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## Editorial

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In this issue of the CMReJOURNAL, two pioneers who have both made landmark contributions to the areas of diabetology and cardiology address two clinically important questions. First, Dr. Wilfred Fujimoto, from the University of Washington, reviews the key findings of a series of important studies conducted by his group which led them to conclude that body fat topography, especially intra-abdominal (visceral) adipose tissue accumulation, was a crucial factor associated with insulin resistance and the risk of developing type 2 diabetes in Japanese Americans [1-3]. Because his research group was among the first teams to show that intra-abdominal adiposity measured by an imaging technique, computed tomography, was a key form of overweight/obesity associated with the risk of type 2 diabetes, Dr. Fujimoto received the Jean Vague/Per Björntorp award recognizing him as one of the early pioneers of the study of regional adipose tissue distribution. Through a series of elegant studies, Dr. Fujimoto and his team have shown why there was a higher prevalence of type 2 diabetes in Japanese individuals living in Seattle than in Tokyo [4]. From astute interpretation of early results, Dr. Fujimoto was able to nicely show that intra-abdominal, but not subcutaneous adiposity, was a key predictor of insulin resistance and of the risk of developing type 2 diabetes [2, 3]. Thus, Dr. Fujimoto was truly a pioneer of the intra-abdominal adiposity concept and results of the studies conducted by his group have confirmed that the clinical observations of Vague reported in the mid-forties and the work of Björntorp published in the early eighties were important and that their theory was valid.

Since then, many groups around the world have followed the path of these investigators. Although the issue of a causal relationship between visceral adiposity and metabolic abnormalities remains uncertain and under debate, it has become clear that excess intra-abdominal adiposity is at least an excellent marker of ectopic fat deposition (including excess liver fat) and of related cardiometabolic abnormalities [5]. In addition, Dr. Fujimoto’s group has also performed intervention studies to show that the intra-abdominal adipose depot can be readily mobilized with a lifestyle modification program despite moderate weight loss [6, 7], another concept which is also supported by other lifestyle intervention studies [8-10].
In the second paper of the Journal, one of the executive board members of the International Chair on Cardiometabolic Risk, Prof. Peter Libby, an academic cardiologist from Harvard University with an international recognition, briefly discusses the importance of inflammation in cardiovascular disease (CVD) and his early work on inflammation affecting processes modulating atherosclerotic plaque stability. Dr. Libby has been extremely active in this area and has published numerous seminal research observations as well as highly cited “classical” review papers on the topic in the very best medical and scientific journals [11-14]. He has pioneered the notion that a state of chronic inflammation may eventually lead to the development of an inflammatory milieu contributing to an increased degradation rate of the atherosclerotic plaque collagen matrix, making it more prone to rupture and to have a thrombotic event. Dr. Libby also makes the point that although it is clear that atherosclerosis/CVD has an inflammatory component, the triggers of this inflammatory process are not completely understood. However, with our current affluent lifestyle characterized by the overconsumption of highly processed foods of high energy density and our sedentary behaviour, Dr. Libby makes the point that there is an emerging new cause of chronic inflammation which needs to be dealt with: obesity, particularly abdominal obesity [11].

In that context, he therefore proposes that an exciting development in our understanding of factors contributing to chronic inflammatory states is the new role of adipose tissue which is now recognized to be much more than an organ solely specialized in triglyceride storage/mobilization. Indeed, available evidence clearly shows that adipose tissue, particularly the intra-abdominal adipose depot, is “inflamed” when expanded in excess, becoming an important source of production of inflammatory cytokines, referred to as adipokines [11]. Dr. Libby reviews interesting work from his group [15] and cites additional evidence [16-18] that there is an adaptive immune response in the expanded adipose tissue. Because of the number of possible mediators and of the complex cross-talk between some of these adipokines and other proinflammatory mediators, this topic will remain a very fertile area of investigation for years to come. Meanwhile, history will show that Prof. Libby clearly documented the link between inflammation and atherothrombosis and foresaw the important mediating role of obesity, particularly of intra-abdominal obesity, as a key driver of this inflammation-mediated atherothrombosis.

