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Review

The usefulness of circulating adipokine levels for the assessment of obesity-related health problems

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Because the prevalence of obesity has increased dramatically in recent years, one of the key targets of public health is obesity and its associated pathological conditions. Obesity occurs as a result of white adipose tissue enlargement, caused by adipocyte hyperplasia and/or hypertrophy. Recently, endocrine aspects of adipose tissue have become an active research area and these adipose tissue-derived factors are referred to as adipokines. These adipokines interact with a range of processes in many different organ systems and influence a various systemic phenomena. Therefore, dysregulated production of adipokines has been found to participate in the development of metabolic and vascular diseases related to obesity. The obese state is also known to be associated with increased local and systemic inflammation. Adipokines influence not only systemic insulin resistance and have pathophysiological roles in the metabolic syndrome and cardiovascular disease, but also contribute toward an increase in local and systemic inflammation. Thus, circulating levels of adipokines can be used as high-throughput biomarkers to assess the obesity-related health problems, including low grade inflammation. This review focuses on the usefulness of measuring circulating adipokine levels for the assessment of obesity-related health problems.

Key words: Adipokine, biomarker, insulin resistance, metabolic syndrome, obesity.

1. Introduction

The prevalence of obesity has increased dramatically as a result of our modern lifestyle and is one of the most important targets of public health programs [1]. Accumulating evidence derived from both clinical and experimental studies highlight the association of obesity with a number of chronic diseases such as type II diabetes mellitus (T2DM), atherosclerosis and cardiovascular disease (CVD). T2DM is a problem not only in developed countries but is also becoming an urgent problem in developing countries owing to the worldwide increase in obesity [2]. Therefore, there is considerable effort to understand the underlying biology of these disease states and to identify the contributing risk factors.

The clustering of CVD risk factors, most notably the simultaneous presence of obesity, T2DM, dyslipidemia, and hypertension was recognized as an important pathophysiological state [3-5]. The coexistence of these diseases has been termed the metabolic syndrome (MS). Insulin resistance (IR) is well known to be a key feature of MS, and is strongly associated with excess adiposity, especially in the intra-abdominal region. Individuals with MS are at increased risk for the development of CVD and other diseases related to plaque formation in artery walls, resulting in stroke and peripheral vascular disease. Because the prevalence of these diseases is increasing, high throughput assessment of disease states accompanied with obesity or MS are important issues from the public health point of view.

Excess white adipose tissue (WAT) is linked to obesity-related health problems. It is also recognized that obesity is accompanied by chronic, low-level inflammation of WAT [6, 7]. Inflammation has been considered to be associated with the development of IR and MS [8]. Recently, WAT has been recognized as an important endocrine organ that secretes a wide variety of biologically active adipokines [9-11]. Since some of these adipokines greatly influence insulin sensitivity, glucose metabolism, inflammation and atherosclerosis, they may provide a molecular link between increased adiposity and the development of T2DM, MS and CVD. The signals from WAT are thought to directly connect with IR and inflammation.

It is expected, therefore, that circulating levels of adipokines may be useful as biomarkers to evaluate the risk of other disease states associated with obesity.

This review describes the usefulness and clinical significance of circulating adipokine levels. First, I focused on three representative adipokines associated with IR, namely adiponectin, retinol binding protein 4 (RBP4) and resistin. Next, I discuss the inflammation-related markers such as tumor necrosis factor (TNF) α, interleukin (IL)-6 and C-reactive protein (CRP). Because leptin has not been recognized directly to be related with IR and inflammation, description of this adipokine was excluded. Finally, I have summarized the significance of other molecules, followed by a brief discussion for future research.

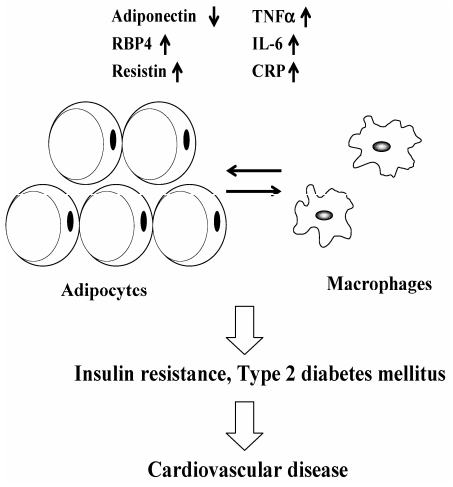

Figure 1. Schematic representation of mechanisms linking adipokine dysreguation and cardiovascular disease in obese state. See text for abbreviations.

2. Adipose tissue as a secretory organ

In 1993, it was discovered that TNFα expression was up-regulated in WAT of obese mice [12]. The role of WAT as a hormone-producing organ became well recognized in 1994 with the discovery of leptin as an adipocyte-secreted protein [13]. Systemic analysis of the active genes in WAT, by constructing a 3'-directed complementary DNA library, revealed a high frequency of genes encoding secretory proteins. Of the gene group classified by function, approximately 20–30% of all genes in WAT encode secretory proteins [14].

