Omentin-1, Type 2 Diabetes and Insulin Resistance

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Abstract:

Omentin-1 a new anti-inflammatory adipokine has been identified as a major visceral (omental) secretory adipokine which plays important roles in glucose homeostasis, lipid metabolism, insulin resistance and diabetes. The aim of our review was to evaluate serum omentin-1 levels in type 2 diabetic patients and assess its relation with glycemic control, insulin resistance and metabolic parameters.

Keywords: Omentin-1, type 2 Diabetes, insulin resistance

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Introduction:

Visceral adipose tissue is an ectopic adipose tissue that plays a role in lipid metabolism as well as energy storage. In addition, it is considered an important endocrine organ, as well as secretion of adipokines. Adipokines regulate important biological processes in target organs such as the endocrine pancreas, skeletal muscle, brain, immune and cardiovascular systems, and the liver ***(1).***

This could explain the close link between obesity and the metabolic and cardiovascular complications. The production of many adipokines is deregulated in obesity and could participate

into disturbances of appetite and satiety, and into changes in the distribution of adipose tissue, hemostasis, endothelial function, insulin secretion, insulin sensitivity, inflammation energy expenditure, angiogenesis, blood pressure, osteoarticular functions and repro-duction ***(2).***

Omentin-1 is a glycoprotein of the adiponectin family released from visceral adipose tissue, endothelial cells and visceral fat stromal–vascular cells. It has anti-inflammatory effect and circulating omentin-1 concentration correlates negatively with waist circumference, insulin resistance and body-mass index (BMI) ***(3)***.

Serum omentin-1 is used as a biomarker of coronary artery disease, obesity, cancer, metabolic syndrome, inflammatory disease, atherosclerosis, and diabetes mellitus ***(4).***

Structure and Biosynthesis of Omentin

Omentin, a newly identified adipokine with 313 amino acids, encoded by a gene present in chromosomal region 1q22-q23. There are two highly homologous isoforms of omentin, omentin-1 and omentin-2; the former is the major circulating form in human plasma ***(5).***

Omentin gene which extracted from the human omental fat also named as intelectin, endothelial lectin and intestinal lactoferrin receptor. Omentin gene is mainly expressed in cDNA library from the human omental adipose tissue. Omentin consists of 313 amino acid protein of full length 1269 bp (base pair) which contain a secretory protein sequence and a fibrinogen related domain. Omentin has been identified in two homologous isoforms, omentin-1 and omentin-2, where omentin-1 is the main omentin present in the human blood ***(1)***.

The two omentin genes were found to be located in 1q22-q23 region adjacent to each other which have linked to type 2 diabetes in various populations. Omentin-1 is mainly expressed in the human omental adipose tissue specifically in the visceral not the subcutaneous tissue and to less extent in the intestine, lung, heart and rarely found in muscle and kidney and not found in other tissues. Omentin-1 is detected in the human blood and its concentration varies from one human to another ***(6).***

A novel 34-kDa adipocytokine originally identified from a human omental adipose tissue cDNA library (AY549722) was designated as omentin. This protein ID is registered as UniProt code Q8WWAO. A homolog with 83% amino acid identity with omentin is referred to as omentin-2. Accordingly, original omentin is now known as omentin-1, intelectin-1, intestinal lactoferrin receptor, endothelial lectin HL-1, or galactofuranose-binding lectin. It is expressed in mesothelial cells, vascular smooth muscle cells (VSMCs) and endothelial cells (ECs), particularly in VAT, epicardial fat, small intestine, colon, thymus, ovary, and testis as well as in intestinal Paneth cells and airway and intestinal goblet cells ***(7).***

In the intestine, intelectin-1 has been detected as both soluble form and brush border membrane bound form. The membrane bound form is regarded as intestinal lactoferrin receptor. The human omentin gene is located on chromosome 1q21.3, and consists of eight exons and seven introns. Full-length omentin-1 consists of 313 amino acids, including an 18-amino acid signal peptide, which is a highly hydrophobic region in the amino-terminal region ***(8).***

An actual cleavage site of human omentin-1 (intelectin-1) is located between Ser-18 and Thr-19. From a different perspective, Gly-16/Trp- 17 and Thr-19/Asp-20 were reported as a putative cleavage site. In any report, mature omentin-1 (intelectin-1) is regarded as a secretory protein ***(9).***

Human omentin-1 and mouse omentin-1 are >81.5% identical. However, mouse omentin-1 is expressed at high levels in intestine, but not VAT. Full-length omentin-2 consists of 325 amino acids, which are 83.0% identical to omentin-1. In fact, omentin-1 was demonstrated to be released from cultured human VAT ***(10).***