Finally, the last paper of the CMReJournal was produced by a young scientist, Dr. Amélie Cartier, who has explored the interactions between adipose tissue mass and distribution and some markers of inflammation which have been linked to excess total/intra-abdominal adiposity. Dr. Cartier also emphasizes the notion that the proinflammatory molecules produced by the hypertrophied adipose tissue are largely, but not entirely produced by infiltrated macrophages. She explores the differential relationships between adiposity/body fat distribution and two key inflammatory cytokines, tumour necrosis factor (TNF)-α and interleukin (IL)-6 [19]. Furthermore, she presents evidence that two other markers of adipokine production/levels, namely soluble TNF receptor type 2 (sTNFR2) and IL-1 receptor antagonist (IL-1Ra) could be relevant to consider when exploring the cardiometabolic consequences of excess abdominal fat deposition [20, 21]. Finally, she also deals with an understudied question: the gender difference in plasma C-reactive protein (CRP) concentrations, showing that the
higher levels observed in women than men are largely explained by the fact that women have more subcutaneous fat than men [22]. Therefore, although relative coronary heart disease risk is increased to essentially the same extent as a function of increasing CRP levels in both men and women, the absolute risk related to a given CRP concentration is likely to be lower in women than in men. Indeed, the increased CRP levels in women than in men are explained by their increased subcutaneous adiposity which is less detrimental to cardiometabolic risk than excess intra-abdominal adiposity [23, 24].

The area of regional adipose tissue distribution has been neglected by the obesity community for decades. Due to the work of pioneers like Jean Vague, Per Björntorp, Wil Fujimoto and others and because of the mounting evidence that body fat distribution is also related to inflammation and CVD, abdominal obesity is now an important issue not only for the field of obesity but also for diabetology and cardiology, making this topic an excellent substrate for cross-fertilisation between the two disciplines.

References
Key Points
The Seattle Japanese American Community Diabetes Study showed in Japanese Americans:
- A high prevalence of diabetes;
- Intra-abdominal (visceral) adiposity to be a key risk factor in obesity-related diseases;
- Lifestyle (diet and physical activity) could favourably affect intra-abdominal adiposity and risk for diabetes (and other obesity-related diseases);
- Lifestyle modification may be able to prevent diabetes (and other obesity-related diseases?).

To receive the Per Björntorp/Jean Vague Lecture Award is a tremendous honour and to present the lecture on behalf of my colleagues in Seattle is a great privilege. What I will do is describe the history behind our research, how the writings of both Per Björntorp and Jean Vague as well as others influenced the direction of our research, and some of our key findings regarding intra-abdominal (visceral) adiposity and obesity-related diseases.

The Seattle Japanese American Community Diabetes Study enrolled the first participant in 1983 and ended in 2001 when I left the University of Washington for retirement in Kailua Kona, Hawaii. A total of 658 men and women were studied over a 10-year follow-up interval with 75.5% of participants returning for follow-up. Among the results of this study was the finding that intra-abdominal adiposity plays a crucial role in the etiopathogenesis of obesity-related diseases.

In 1971, at the annual meeting of the American Diabetes Association in San Francisco a Japanese diabetologist said to me: “Diabetes rates are quite low in Japan when compared to your country. There are many Japanese people who were born and grew up in the United States. How do these Japanese Americans compare to our Japanese?” At that time I was about to complete a fellowship in endocrinology at the University of Washington. My research was conducted entirely at the lab bench, using cultures of islet cells, fibroblasts, and later on, adipose cells to examine islet hormone production and insulin action. I had funding for this research from the National Institutes of Health and the
American Diabetes Association and had no reason to change the direction of my career except that I kept thinking about this earlier conversation. In 1977, I went to Index Medicus (there was no PubMed at that time) and came across a paper authored by Sloan [1] and published in JAMA in 1963. Sloan reported diabetes rates to be almost 3-fold higher in Japanese than in Caucasians living on the island of Oahu in Hawaii. This difference was very striking and unexpected based upon reports of low diabetes rates in Japan. This piqued my interest in the etiology and pathogenesis of type 2 diabetes in Japanese Americans and in retrospect probably marked the turning point in the direction of my academic career.