In adults, most organ systems have reached their final size and are programmed to be maintained at steady state. However, WAT is unique because of its almost unlimited expansion potential. Thus, WAT can become one of the largest organs in the body, and the total amount of an adipokine secreted from WAT may affect whole-body homeostasis. WAT contains various types of cells that include preadipocytes, adipocytes and stromal vascular cells. Moreover, bone marrow-derived macrophages home to WAT in obesity [6, 7]. The massive increase in fat mass leads to a dysregulation of circulating adipokine levels that may have pathogenic effects associated with obesity. Thus, dysregulated secretion of adipokines, not only from adipocytes but also from macrophages in WAT, will contribute to the pathogenesis of obesity by triggering IR and systemic inflammation (Fig. 1). It is expected, therefore, that circulating levels of adipokines can be used as a high-throughput biomarker to assess obesity-related health problems.

3. Adiponectin

Adiponectin is the most abundantly expressed adipokine in WAT [14]. The average levels of adiponectin in human plasma are 5–10 μg/ml [15]. Adiponectin is a multifunctional protein that exerts pleiotropic insulin-sensitizing effects. It lowers hepatic glucose production [16] and increases glucose uptake and fatty acid oxidation in skeletal muscle [17]. Moreover, adiponectin may possess anti-atherogenic properties by inhibiting the expression of adhesion molecules and smooth muscle cell proliferation, as well as suppressing the conversion of macrophages to foam cells [18, 19]. An anti-inflammatory role of adiponectin has also been reported [20].

A number of studies reported the significance of circulating levels of adiponectin (Table 1). Unlike most adipokines, adiponectin mRNA in WAT and serum levels are decreased in obesity [21]. Adiponectin is the only adipokine that is known to be down-regulated in obesity. Plasma concentrations are negatively correlated with body mass index (BMI) [15]. A longitudinal study in primates suggests that adiponectin decreases with weight gain as animals become obese [22]. In contrast, weight loss results in significant increases in circulating adiponectin levels [23, 24]. In addition to the association with whole-body fat mass, adiponectin levels differ with the distribution of body fat. Plasma levels of adiponectin exhibit strong negative correlations with intra-abdominal fat mass [25]. Visceral, but not subcutaneous abdominal fat, was reported to be inversely associated with plasma adiponectin levels in healthy women [26]. A low waist to hip ratio has been reported to be associated with high levels of plasma adiponectin independent of the body fat percentage [27].

Table 1 Clinical studies of circulating adiponectin levels

Subjects	Major findings	References
Obese subjects	Decreased in obese subjects	Hu et al., (1996) [21]
		Arita et al., (1999) [15]
Patients with CVD	Decreased in patients with CVD	Ouchi et al., (1999) [37]
Nondiabetic and T2DM subjects	Decreased in T2DM patients	Hotta et al., (2000) [28]
Obese subjects	Increased after weight loss	Yang et al., (2001) [23]
Caucasians and Pima Indians	Associated with IR	Weyer et al., (2001) [153]
Pima Indian	Low plasma concentration precedes a decrease in insulin sensitivity	Stefan et al., (2002) [29]
Pima Indian	Decreased in T2DM patients	Lindsay et al., (2002) [30]
Pima Indian children	An inverse relationship to adiposity	Stefan et al., (2002) [154]
Nondiabetic Japanese women	Negative correlation with serum triglyceride	Matsubara et al., (2002) [155]
Obese subjects	Increased after weight loss	Bruun et al., (2003) [24]
Middle-aged population	Associated with intra-abdominal fat	Cnop et al., (2003) [25]
Nondiabetic white volunteers	Positive correlation with HDL-cholesterol	Tschritter et al., (2003) [31]
Hypertensive patients	Correlation with vasodilator response	Ouchi et al., (2003) [34]
Japanese men	Decreased in patients with CVD	Kumada et al., (2003) [38]
Japanese subjects	Connected with endothelial dysfunction	Shimabukuro et al., (2003) [156]
Japanese subjects	Decreased in patients with T2DM	Daimon et al., (2003) [157]
Apparently healthy individuals	Associated with the risk of T2DM	Spranger et al., (2003) [158]
Asian Indians with IGT	Low adiponectin was a strong predictor of T2DM	Snehalatha et al., (2003) [159]
Nonobese and obese subjects	Correlation with advantageous lipid profile	Baratta et al., (2004) [32]
Japanese men	Decreased in hypertensive men	Iwashima et al., (2004) [33]
Male participants	High adiponectin was associated with lower risk of myocardial infarction	Pischon et al., (2004) [39]
Whites and African Americans	Higher adiponectin was associated with a lower incidence of T2DM	Duncan et al., (2004) [160]
Patients with CVD	Decreased in patients with CVD	Nakamura et al., (2004) [161]
Pregnant women	Decreased in patients with gestational DM	Ranheim et al., (2004) [162]
Nondiabetic subjects	Obesity-independent association of IR with adiponectin levels	Abbasi et al., (2004) [163]
Obese individuals	Decreased in subjects with MS	Xydakis et al., (2004) [164]
Healthy premenopausal women	Associated with visceral fat mass	Kwon et al., (2005) [26]
Obese juveniles	An inverse relation with the intima media thickness of common carotid arteries	Pilz et al., (2005) [40]
Patients with chronic heart failure	High adiponectin was a predictor of mortality	Kistorp et al., (2005) [42]
British women	No association with CVD risk	Lawlor et al., (2005) [43]
American Indian	No association with later development of CVD	Lindsay et al., (2005) [44]
Hispanic children	Inversely associated with IR	Butte et al., (2005) [52]
Patients with CVD	Decreased in patients with CVD	Rothenbacher et al., (2005) [165]
Middle-aged men	Positive association with lower fat mass	Buemann et al., (2005) [166]
Obese children	Low adiponectin was associated with components of MS	Winer et al., (2006) [36]
Older Black Americans	High adiponectin was associated with higher risk of CVD	Kanaya et al., (2006) [45]
Patients with CVD	High adiponectin was a predictor of mortality	Cavusoglu et al., (2006) [46]
Patients with CVD	High adiponectin was a predictor of mortality	Pilz et al., (2006) [50]
Pregnant women	Elevated with preeclampsia	Haugen et al., (2006) [59]
Patients with congestive heart failure	Positive correlation with disease severity	George et al., (2006) [167]
Caucasian	High adiponectin increased the risk of death from all causes	Laughlin et al., (2007) [48]
Aged men	High adiponectin increased the risk of death from all causes	Wannamethee et al., (2007) [49]
Patients with incident CVD	No association with the prognostic outcome	von Eynatten et al., (2008) [41]
General Dutch population	High levels of adiponectin predict mortality	Dekker et al., (2008) [51]

