Omentin: A Novel Link Between Inflammation, Diabesity, and Cardiovascular Disease

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Obesity has reached pandemic proportions and is associated with serious cardiometabolic sequealae including insulin resistance, diabetes, dyslipidemia, hypertension, and cardiovascular disease, where adipose tissue–secreted cytokines, that is, adipokines, have been implicated in these processes. Omentin is a novel adipokine preferentially produced by visceral adipose tissue with insulin-sensitizing effects, where circulating levels are decreased in insulin-resistant states, for example, obesity and diabetes. With respect to vascular biology, omentin causes vasodilatation of blood vessels and attenuates C-reactive protein–induced angiogenesis potentially via the nuclear factor B signaling pathway, a potent proinflammatory signaling pathway. Thus, omentin may have beneficial effects on the metabolic syndrome and could potentially be used as a biologic marker and/or pharmacologic agent in this respect. (Trends Cardiovasc Med 2010;20:143–148)

• Introduction

The metabolic syndrome is associated with excessive accumulation of central body fat, that is, visceral obesity. As well as adipocytes, adipose tissue (AT) contains stromal vascular cells, immune cells, and nervous tissue; these components function in concert making AT an endocrine organ (Kershaw and Flier 2004). AT produces cytokines termed *adipokines* that have widespread effects on carbohydrate and lipid metabolism and are implicated in the pathogenesis of insulin resistance, diabetes, and atherosclerosis (Kershaw and Flier 2004). Adipokines that are produced and secreted from adipocytes such as leptin and adiponectin are considered true adipokines in contrast to those derived from the nonadipocyte fraction of AT, for example, tumor necrosis factor–α (TNF-α). Furthermore, the accumulation of visceral AT poses a greater cardiometabolic risk than subcutaneous AT because there is higher lipolytic activity in visceral AT compared with other AT depots (Wajchenberg 2000). The increased release of free fatty acid (FFA) and glycerol from visceral AT is dependent on the sympathetic nervous system; there is an increase of β-adrenoreceptors (lipolysis) and a decrease in α2-adrenoreceptors (antilipolysis) (Wajchenberg 2000). Consequently, the increased FFA transport to the liver decreases hepatic insulin removal; this results in systemic hyperinsulinemia as well as inhibiting the suppression of hepatic glucose production by insulin. Chronic exposure to high levels of FFA leads to β-cell complications, which predisposes to type 2 diabetes mellitus (T2DM) and its attending cardiometabolic risks (Wajchenberg 2000). In addition, removal of visceral rather than subcutaneous AT has been shown to improve insulin sensitivity (Thörne et al. 2002). A crucial link between visceral obesity and insulin resistance is inflammation.

The relationship between inflammation and insulin-resistant states (obesity and diabetes) is well established. Obesity and T2DM, that is, diabesity, are associated with an increased risk of cardiovascular complications, for example, atherosclerosis, myocardial infarction, and stroke (De Flines and Scheen 2010). It has been reported that the proinflammatory cytokine TNF-α is increased in adipocytes of obese animals; the attenuation of TNF-α by soluble TNF-α receptor decreased insulin resistance in these animals (Hotamisligil et al. 1993). Furthermore, AT from obese individuals exhibits increased macrophage infiltration; these macrophages are a source of proinflammatory elements that have detrimental metabolic effects (Weisberg et al. 2003).

• Omentin: the New Adipokine on the Block

Omentin/intelectin was initially described in intestinal Paneth cells; omentin/intelectin associates with galactofuranose within carbohydrate moieties of bacterial cell walls and has been implicated in the gut defensive mechanisms against pathogenic bacteria, for example, *Escherichia coli* (Komiya et al. 1998). In addition, a homolog of omentin/intelectin has been reported sharing 83% amino acid identity with omentin/intelectin designated as omentin 2. Omentin 1 is the major circulating form of omentin and has been predominantly studied by researchers; for

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the rest of this review article omentin refers to omentin 1 (De Souza Batista et al. 2007). Omentin is expressed in the heart, lungs, ovary, and placenta (Schäffler et al. 2005, Yang et al. 2006). Recently, omentin has been reported as a novel adipokine preferentially produced and secreted by visceral AT (predominantly expressed in AT stromal vascular cells) compared with subcutaneous AT; in vitro experiments revealed that omentin enhances insulin-stimulated glucose uptake in human adipocytes and triggers Akt signaling (Yang et al. 2006). Akt is a serine/threonine protein kinase that plays an important role as a second messenger in multiple cellular functions, for example, glucose metabolism, cell proliferation, and apoptosis. It has also been reported that high omentin levels were present in umbilical cord blood. Insulin is important in increasing glucose uptake by fetal AT and muscle, which is essential for fetal growth; thus, omentin may exert a growth-promoting effect in the fetus via its insulin-sensitizing actions (Briana et al. 2011). With the aforementioned and given the relationship between insulin signaling and inflammation (Dandona et al. 2005), could there be a connection between omentin and inflammation?