I had no prior experience in the field of clinical epidemiology. But I was keenly interested in learning more about diabetes in Japanese Americans. In order to obtain research funding to follow through on this interest, I had to demonstrate both the capability of leading a clinical epidemiologic study and of obtaining some preliminary data. To accomplish this, we obtained funding for a pilot study from both the American Diabetes Association and the Kroc Foundation as well as funding from the Japan Society for the Promotion of Science to support a sabbatical at the University of Tokyo. We conducted the pilot study from 1978 to 1980 and I was on sabbatical from 1979 to 1980. By comparing diabetic Japanese men in Tokyo and Seattle and diabetic Caucasian men in Seattle, we found that Japanese Americans were fatter than native Japanese but leaner than Caucasians, Japanese Americans and Japanese consumed similar amounts of food and less than Caucasians but Japanese Americans took in more total fat and less carbohydrates than Japanese, and Japanese Americans consumed as much fat percentage as Caucasians [2, 3]. These observations raised several questions, including: 1) Is there anything else besides body size that is important? 2) How do diabetes rates in Japanese Americans compare to rates in Japanese? 3) How is lifestyle related to the etiopathogenesis of type 2 diabetes?

Although it seemed that “fatness” was important, we wondered whether there might be something else that was important. It was while we were preparing our National Institutes of Health grant application that we became aware of several key papers that greatly influenced us: Vague’s publication [4] in the American Journal of Clinical Nutrition in 1956, “The Degree of Masculine Differentiation of Obesities” in which he described the characteristics of gynoid and android obesity; another by Kissebah et al. [5] in the Journal of Clinical Endocrinology and Metabolism in 1982, “Relation of Body Fat Distribution to Metabolic Complications of Obesity”; and a third by Krotkiewski et al. [6] (including Björntorp) in Journal of Clinical Investigation in 1983, “Impact of Obesity on Metabolism in Men and Women”. In addition, we also became aware of the application of computed tomography (CT) to assess intra-abdominal body fat from a report by Borkan et al. [7] presented initially at a scientific meeting and subsequently published in the American Journal of Clinical Nutrition in 1982, “Assessment of Abdominal Fat Content by Computed Tomography”. This was followed in 1983 by a paper by Tokunaga et al. [8] from Japan in the International Journal of Obesity, “A Novel Technique for the Determination of Body Fat by Computed Tomography”. Based on all of these reports, we used both anthropometry and CT to assess body fat distribution in our Japanese-American participants.
When we performed an oral glucose tolerance test in diabetic men in Tokyo and Seattle, men in Seattle had much higher plasma insulin levels than Tokyo men despite similar glucose levels, suggesting that Seattle men were more insulin resistant [9]. After adjusting for the higher body mass index (BMI) in Seattle, fasting insulin remained significantly greater in Seattle. Although body fat distribution was not assessed in Tokyo, it became quickly apparent in Seattle that diabetic men tended to have higher amounts of intra-abdominal fat than normal men (Figure 1). This was subsequently confirmed in Japanese-American women as well and validated the importance of this measurement in this population.

Over the course of the 10-year follow-up of our study participants, we examined the incidence of obesity-related diseases and found that intra-abdominal adiposity was an independent precursor to coronary heart disease, hypertension, diabetes, impaired glucose tolerance, and metabolic syndrome whereas other measurements of body size and shape (e.g., BMI, total CT fat area, subcutaneous fat area, waist circumference) did not independently predict these diseases when intra-abdominal fat area was in the analysis [10-15]. All of these have also been reported to be associated with insulin resistance. We therefore asked: “Does intra-abdominal adiposity predict insulin resistance?” Shown in the Table are results from a model that included both intra-abdominal fat and abdominal subcutaneous fat in predicting future insulin resistance. Other models substituting total subcutaneous fat area, total fat area, BMI, and waist circumference also showed that intra-abdominal fat was an independent predictor of insulin resistance [16].