Plasma adiponectin concentrations are lower in people with T2DM than in BMI-matched controls [28]. The plasma concentrations have been shown to correlate strongly with insulin sensitivity, which suggests that low plasma concentrations are associated with IR [29]. In a study of Pima Indians, a population that has one of the highest prevalence of obesity, IR and T2DM, individuals with high adiponectin levels were less likely to develop T2DM than those with low concentrations [30]. The high adiponectin concentration was, therefore, a predictive marker for the development of T2DM. Plasma concentrations of adiponectin are also reported to be associated with components of MS. High plasma concentrations of adiponectin were found to be related to an advantageous blood lipid profile [31, 32]. Plasma adiponectin levels are decreased in hypertensive humans, irrespective of the presence of IR [33]. Endothelium-dependent vasoreactivity is impaired in people with hypoadiponectinemia [34], which might be one of the mechanisms involved in hypertension in visceral obesity. A reciprocal association between CRP and adiponectin mRNA levels was reported in human WAT, suggesting that hypoadiponectinemia appears to contribute to low-grade

systemic chronic inflammation [35]. All these mechanisms may underlie the protective effects against the progression of atherosclerosis of adiponectin. A recent study revealed that adiponectin may function as a biomarker for MS, even in childhood obesity [36]. Collectively, adiponectin has been recognized as a key molecule in MS and has the potential to become a clinically relevant parameter to be measured routinely at general medical check ups.

Plasma concentrations of adiponectin are also known to be lower in people with CVD than in controls, even after matching for BMI and age [37]. A case-control study performed in Japan revealed that the people with hypoadiponectinemia with the plasma levels less than 4 μg/ml had increased risk of CVD and multiple metabolic risk factors, indicating that hypoadiponectinemia is a key factor in MS [38]. Retrospective case-control studies have demonstrated that patients with the highest levels of adiponectin have a dramatically reduced 6-year risk of myocardial infarction compared with case controls with the lowest adiponectin levels, and this relationship persists even after controlling for family history, BMI, alcohol, history of diabetes and hypertension, hemoglobin A1c, CRP, and lipoprotein levels [39]. An inverse relationship between serum adiponectin levels and the intima media thickness of common carotid arteries was also reported [40]. These clinical studies clearly indicate that hypoadiponectinemia is a strong risk factor for CVD.

Although the above studies support the notion that adiponectin would protect against vascular diseases, recent epidemiological studies have failed to support this notion [41-51]. A recent prospective study reported adiponectin levels were not significantly associated with future secondary CVD events [41]. Thus, measurement of adiponectin may add no significant value to risk stratifications in patients with incident CVD, and effects of adiponectin may be more of importance in the early phases of atherosclerosis. Kistorp et al. reported that adiponectin was positively related to increased mortality in patients with chronic heart failure [42]. These authors suspect that the high adiponectin concentrations may reflect a wasting process in subjects with increased risk of death. Pilz et al. reported that high adiponectin levels predict all-cause, cardiovascular and noncardiovascular mortality [50]. A recent study also reported that a high adiponectin level was a significant predictor of all-cause and CVD mortality [51]. These authors hypothesized that a counter-regulatory increase in adiponectin occurs, which represents a defense mechanism of the body against cardiovascular alterations and a pro-inflammatory state associated with CVD. Thus, yet-unknown mechanisms may underlie the association between adiponectin and the risk of death, the prognostic value of adiponectin remains unresolved. Further prospective studies will be required to provide conclusive results about the association of adiponectin and mortality. It is also necessary to understand the underlying molecular mechanisms of elevated adiponectin concentrations in these disease states.