- **Omentin and Inflammation**

Omentin messenger ribonucleic acid (mRNA) expression is decreased in omental AT of subjects with Crohn's disease (chronic inflammatory bowel disorder); this paucity of omentin may be important in the pathogenesis of transmural intestinal inflammation in these patients (Schäffler et al. 2005). Furthermore, omentin levels are decreased in synovial fluid of patients with rheumatoid arthritis (chronic inflammatory joint disorder) (Senolt et al. 2010).

Recently, we have reported that C-reactive protein (CRP) and TNF-α–induced nuclear factor κ-light-chain-enhancer of activated B cell (NF-κB) activation in human endothelial cells were significantly decreased by omentin; in addition, we had shown that changes in CRP levels were predictive of changes in circulating omentin levels after metformin treatment in overweight, insulin-resistant women with polycystic ovary syndrome (PCOS), another chronic inflammatory disorder (Tan et al. 2010).

Thus, omentin plausibly may have an anti-inflammatory role in proinflammatory states. In addition, because omentin is mainly expressed in the stromal vascular cells of visceral AT, could this potential anti-inflammatory role be important in modulating the proinflammatory elements in visceral AT, particularly, AT macrophages? Future studies are needed to address this concept.

- **Omentin in Obesity, Diabetes, Insulin-Resistant, and Proinflammatory States**

Circulating omentin and omentin gene expressions in visceral AT were reported to be decreased in obese subjects. In addition, circulating omentin levels were negatively correlated with markers of obesity, that is, body mass index, waist circumference, and circulating leptin; thus, obesity and, possibly, leptin may regulate omentin levels (De Souza Batista et al. 2007). In addition, given that obesity is associated with low levels of chronic inflammation, inflammatory factors may also regulate omentin levels, as discussed in the previous section. In addition, circulating omentin levels and omental AT omentin mRNA expression were found to be significantly lower in impaired glucose tolerant (IGT) and T2DM subjects compared with matched controls (Cai et al. 2009, Pan et al. 2010). We have reported decreased circulating omentin and omental AT omentin mRNA and protein levels in overweight insulin-resistant women with PCOS (Tan et al. 2008a). PCOS, the commonest endocrine disorder in women, affecting 5% to 10% of women in the reproductive age, characterized by irregular menses and hyperandrogenism, is associated with the metabolic syndrome and its attending cardiovascular complications (Dunaif 1997). Thus far, we have discussed descriptive studies and the associations of omentin with various metabolic parameters. What are the functional studies with regard to the regulation of omentin levels?

It has been reported that circulating omentin levels were significantly increased after weight loss induced by a hypocaloric diet; this was associated with a parallel improvement in insulin sensitivity (Moreno-Navarrete et al. 2010). Furthermore, in human omental AT explants, insulin and glucose have been shown to decrease omentin mRNA expression, protein levels, and secretion into conditioned media. In addition, hyperinsulinemic induction via a prolonged insulin-glucose infusion in healthy subjects culminated in reduced circulating omentin levels (Tan et al. 2008a). However, Wurm et al. (2007) recently described no significant changes in circulating omentin levels before and 2 hours after glucose intake, albeit semi-quantified by Western immunoblotting. With regard to insulin, there is good evidence that insulin exerts anti-inflammatory effects (Dandona et al. 2001; Dandona et al. 2005); thus, insulin-induced suppression of omentin appears paradoxical, given the postulated anti-inflammatory actions of omentin. However, there is ex vivo (Madonna et al. 2008) and in vivo (Coletta et al. 2008) data to suggest that insulin could be proinflammatory; further research is needed to clarify the relationship between insulin and omentin. We have also shown that there was a significant increase in circulating omentin levels after metformin treatment (6 months treatment; 850 mg twice daily) in overweight insulin-resistant subjects with PCOS (Tan et al. 2010).

Diabetes has reached pandemic proportions and is associated with serious cardiometabolic sequelae. It is well known that the more common form, namely, T2DM, is closely linked to obesity, insulin resistance, and inflammation (Eckel et al. 2005). Subjects with T2DM also have increased cardiovascular morbidity and mortality. A historical cohort study spanning over a 22-year period reported that compared with nondiabetic controls, patients with T2DM showed higher cardiovascular morbidity (risk ratio, 1.76; 95 % confidence interval, 1.34-2.30) and a higher cardiovascular mortality rate (risk ratio, 2.05; 95 % confidence interval, 1.24-3.37) (De Grauw et al. 1995). In addition, it has been recognized that type 1 DM (T1DM) is a proinflammatory state (Devaraj et al. 2008). In addition, in obese subjects with T1DM, insulin resistance can accelerate progression of T1DM complications (Bingley et al. 2008). Recently, we reported decreased circulating omentin and increased adiponectin levels in subjects with T1DM. Adiponectin is an adipokine that circulates at high levels, with lower levels in obesity and cardiovascular disease (Fasshauer et al. 2004). Furthermore, there were no significant differences between fasting and postprandial circulating omentin and adiponectin levels in nondiabetic controls as well as in subjects with T1DM (Tan et al. 2008b). As mentioned above,