![Figure 1: Distribution of intra-abdominal fat area: normal and diabetic Japanese-American men](image-url)
We identified a “diabetogenic” lifestyle in Japanese Americans, one that included a diet high in saturated fat content (and lower in carbohydrates) and lower physical activity (lower energy expenditure). This lifestyle was related to greater plasma glucose levels [17]. Moreover, change in intra-abdominal fat appeared to be directly correlated with the amount of daily saturated fat intake. We therefore designed a small randomized clinical trial to examine this further.

Japanese Americans with impaired glucose tolerance were randomized in two groups: 1) a treatment group that was given instruction in aerobic exercise and a diet with saturated fat reduced to 7% of total calories; 2) a comparison group that was given instruction in stretching exercise and a diet with saturated fat reduced to 10% of total calories. Both groups were followed for 24 months, closely for the first 6 months, less closely for the next 6 months, and even less closely for the final 12 months. The treatment group showed significant reduction in BMI (although weight loss was not a goal) and improvement in body fat distribution, glucose levels, and insulin sensitivity, but there was no effect upon β-cell function (Figure 2) [18, 19]. Thus, lifestyle modification may be an effective approach to preventing or delaying type 2 diabetes in at-risk Japanese Americans.

Table: Multivariate model showing intra-abdominal fat to be an independent predictor of future insulin resistance

<table>
<thead>
<tr>
<th>Independent variables (baseline)</th>
<th>Logₑ (HOMA-IR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-abdominal fat area</td>
<td>0.0631</td>
</tr>
<tr>
<td>Abdominal subcutaneous fat area</td>
<td>-0.0003</td>
</tr>
<tr>
<td>HOMA-IR *</td>
<td>0.1327</td>
</tr>
<tr>
<td>Incremental insulin response</td>
<td>0.0003</td>
</tr>
<tr>
<td>2-hour plasma glucose</td>
<td>0.0002</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0033</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.0692</td>
</tr>
</tbody>
</table>

Model R²: 0.362

* Similar findings when fasting insulin was substituted for homeostasis model assessment of insulin resistance (HOMA-IR)
In summary, the Seattle Japanese American Community Diabetes Study showed in Japanese Americans:

- A high prevalence of diabetes;
- Intra-abdominal adiposity to be a key risk factor in obesity-related diseases;
- Lifestyle (diet and physical activity) could favourably affect intra-abdominal adiposity and risk for diabetes (and other obesity-related diseases);
- Lifestyle modification may be able to prevent diabetes (and other obesity-related diseases).

References


Abundant evidence supports the fundamental contribution of inflammation to the genesis of atherosclerosis and its complications. We recognize the recruitment of inflammatory leukocytes from the blood as an early step in atherogenesis. The molecular mediators of leukocyte recruitment, including endothelial adhesion molecules and chemoattractant cytokines, increase in response to risk factors including constituents of modified lipoproteins or angiotensin II. Not only does early atherogenesis involve inflammation, but so do the thrombotic complications that lead to clinical events, such as myocardial infarction or ischemic stroke. The propensity of a plaque to rupture and provoke thrombosis depends on the content of collagen in the plaque’s fibrous cap. Inflammatory signalling tightly controls the level of interstitial collagen in the plaque. For example, activated inflammatory cells secrete proteinases that can break down collagen, elastin, and other constituents of the arterial extracellular matrix, rendering the plaque fragile and susceptible to rupture, a common cause of thrombotic complications.