It must be highlighted that several physiological factors affect the circulating levels of adiponectin. First, aging, gender and puberty have effects on circulating adiponectin levels [52, 53]. An age-associated elevation of plasma adiponectin levels has been reported [51, 54]. Plasma adiponectin levels were significantly higher in female subjects, indicative of a sex hormone affect on circulating adiponectin levels [51, 55]. Adiponectin levels tend to decrease throughout puberty, which parallels the development of IR [36, 56]. Second, the glomerular filtration rate has been recognized as a strong inverse predictor of adiponectin. The clearance of adiponectin by the kidney may have a strong influence on its concentration [57]. Hence, high adiponectin levels may reflect impaired renal function. Last but not least, an increased adiponectin level has been suggested to act as a compensatory mechanism to dampen inflammation. Indeed, elevated plasma adiponectin concentrations are observed in several diseases associated with inflammation: arthritis [58], preeclampsia [59], and end-stage renal disease [60]. All of these factors must be considered when evaluating the clinical significance of circulating adiponectin levels in MS or vascular diseases related to obesity.

Circulating adiponectin forms several different complexes in the adipocyte before being secreted into the blood [61]. Commercial assays measure the total plasma concentration of adiponectin. Thus, the vast majority of clinical studies published to date have evaluated correlations between total adiponectin levels and various markers of MS. The most basic form of adiponectin secreted is the trimer. Adiponectin forms two higher-ordered structures through the noncovalent binding of two trimers (hexamers) and six trimers (18mers). The native protein circulates in serum as low molecular weight (LMW) hexamers and as larger multimeric structures of high molecular weight (HMW). Of these higher-ordered structures, the 18mer (HMW) form is assumed to act beneficial against IR; the function of the hexamer (LMW) form is suggested to play a pro-inflammatory role [55, 62]. Thus, the HMW form is more strongly associated with insulin sensitivity than is total adiponectin [63-65]. Overall, these results suggest that the assessment of total adiponectin may be insufficient and that the analysis of the levels of the

multimeric forms should be favorable to assess the significance of adiponectin.

4. Retinol binding protein 4 (RBP4)

RBP4 is a protein that is the specific carrier for retinol in the blood. It is one of a large number of proteins that solubilize and stabilize the hydrophobic and labile metabolites of retinoids in aqueous spaces in both extra- and intracellular spaces. Its physiological function appears to be to bind retinol and prevent its loss through the kidneys. RBP4, although largely produced in liver, is also made by adipocytes, with increased levels in obesity contributing to impaired insulin action [66]. Studies in transgenic rodent models showed overexpression of human RBP4 or injection of recombinant RBP4 induced IR in mice, whereas RBP4 knockout mice showed enhanced insulin sensitivity [66]. The same authors reported that high plasma RBP4 levels are associated with IR states in humans and suggested that RBP4 is an adipokine responsible for obesity-induced IR and, thus, a potential therapeutic target in T2DM [66, 67]. Since then, a number of clinical studies have been conducted to assess the significance of circulating levels of RBP4 (Table 2).

Table 2 Clinical studies of circulating RBP4 levels

Subjects	Major findings	References
Obese and T2DM subjects	Elevated in subjects with T2DM	Yang et al., (2005) [66]
IGT and T2DM subjects	Correlation with the magnitude of IR	Graham et al., (2006) [67]
IGT and T2DM subjects	Elevated in subjects with IGT or T2DM than normal glucose tolerance	Cho et al., (2006) [68]
Caucasian menopausal women	No correlation with adiposity	Janke et al., (2006) [72]
Japanese subjects	No correlation with BMI	Takashima et al., (2006) [168]
IGT and T2DM subjects	No correlation with IR	Erikstrup et al., (2006) [169]
Chinese subjects	Correlation with the components of MS	Qi et al., (2007) [69]
Healthy women	Associated with visceral fat	Lee et al., (2007) [70]
Chinese subjects	Correlation with visceral adiposity	Jia et al., (2007) [71]
Non diabetic person	No correlation with IR	Yao-Borengasser et al., (2007) [73]
Subjects with BMI from 18 to 30	Negative correlation with insulin sensitivity	Gavi et al., (2007) [74]
Caucasian without T2DM	Associated with liver fat	Stefan et al., (2007) [76]
Nondiabetic individuals	Reflected ectopic fat accumulation	Perseghin et al., (2007) [77]
Obese children	Associated positively with CRP	Balagopal et al., (2007) [170]
Subjects with morbid obesity	Reduction after weight loss	Haider et al., (2007) [171]
Obese women	Reduction after weight loss	Vitkova et al., (2007) [172]
Patients with T2DM	Associated with IR	Takebayashi et al., (2007) [173]
Women with polycystic ovary syndrome	Elevated than BMI-matched subjects	Tan et al., (2007) [174]
Nondiabetic men	Negatively associated with insulin secretion	Broch et al., (2007) [175]
Patients with chronic liver disease	Decreased compared with control subjects	Yagmur et al., (2007) [176]
Patients with T2DM or CVD	Associated with pro-atherogenic lipoprotein levels	von Eynatten et al., (2007) [177]

