been demonstrated to interfere with insulin signalling in adipose tissue and in the liver [3, 4]. Moreover, TNF-α [5] as well as IL-6 [6] are also known to promote lipolysis and

Key Points
As our knowledge of inflammatory mechanisms in adipose tissue has increased, a number of key points have emerged:
- The overexpression of proinflammatory molecules generated by an expanding adipose tissue are produced mainly by infiltrated macrophages;
- Abdominal adiposity, particularly intra-abdominal (visceral) adipose tissue, is the obesity phenotype associated with the increased expression and circulating levels of several adipocytokines;
- The regional distribution of body fat appears to explain the age-related variation as well as the sex differences observed in plasma CRP concentrations.
secretion of free fatty acids (FFA) from adipose tissue into the circulation, a phenomenon which contributes to insulin resistance in the skeletal muscle and to an increase in hepatic glucose production (Figure 2).

Given the well-known metabolic complications associated with intra-abdominal (visceral) adiposity, we found that even though IL-6 and TNF-α were significantly correlated with total adiposity indices such as body mass index and fat mass, circulating IL-6 levels were mostly associated with intra-abdominal adiposity compared to TNF-α levels which appeared to be more related to total adiposity [7]. Moreover, we observed an independent contribution of circulating IL-6 and TNF-α concentrations to the variation in insulin resistance. There is no question concerning the increase of adipose tissue TNF-α expression in human obesity. However, controversies remain regarding circulating levels of TNF-α and it is suggested that circulating TNF-α is a rather poor indicator of its autocrine and paracrine action. Two cell-surface TNF-α receptors have been described in humans: TNF-α receptors 1 [TNFR1 (p60)] and 2 [TNFR2 (p80)] [8, 9]. Soluble forms of both receptors (sTNFR1 and sTNFR2) are present in the circulation. These sTNFRs can compete for TNF-α with the cell surface receptors and thus block its activity or in contrast affect TNF-α function by stabilizing its activity [10]. Since plasma TNF-α values are usually low and do not give precise information about its action in obesity and as sTNFR2 is a much more stable protein, it was therefore proposed that sTNFR2 might serve as a better predictor of local TNF-α system activation and as a diagnostic marker for obese individuals with TNF-related insulin resistance [11]. It has been reported that both TNFR1 and TNFR2 are expressed in human adipose tissue. As levels of soluble TNFR2 in the systemic circulation correlate positively with obesity [11], it has been suggested that TNFR2 could play a role in the induction of insulin resistance [12, 13]. In this regard, we have found that circulating sTNFR2 levels are more closely related to abdominal adipose tissue accumulation.

Figure 1: The inflammatory profile associated with abdominal obesity could be the link with the development of metabolic and cardiovascular disease.
rather than total adiposity in men [14]. Moreover, sTNFR2 also appeared to be a stronger independent marker of insulin resistance than TNF-α even after controlling for intra-abdominal adipose tissue.

Among the wide varieties of cytokines produced by the adipose tissue, a more recent and less studied adipocytokine caught our attention, the anti-inflammatory cytokine IL-1 receptor antagonist (IL-1Ra). IL-1Ra is a natural antagonist to the proinflammatory cytokine IL-1 and acts by binding to IL-1 receptors without inducing a cellular response [15]. It has been recently reported that plasma IL-1Ra levels are elevated in human obesity and reduced after bariatric surgery [16]. Human adipose tissue also appears to be a major source of plasma IL-1Ra and its expression in this tissue is markedly increased in obesity [17]. Moreover, plasma IL-1Ra levels are also strongly correlated with insulin resistance [16]. We therefore explored the association between plasma levels of IL-1Ra and abdominal adipose tissue depots measured by computed tomography. Our study revealed that circulating IL-1Ra concentrations were influenced to a greater extent by intra-abdominal than subcutaneous adiposity [18]. We also found that plasma IL-1Ra levels increased with the number of metabolic abnormalities. Furthermore, we found an association between IL-1Ra levels and several cardiometabolic risk variables which appeared to be partly independent from the variation in intra-abdominal adiposity.

These adipocytokines, in particular IL-6, are part of the inflammatory cascade which leads to the induction of the acute-phase protein C-reactive protein (CRP) by the liver. Since CRP has been extensively studied to predict the risk of cardiovascular disease in healthy individuals as well as in patients for primary or secondary prevention, we have investigated the impact of two important factors such as age and sex to the variation of CRP concentrations in the context of abdominal obesity. CRP has been shown to independently predict cardiovascular events in both men and women [19, 20].

![Figure 2: Different pathways through which adipokines generated by an expanding adipose tissue can contribute to the development of the metabolic complications associated with abdominal obesity such as insulin resistance and atherogenic dyslipidemia.](image.png)
However, CRP concentrations have been found to be higher in pre-menopausal women compared to men, presumably because of the increasing effect of estrogens on CRP levels [21]. This difference in CRP levels between women and men may appear at first glance as a contradictory observation as pre-menopausal women are generally at lower cardiovascular disease risk than men. Since body fat distribution is very different between men and pre-menopausal women, we investigated the contribution of intra-abdominal adipose tissue to the gender difference in inflammatory markers. We found that CRP concentrations were largely influenced by intra-abdominal adiposity in men, whereas subcutaneous adiposity was the key correlate of CRP in women [22]. Therefore, the CRP levels observed in women are probably not associated to the same degree of risk when compared to similar levels in men. Sex-specific cut-off levels of CRP should be determined to properly evaluate the gender difference in cardiovascular disease risk. Increases in circulating CRP, IL-6 and TNF-α have been demonstrated in apparently healthy older individuals. One proposed mechanism is the reduced influence of the normally inhibiting sex steroids on endogenous IL-6 and TNF-α expression. Moreover, ageing is associated with changes in body composition reflected by increased abdominal adipose tissue accumulation. Our work provided further evidence that the age-related variation in circulating CRP and IL-6 levels were partly explained by changes in adiposity, more specifically differences in intra-abdominal adiposity [23].

These findings highlight the important contribution of intra-abdominal adipose tissue to the variation in circulating adipocytokine levels. Further studies are needed to understand the triggers that initiate inflammation in adipose tissue and the role of each adipokine in the pathogenesis of insulin resistance.

References