Dexamethasone stimulates the expression of omentin-1 in human VAT. Fibroblast growth factor-21 also stimulates the omentin-1 secretion from human perivascular preadipocytes. In contrast, the expression and secretion of omentin-1 are decreased by glucose and insulin in human adipose tissue explants. It is noticeable that hyperinsulinemia strongly decreases its expression level and secretion into conditioned media ***(11).***

Omentin-1 is the major circulating form of omentin and also abundant in human plasma, with levels in women being higher than those in men. Circulating omentin-1 levels are known to be negatively correlated with free testosterone, androgen, leptin, TNF-α, and inteleukin-6 levels but be positively correlated with adiponectin levels in normal and overweight subjects. A prolonged insulin-glucose infusion decreases serum omentin-1 levels in healthy subjects ***(12).***

In vitro studies showed that omentin-1 has a half-life of 30 h in mammalian reticulocytes. However, its half-life in the plasma is unclear. Omentin-2 is expressed in VAT and mainly released to the intestinal lumen but is not detected in plasma. In addition to its hormonal (endocrine) roles, omentin-1 (intelectin-1) is largely secreted into the intestinal lumen and the airway (exocrine), and nonmammalian homologs, such as the Xenopus cortical granule lectin family XCGL and XCGL2 in chordates and Xenopus embryonic epidermal lectin in frogs, are secreted to outside of body. These observations suggest that the basic physiological role of omentin may be an effector for external substances ***(13).***

Biology of Omentin

Human recombinant omentin-1 (full length, Trp-17–Arg-313, Thr-19–Arg-313, etc) is now being produced in HEK293 cells, CHO cells, and Escherichia coli. Polyclonal and monoclonal

antibodies to human and mouse omentin-1 are also being synthesized. Concentrations of human omentin-1 in human plasma, serum, and other body fluid are measured by enzyme-linked immunosorbent assay (ELISA). All the reagents regarding omentin-1 as well as human recombinant omentin-2, and polyclonal and monoclonal antibodies to human and mouse omentin-2 are purchased from commercial sources ***(14).***

Circulating blood levels of omentin-1 in healthy subjects vary from approximately 5 to 800 ng/mL according to the manufacturer of the ELISA kit ***(15).***

Roles of Omentin

The roles of omentin-1 in physiological, pathophysiological, and clinical features have been a subject of increasing interest. However, the biological roles of omentin- 1 are still not well known. As omentin-1 (intelectin-1) initially found in intestinal Paneth cells was associated with galactofuranose within carbohydrate moieties of the bacterial cell wall, this peptide has been implicated in the gut defensive mechanisms against pathogenic bacteria, for example, Escherichia coli. Omentin- 1 has properties necessary to function in the immune system's surveillance complex ***(16).***

Omentin-1 targets Streptococcus pneumoniae serotypes by selectively binding to surface glycans through calcium ion-dependent coordination of a conserved exocyclic, terminal 1,2-diol, suggesting that omentin-1 functions in microbial surveillance. On the other hand, omentin-2 has no conserved ligand-binding site substitutions unlike omentin-1. There are ligand-binding site residue variations between human omentin-2 and mouse omentin-2 with no known biochemical and functional consequences. In addition, omentin-1 (intelectin-1) expressed in intestinal epithelia also acts as a receptor for an iron-binding protein, lactoferrin ***(17).***

Lactoferrin is taken by enterocytes via receptor-mediated endocytosis. Several lines of experimental and clinical evidence have explored a wide range of topics, including omentin-1-mediated cardiovascular protective effects and the use of circulating omentin-1 levels as a bone metabolism marker and a biomarker of cancers, polycystic ovary syndrome (PCOS), obstructive sleep apnea syndrome (SAS), preeclampsia, inflammatory disease, metabolic disorders including diabetes and metabolic syndrome, endothelial dysfunction, and atherosclerosis ***(16).***

Omentin-1 and pancreas

Reduction in omentin levels causes adverse metabolic outcomes, which were first described in diabetic patients. The omentin gene is localized on chromosome 1. Additionally, in some populations, type 2 diabetes is related with abnormalities on chromosome 1. Recombinant omentin-1 was found to improve glucose uptake stimulated by insulin in adipocytes. Furthermore,

omentin-1 levels have been shown to be decreased in several diseases characterized by insulin resistance ***(18).***