Cho et al. reported that plasma concentrations of RBP4 were higher in people with impaired glucose tolerance (IGT) or T2DM than in people with normal glucose tolerance [68]. A recent cross-sectional study of 3289 middle-aged population showed that plasma RBP4 levels increased gradually with increasing numbers of MS components [69]. Similar to other adipokines, circulating levels of RBP4 is associated with body fat distribution rather than body weight *per se*. RBP4 was reported to be more highly correlated with waist-to-hip ratio or visceral fat areas than with BMI [67, 70, 71]. However, Janke et al. reported that, in human abdominal subcutaneous (sc) adipose tissue, RBP4 mRNA is down-regulated in obese women, whereas circulating RBP4 concentrations were similar in lean, overweight, and obese women [72]. Yao-Borengasser et al. also reported that neither sc adipose tissue RBP4 mRNA expression nor circulating RBP4 levels show any correlation with BMI [73]. It is not clear why such differences are present among similarly conducted human studies. These inconsistencies most likely result from differences in age, ethnicity, sample size, and assay methods used. For example, sex and age were found to be independent determinants of plasma RBP4 concentrations [68, 74]. A recent study suggested that the sandwich ELISA kit commercially available for the assessment of RBP4 may overestimate the circulating levels [75]. Those authors also claimed that competitive EIAs may underestimate serum RBP4 levels in the setting of IR owing to assay saturation. Thus, it is probable that the reported RBP4 associations would become clearer if more reliable assays were employed.

Two recent studies have indicated that high circulating RBP4 is associated with elevated liver fat and, presumably, hepatic insulin resistance [76, 77]. In ro-

dents, only 20% of systemic RBP4 is produced by adipocytes, and RBP4 gene expression in adipocytes was 20% compared with expression in the liver [78]. Thus, it is possible that the increase in systemic RBP4 concentrations is not explained by increased RBP4 production in WAT. RBP4 is a transporter for retinol, which serves as a precursor for the synthesis of ligands for nuclear hormone receptors such as retinoid X receptor and retinoic acid receptor. Thus, circulating RBP4 can modulate metabolic pathways via these nuclear hormone receptors. Certainly, future prospective studies are needed to clarify whether a high RBP4 level plays a causal role in the development of MS, T2DM, and eventually for the development of CVD.

5. Resistin

After the identification of resistin as an adipokine in 2001 [79], several studies have been conducted to investigate the role and significance of this molecule. Resistin was discovered as a result of a hypothesis that WAT secretes a hormone that mediates IR and that insulin sensitizing drug thiazolidinediones act by suppressing the production of this hormone. Resistin is secreted by mature adipocytes in proportion to the level of obesity and acts on insulin-sensitive cells to antagonize insulin-mediated glucose uptake and utilization in mice. Treatment of wild-type mice with recombinant resistin resulted in IR, whereas administration of an anti-resistin antibody increased insulin sensitivity in obese and insulin-resistant animals [79]. However, human resistin is 59% homologous at the amino acid level to the mouse molecule, a relatively low degree of sequence conservation. Moreover, in contrast to mice, human resistin is expressed at lower levels in adipocytes but at higher levels in circulating blood monocytes [80]. As a result, there is still uncertainty about possible relationships between serum concentrations of resistin and markers of IR (Table 3).

Table 3 Clinical studies of circulating resistin levels

Subjects	Major findings	References
Healthy Greek students	Correlation with body fat mass	Yannakoulia et al., (2003) [81]
Non-diabetic subjects	Correlation with IR	Silha et al., (2003) [82]
Patients with essential hypertension	Elevated in T2DM patients	Zhang et al., (2003) [83]
Patients with inflammatory diseases	Correlation with inflammatory markers	Stejskal et al., (2003) [91]
Obese subjects	Correlation with BMI	Azuma et al., (2003) [178]
Lean and obese subjects	Increase in obese subjects	Degawa-Yamauchi et al., (2003) [179]
Women	No relation with fat mass or IR	Lee et al., (2003) [180]
Patients with T2DM	No correlation with IR	Pfutzner et al., (2003) [181]
Obese subjects	Not changed after weight loss	Monzillo et al., (2003) [182]
Diabetic subjects	Correlation with CRP	Shetty et al., (2004) [87]
Obese Caucasian subjects	Correlation with HOMA-R	Silha et al., (2004) [183]
Non obese subjects	Correlation with insulin sensitivity	Heilbronn et al., (2004) [184]
Pima Indians	Correlation with fat mass but not IR	Vozarova de Courten et al., (2004) [185]
Diabetic subjects	Elevated in T2DM patients	Youn et al., (2004) [186]
Japanese subjects	Elevated in T2DM patients	Fujinami et al., (2004) [187]
Patients with T2DM	Correlation with hepatic fat content	Bajaj et al., (2004) [188]
Women	Associated with the presence of CVD	Pischon et al., (2005) [88]
Subjects who had a family history of premature coronary artery disease	Correlation with the levels of inflammatory markers	Reilly et al., (2005) [90]
Japanese subjects	Associated with the presence and severity of CVD	Ohmori et al., (2005) [189]
Men	Correlation with CRP	Bo et al., (2005) [190]
Patients with rheumatoid arthritis	Elevated than the patients with osteoarthritis	Senolt et al., (2007) [89]

The role of resistin in the pathophysiology of obesity and IR in humans is controversial. Several studies have shown positive correlations of circulating resitin levels with body fat mass [80, 81] or IR [82, 83]. However, the other studies found no relationship between resistin gene expression and body weight or insulin sensitivity [84-86]. These conflicting data may reflect variations in the study design and the lack of adjustment for potential confounding factors. It also seems possible that resistin is a marker for, or contributes to, IR in a specific population. The predominantly paracrine role of resistin might explain the weakness of the correlations between circulating resistin levels and some of the metabolic variables.