While indubitable evidence supports the operation of inflammation during all stages of atherosclerosis, our knowledge of the triggers for this inflammation remains incomplete. While traditional risk factors, such as high levels of LDL or hypertension, link causally with inflammation and oxidative stress, tight control of blood pressure and of LDL has not eliminated the complications of this disease. Therefore, we must seek novel triggers for inflammation to understand this process more fully and to identify...
novel therapeutic targets. The residual burden of cardiovascular risk demands a deeper understanding of the triggers of atherosclerosis.

In this context, burgeoning evidence supports obesity [and particularly intra-abdominal (visceral) adiposity] and diabetes as instigators of inflammation. The former concept of adipose tissue as an energy storage depot where triglyceride droplets push an inactive nucleus to the side of the adipocyte has undergone remarkable revision in the last decade. We now recognize that the adipocyte itself, and inflammatory cells that accumulate in adipose tissue, secrete abundant proinflammatory cytokines. In particular, intra-abdominal adipose tissue is strategically located to inundate the liver with proinflammatory cytokines via the portal circulation. These mediators from intra-abdominal adipose tissue impinge directly on the liver and can alter the program of hepatic protein synthesis. Among the proteins of the acute phase response solicited by inflammatory cytokines, fibrinogen and plasminogen activator inhibitor-1 participate causally in thrombus formation and accumulation. Levels of these proteins increase in obese subjects and in patients with diabetes. These alterations likely contribute to the thrombotic diathesis associated with these conditions. Among the acute phase reactants, C-reactive protein serves as a readily measured analyte that can disclose inflammatory status in a reliable way. Indeed, C-reactive protein levels increase in proportion to accumulation of intra-abdominal adipose tissue, a finding that underscores the inflammatory burden associated with intra-abdominal fat accumulation.

While numerous studies over the last decade have highlighted the role of innate immune cells such as the mononuclear phagocytes in intra-abdominal adipose tissue, the role of adaptive immunity in adipose tissues has remained relatively unexplored until recently. As considerable crosstalk characterizes the operation of innate and adaptive immunity, our group [1] and others have recently hypothesized that T lymphocytes may regulate the inflammatory response in adipose tissue. In particular, we have found evidence of activated T lymphocytes in intra-abdominal adipose tissue in obese mice. Local overexpression of class II histocompatibility antigens served as the signature of elaboration of the T helper cell type 1 (Th1) cytokine interferon-gamma (IFN-γ) locally in intra-abdominal adipose tissue. Subsequent studies have shown that IFN-γ could induce numerous proinflammatory mediators, including chemokines that can recruit further lymphocytes to the plaque. Mice deficient in IFN-γ rendered obese by a high-fat diet showed not only decreased chemokine and inflammatory cell accumulation, but also improved glucose tolerance. Work from the laboratories of Ballantyne and Marx [2-4] has also highlighted the operation of adaptive immunity in intra-abdominal adipose tissue.

The presence of inflammatory stimuli often elicits counter-regulatory mechanisms to mute the inflammatory response and prevent an untrammeled phlogistic amplification of inflammation. In this regard, several investigators have hypothesized a role for adiponectin as an endogenous anti-inflammatory mediator related to obesity. Individuals with intra-abdominal adiposity have lower circulating levels of this anti-inflammatory adipokine than do their lean counterparts. We explored the anti-inflammatory effects of adiponectin on human macrophages, and identified a coordinate suppression of the expression of T lymphocyte chemoattractants of the CXCR3 ligand family due to
adiponectin treatment. In vivo experiments in mice genetically engineered for atherosclerosis susceptibility and absence of adiponectin showed increased T cell accumulation and a modest but significant increase in atherosclerotic lesion size at the level of the aortic root [5]. While not all laboratories have found increased atherosclerosis in adiponectin-deficient animals, these findings together indicate that adiponectin not only suppresses innate immune responses, but also may limit adaptive immunity. Thus, inflammation represents a common thread that unites the fundamental aspects of the pathophysiology of atherosclerosis, obesity, and diabetes.

References
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.
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
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