Adiponectin is known to be decreased in insulin resistance and related clinical conditions. Serum adiponectin levels in patients with acute pancreatitis are inversely correlated with body mass index (BMI) and organ dysfunction. The severity of pancreatitis in obese mice was inversely related to the circulating adiponectin levels. Hypoadiponectinemia could enhance the severity of pancreatitis ***(19).***

A significant increase in serum omentin levels reflected early-stage pancreatic damage. An increase in omentin in this phase may cause a reduction in the systemic inflammatory response due to the anti-inflammatory effects of omentin, and the decrease in glucotoxicity is due to the beneficial effects of omentin in insulin resistance ***(20).***

It is well known that obesity increases the risk of systemic complications in pancreatitis. Omentin levels are reduced in obese people compared with those at a healthy weight. It can be hypothesized that lower omentin levels may mediate such effects of obesity in pancreatitis ***(21).***

Omentin-1 is an adipokine with an anti-inflammatory function; it decreases expression of C-reactive protein and tumour necrosis factor. It increases insulin- -induced glucose uptake in yellow adipose tissue and nitric oxide synthesis, therefore preventing the development of diabetes and ischemic heart disease. Its link to neoplastic diseases remains unknown. Omentin-1 may have an anti-proliferative effect, whereas some claim that it stimulates proliferation. Omentin-1 concentration is increased in colon and prostate cancer ***(22).***

The role of investigated adipokines in pancreatic cancer carcinogenesis remains unclear. Omentin-1 may inhibit neoplastic cell growth in vitro via TP53 protein activity stimulation through posttranslational modification. In addition, a positive influence of omentin-1 on tumour progression via Akt signaling pathway. Stimulating role of adipokine in this pathway was confirmed in a human osteoblast culture in vitro ***(23).***

There is also evidence, that Akt signaling inhibition induces neoplastic cell apoptosis. It is uncertain whether neoplastic cells produce omentin-1, which may have an anti-apoptotic affect via stimulation of Akt autocrine pathway, or if elevated adipokine concentration occurs due to its increased secretion in adipose tissue, therefore making adipose tissue presence related to induction of tumour growth ***(24).***

Omentin-1, type 2 Diabetes, and insulin resistance

The altered fat distribution, dysfunction and inflammation of adipose tissue, and the production of adipocytokines are thought to contribute to insulin resistance and type 2 diabetes ***(25).***

Long-standing diabetes causes vascular complications which is a major reason for mortality worldwide. Several pathological mechanisms lead to the development of microvascular and macrovascular complications of diabetes. Visceral adipose tissue, an active endocrine organ, is a source of various adipokines, including leptin, adiponectin, visfatin, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) ***(26).***

These are the bioactive mediators which decrease inflammation and regulate glucose metabolism by enhancing insulin-mediated glucose transport. The anti-inflammatory effect of adipokines occurs through inhibition of TNF-α induced superoxide production which plays a role in maintaining the health of vascular smooth muscle cells. They have variable effects on carbohydrate and lipid metabolism as well ***(27).***

Plasma omentin-1 was found to have anti-diabetogenic and anti-atherogenic properties, whereas its levels are directly related to serum adiponectin and high-density lipoprotein-cholesterol (HDL-C) levels and inversely related with insulin resistance (IR), hyperlipidemia, obesity, and diabetes mellitus, thus, increasing the risk of diabetic complications ***(3).***

Recently, many adipocyte-secreted proteins as well as adipokines have been introduced as novel links to DM. It is widely accepted that the adipokines participate in many metabolic processes, including energy expenditure, appetite control, insulin sensitivity, and regulation of adipogenesis. Omentin-1, an important adipokine, is secreted from the visceral fat adipose tissue. Evidence has shown that, compared to subcutaneous obesity, Omentin-1 is more influential in the prognosis of DM. As regards its development, Omentin-1 is made by vascular cells of visceral fat adipose tissue, when it exerts its actions in the manner as endocrine, paracrine, and autocrine ***(16).***

These adipokines have crucial effects on glucose and lipid metabolism, insulin resistance, diabetes, atherosclerosis, vascular endothelium, inflammation, and cardiovascular function. Adiponectin, resistin, leptin, TNFα, IL-6 are some examples of many secreted adipokines ***(28).***

It is well known that there are direct and indirect hypothetical mechanisms that play an important role in it. Moreover, these hypothetical mechanisms suggest that altered omentin-1 secretion might changes into glucose homoeostasis, and subsequently contribute to the development of diabetes ***(29).***