Two studies have shown that among the blood markers, the most significant association of the circulating resistin level was with plasma CRP [87, 88]. Thus, higher resistin levels may be a marker of systemic inflammation. Indeed, the circulating level of resistin is up-regulated in patients with rheumatoid arthritis [89]. The circulating resistin level is also reported to be an inflammatory marker of atherosclerosis

[90]. Considering that the resistin concentration is elevated in the patients with severe inflammatory disease [91], hyperresistinemia may be a biomarker and/or a mediator of inflammatory states in humans. Overall, the resistin levels in humans are thought to correlate more closely with inflammation than with IR.

6. Inflammation-related molecules

Obesity is associated with a state of chronic, low-grade inflammation characterized by abnormal cytokine production and the activation of inflammatory signaling pathways in WAT [92]. Obese hypertrophic adipocytes and stromal cells within WAT directly augment systemic inflammation. Although WAT is usually populated with 5-10% macrophages, diet-induced weight gain causes a significant macrophage infiltration, with macrophages comprising up to 60% of all cells found in WAT in a rodent model [6]. Thus, several adipokines implicated in inflammation are cytokines which are produced by macrophages. The accumulation of WAT resident macrophages and elaboration of inflammatory cytokines have been implicated in the development of obesity-related IR. Indeed, increases in inflammatory cytokine expression by WAT are associated with a parallel increase in WAT macrophage content [6, 7, 93]. Thus, obesity leads to increased production of several inflammatory cytokines, which play a critical role in obesity-related inflammation and metabolic pathologies.

A number of studies have reported that several humoral markers of inflammation are elevated in people with obesity and T2DM [94, 95] (Table 4). Pfeiffer et al. showed that men with T2DM had higher TNFα concentrations compared with nondiabetic subjects [96]. However, several studies reported no association between circulating levels of TNFα and insulin sensitivity [97, 98]. Since there was no arteriovenous difference with TNFα [99], TNFα is considered to work mainly in an autocrine or paracrine manner, where the local concentrations would be more likely to exert its metabolic effects [99, 100]. Moreover, circulating TNFα has been reported to be associated with a soluble receptor that inhibits its biological activity [101], suggesting that the action of TNFα is primarily a local one. Therefore, it seems unlikely that the circulating levels of TNFα would be a good biomarker to reflect the IR state of the whole body.

Table 4 Clinical studies of circulating inflammatory markers

Subjects	Major findings	References
TNFα		
Nondiabetic offsprings of T2DM patients	Not major contributing factor for obesity induced IR	Kellerer et al., (1996) [97]
Adult males	Elevated in patients with T2DM	Pfeiffer et al., (1997) [96]
Obese patients with T2DM	Correlation with the visceral fat area	Katsuki et al., (1998) [191]
T2DM subjects	Elevated in T2DM as compared to control	Winkler et al., (1998) [192]
Aged men	Correlation with BMI	Nilsson et al., (1998) [193]
Canadian population	Positive correlation with IR	Zinman et al., (1999) [194]
Obese subjects	Elevated in obese subjects than in controls	Corica et al., (1999) [195]
Normotensive obese patients	Elevated in patients with android obesity than gynoid obesity	Winkler et al., (1999) [196]
Obese subjects	No relationship with BMI	Kern et al., (2001) [98]
Premenopausal obese women	Reduced after weight loss	Ziccardi et al., (2002) [197]
Nondiabetic obese women	Associated with fat amount	Maachi et al., (2004) [198]
Premenopausal obese women	Reduced after weight loss	Marfella et al., (2004) [199]
IL-6		
White nondiabetic subjects	Correlation with BMI	Yudkin et al., (1999) [100]
Healthy middle-aged women	Associated with BMI	Hak et al., (1999) [200]
Obese nondiabetic women	Reduced after weight loss	Bastard et al., (2000) [103]
Obese subjects	Correlation with obesity and IR	Kern et al., (2001) [98]
Pima Indians	Correlation with IR	Vozarova et al., (2001) [102]
Premenopausal obese women	Reduced after weight loss	Ziccardi et al., (2002) [197]
Premenopausal obese women	Reduced after weight loss	Esposito et al., (2003) [104]
Obese patients	Reduced after weight loss	Kopp et al., (2003) [105]
Obese subjects	Reduced after weight loss	Monzillo et al., (2003) [182]
Premenopausal obese women	Reduced after weight loss	Giugliano et al., (2004) [106]
Nondiabetic offspring of patients with T2DM	Not associated with the components of MS	Salmenniemi et al., (2004) [110]
Premenopausal obese women	Reduced after weight loss	Marfella et al., (2004) [199]
Japanese men	Not associated with the components of MS	Matsushita et al., (2006) [111]
T2DM subjects	Associated with IR	Natali et al., (2006) [201]
Adolescents	Positive correlation with BMI	Herder et al., (2007) [135]

CRP		
White nondiabetic subjects	Positive correlation with BMI	Yudkin et al., (1999) [100]
Healthy middle-aged women	Associated with BMI	Hak et al., (1999) [200]
Young adults	Elevated in obese person	Visser et al., (1999) [202]
Adult men	Correlation with body fat mass	Lemieux et al., (2001) [115]
Obese women	Reduced after weight loss	Heilbronn et al., (2001) [117]
Middle-aged men	Predictor of T2DM development	Freeman et al., (2002) [116]
Obese postmenopausal women	Reduced after weight loss	Tchernof et al., (2002) [118]
Premenopausal obese women	Reduced after weight loss	Ziccardi et al., (2002) [197]
Healthy obese women	Correlation with IR independent of obesity	McLaughlin et al., (2002) [203]
Premenopausal obese women	Reduced after weight loss	Esposito et al., (2003) [104]
Healthy American women	Prognostic marker to the MS	Ridker et al., (2003) [114]
Premenopausal obese women	Obesity is the major determinant of elevated CRP levels	Escobar-Morreale et al., (2003) [204]
Premenopausal obese women	Reduced after weight loss	Marfella et al., (2004) [199]
Obese subjects	Correlation with serum TNFα levels	Shadid et al., (2006) [86]
T2DM subjects	Associated with IR	Natali et al., (2006) [201]
Overweight women	Reduced after weight loss	Moran et al., (2007) [205]

A considerable proportion of circulating IL-6 is derived from WAT, and WAT is estimated to produce about 25% of the systemic IL-6 in vivo [99]. Fasting plasma IL-6 concentrations were negatively correlated with the rate of insulin-stimulated glucose disposal in Pima Indians [102]. Bastard et al. reported that the IL-6 values were more strongly correlated with obesity and IR parameters than TNFα, and a very low-calorie diet induced significant decreases in circulating IL-6 levels in obese women [103]. Other studies have also showed that weight loss results in decreased circulating levels of IL-6 [104-106]. Although several reports have indicated that IL-6 plays a role in the development of IR [95, 107], some investigators have insisted that IL-6 prevents IR [108, 109]. Some of these discrepancies may be explained by the widely different characteristics of the study populations regarding age, sex, glucose tolerance status, and degree of obesity. Overall, the association of IL-6 and IR seems complex and IL-6 alone might not be an appropriate marker of IR or MS [110, 111].

IL-6 derived from visceral adipose tissue draining directly into the portal system and causes the obesity-associated rise of liver CRP production [112]. Although CRP was traditionally thought to be produced exclusively by the liver in response to inflammatory cytokines, emerging data indicate that CRP can also be produced by nonhepatic tissues. Adipocytes isolated from human WAT produced CRP in response to inflammatory cytokines [113]. Adiponectin has been suggested to play a role in modulating CRP levels. In fact, adiponectin knockout mice showed higher CRP mRNA levels in WAT compared with the wild-type mice [35]. Therefore, hypoadiponectinemia also appears to be responsible for a low-grade systemic chronic inflammatory state, which is closely related to high CRP levels.

Several studies have shown that CRP is more strongly associated with IR than either TNFα or IL-6 [110, 111, 114]. CRP has been reported to be associated with body fat and other inflammatory markers [86, 115]. Abundant evidence has accumulated to show that CRP is associated with MS and predicts T2DM and CVD events independently of traditional risk factors [114, 116]. Thus, elevated CRP levels in obesity, and the decreases associated with weight loss indicate a link between CRP and obesity-associated risks for CVD [104, 117, 118].

7. Chemokines: monocyte chemoattractant protein-1 and IL-8

Monocyte chemoattractant protein-1 (MCP-1) is a chemokine, which plays a pivotal role in the recruitment of monocytes and T lymphocytes to the sites of inflammation. MCP-1 is expressed in adipocytes and considered to be an adipokine [119, 120]. MCP-1 mediates the infiltration of macrophages into WAT in obesity and may play an important role in establishing and maintaining a proinflammatory state that predisposes to the development of IR and MS [121]. Macrophage infiltration into WAT is increased by the secretion of MCP-1, which is expressed by adipocytes, as well as by macrophages and other cell types, especially in obese, insulin-resistant subjects [122]. A number of studies have reported significantly higher circulating MCP-1 levels in obese [122, 123] or T2DM patients [124, 125]. Conversely, obese patients who lost weight showed decreased levels of MCP-1 [122, 126]. However, a recent study indicated that there was no difference in circulating MCP-1 levels between nonobese and obese subjects, when either abdominal venous or arterialized blood was analyzed [127]. Previous studies showed that plasma MCP-1 levels were influenced by numerous factors, including aging [128], hypertension [129], hypercholesterolemia [130], vascular disease

[131], and renal failure [132]. Moreover, MCP-1 is also produced by other cell types, such as vascular smooth muscle cells, endothelial cells, fibroblasts, mesangial cells, and lymphocytes. Thus, undetectable conditions might have influenced the circulating MCP-1 levels, and it seems improbable that the circulating levels of MCP-1 merely reflect obesity-related disease states.