Plasma omentin-1 levels are inversely related to diabetic complications. There is very limited information about the relationship between plasma omentin-1 and diabetic complications. It was found that omentin-1 levels in diabetic patients with peripheral artery disease (PAD) are

statistically lower than in diabetic patients without PAD. It is indicated that omentin-1 is not only engaged in energy balancing but also has a protective impact on diabetic patients due to its involvement in lipid metabolism and inflammation, both of which contribute to diabetes-related vascular problems ***(30).***

Diabetic patients had considerably lower plasma omentin-1 levels than the overall population in investigation ***(31).***

Omentin has also been shown to have anti-inflammatory and insulin sensitizing properties. Inflammation is a key factor in the development of atherosclerotic plaque, especially in diabetic patients. The onset and progression of atherosclerotic disease might result in a state of latent chronic inflammation. This inflammation is triggered by a variety of routes, mediated by hyperglycemia, and is influenced by oxidation-reduction state and inflammatory cytokine release ***(20).***

Through the production of cytokines that directly or indirectly enhance inflammatory pathways, adipose tissue is a major source of inflammation. Diabetes and its complications are associated with significant morbidity and mortality. It is important to identify any biomarker that may predict complications or be a potential treatment opportunity ***(32).***

Omentin-1 is an anti-inflammatory adipokine produced mainly in visceral adiposity has insulin sensitivity effects and has linked to obesity and obesity related disorders as insulin resistance and diabetes. The exact physiological role of omentin-1 in glucose homeostasis is still understood. Circulating omentin-1 levels were documented to be negatively correlated to waist circumference, BMI, HOMA-IR, fasting glucose and insulin and positively correlated to HDL ***(33).***

The exact mechanisms leading to decreased omentin-1 levels in obesity and type 2 diabetes are still unknown. It has reported that insulin and glucose significantly decrease the omentin mRNA expression and omentin protein production in vitro omental adipose tissue therefore hyperinsulinemia leads to decrease the circulating omentin-1 level significantly in normal subjects and this lead insulin and glucose play a role in the regulation of omentin-1 synthesis either directly or indirectly ***(8).***

Omentin-1 has found to enhance the insulin sensitivity and glucose metabolism as it increases the insulin transduction by activating the Akt protein kinase B in both visceral and subcutaneous adiposity. Visceral adiposity has found to be more pathogenic than subcutaneous adiposity through accelerating insulin resistance, type 2 diabetes and cardiovascular disorders. Body fat distribution, waist and hip circumference were known to reflect the visceral adiposity ***(16).***

Regarding these observations changes in circulating omentin-1may be used as a marker for leanness and a useful marker to counteract the obesity related metabolic disorders. Patients were obese and had insulin resistance and these 2 factors were found to be associated with increased internal cholesterol synthesis with decreased cholesterol absorption when compared to healthy subjects ***(34).***

Omentin-1 has known to have anti-atherogenic effects through its role in endothelial dysfunction, preventing arterial calcification, vasodilator effect on isolated blood vessels through inducing the secretion of endothelial nitric oxide, inhibiting TNF-α which induce vascular endothelial inflammation and as inhibitor to the inflammatory cascade ***(11).***

Omentin-1 is negatively associated with diabetes and its complications, and it has a protective role in diabetic patients. Therefore, adequate levels of omentin-1 are needed in order to prevent diabetic complications. Plasma omentin-1 levels correlate with disease severity. Hence, its level can be used by clinicians for the early diagnosis and management of diabetes. It can be a potential biomarker to predict the development of complications in diabetic patients ***(35).***

Omentin-1 accelerates only insulin mediated glucose transport and has no effect on the basal glucose transport which indicates that it hasn't intrinsic insulin like activity ***(36).***

Removal of visceral rather than subcutaneous adipose tissue has been shown to improve insulin sensitivity. On the other hand since it is secreted in the human blood it accelerates insulin sensitivity and glucose metabolism at distant sites as muscles, liver, subcutaneous fat so it may take part in the process of food storage and breakdown. Due to the main expression of omentin-1 in the human visceral omental tissue, omentin-1 levels are decreased in obese subjects ***(37).***

There is significant decrease in serum omentin-1 levels in type 2 diabetic obese insulin resistant females. Serum omentin-1 levels are inversely related to obesity, insulin resistance and systolic blood pressure. No significant associations have been found between fasting glucose, HbA1c, fasting lipids and serum omentin-1 levels. Regarding results the abnormalities in circulating omentin-1 may be used as a biomarker for obesity and associated metabolic and vascular disorders ***(4).***

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