IL-8 is responsible for the recruitment of neutrophils and T lymphocytes into the subendothelial space and considered to be an atherogenic factor that leads to intimal thickening. IL-8 is produced and secreted by human adipocytes [133]. Plasma IL-8 levels are increased in obese subjects, linking obesity with increased cardiovascular risk [134]. The circulating IL-8 level is associated with obesity-related parameters such as BMI, waist circumference and CRP [123]. However, Herder et al. reported that, among the seven immunological mediators (IL-6, IL-18, TNFα, IL-8, MCP-1, IP-10, and adiponectin) expressed and secreted by WAT, high BMI was significantly associated with elevated circulating levels of IL-6, IL-18, and IP-10 as well as lower levels of adiponectin [135]. Thus, the clinical relevance of circulating levels of MCP-1 and IL-8 to predict obesity-related disease conditions is still unresolved.

8. Other molecules

Plasminogen activator inhibitor-1 (PAI-1) is an important endogenous inhibitor of tissue plasminogen activator and is a main determinant of fibrinolytic activity. PAI-1 contributes to the pathogenesis of atherothrombosis and CVD. Experimental data indicate that WAT has a capacity to produce PAI-1 [136]. Much of the elevation of circulating levels of PAI-1 in obesity is attributable to upregulated production from WAT [136-138]. The increased plasma PAI-1 levels in obesity and positive correlations with visceral fat depots are reported in several studies [139-142]. Conversely, weight loss is associated with reduced PAI-1 activity in obese subjects [143]. Hyperinsulinemia caused by IR may increase both adipocyte and hepatic synthesis of PAI, which could play a role in the development of the vascular complications [144, 145].

Obesity is associated with expansion of the capillary bed in regional fat depots. Adipocytes or other cell types present in WAT secrete angiogenic factors such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), which act in an autocrine or paracrine manner within WAT but may have endocrine effects throughout the body. Serum VEGF levels were found to positively correlate with BMI [146, 147]. HGF has also been reported to be elevated in obese subjects [148] and elevated serum HGF in obese subjects is reduced with weight loss [149]. These angiogenic factors may be involved in the development of obesity-related metabolic disorders such as inflammation and CVD.

Cathepsin S was recently identified as a novel adipokine [150]. Cathepsin S is a cysteine protease that has the ability to degrade many extracellular elements and is involved in the pathogenesis of atherosclerosis [151]. Cathepsin S is secreted by adipocytes and its circulating levels are increased in obese subjects than in nonobese subjects [152]. Conversely, weight loss is associated with a decrease in circulating cathepsin S levels as well as WAT cathepsin S content [152]. Thus, cathepsin S could constitute a novel biomarker of adiposity that may be linked with enlarged WAT and may also play a role in vascular pathogenesis in obesity.

9. Conclusions

Obesity is recognized as a worldwide public health problem that contributes to a wide range of disease conditions. The development of a method for convenient prediction of obesity-related health problems represents a major challenge for public policy makers facing the epidemic of obesity. WAT is an endocrine organ that communicates with other tissues via secretion of adipokines. Adipokines, which integrate metabolic and inflammatory signals are attractive candidates for predicting the risk of CVD. With obesity, the production of most adipokines is enhanced, except for the anti-inflammatory and insulin-sensitizing effector, adiponectin. Enlarged adipocytes and macrophages embedded within WAT produce more RBP4, resistin and proinflammatory cytokines, such as TNFα and IL-6. Markers of inflammation including CRP have been proposed for use in clinical practice to aid in the identification of asymptomatic patients at high risk for CVD. Thus, measurement of adiponectin and inflammatory markers could be used to assess the risk of developing CVD.

It is important to note, however, that only a limited number of adipokines are released into the bloodstream at levels that are detectable with current assays, resulting in increased circulating levels in the obese state. Some adipokines acting in a paracrine or autocrine manner may play an important role; thus, circulating levels of the adipokines may represent only spillover from WAT and may not be associated with the disease condition. Moreover, except for adiponectin, many of the adipokines are not expressed exclusively in WAT. Thus, there remains uncertainty as to the most appropriate and optimal marker for use in clinical practice. Since various WAT in different regions may have unique characteristics related to differential expression of adipokines, different types of

fat distribution may offer the explanations for the discrepancies observed between different studies. Further epidemiological studies with solid clinical end points are needed to determine which combination of adipokines can be a reliable risk marker for CVD and may provide an improved method for identifying persons at risk for future cardiovascular events. Elucidation of the significance of circulating adipokines may provide a therapeutic target for adipokine-based pharmacological and/or interventional therapies in obesity and related complications.

Abbreviations

BMI: body mass index; CRP: C-reactive protein; CVD: cardiovascular disease; IL: interleukin; IR: insulin resistance; MCP-1: monocyte chemoattractant protein-1; MS: metabolic syndrome; RBP4: retinol binding protein 4; T2DM: type 2 diabetes mellitus; TNF: tumor necrosis factor; WAT: white adipose tissue.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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