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journal homepage: <http://www.curipms.umlub.pl/>**Omentin - a new adipokine with many roles to play**MAGDALENA HALABIS^{1*}, MARCIN DZIEDZIC¹, JOANNA WARCHULINSKA²,
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Accepted 15 September 2015**Keywords:**omentin,
obesity,
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Adipose tissue is at a point of high interest in medical research, not only as an energy depot, but also because it secretes nearly more than 600 cytokines. These are termed, adipokines. Human adipokines are involved in numerous metabolic processes, including the regulation of appetite, energy expenditure, insulin sensitivity, inflammation and cardiovascular activity. Thus, these could be clinically important as a markers of adipose tissue function and increased metabolic risk. The search for novel adipokines linking obesity to related co-morbidities has become a major topic in obesity research. In such work, there is an increasing need to define their function, their molecular targets and their potential clinical relevance as biomarkers or in the treatment of obesity and other metabolic diseases.

Omentin (34 kDa) is a recently identified fat deposition-specific adipokine with multiple interactions. Concentrations of omentin have been shown to be decreased in patients with obesity and impaired glucose regulation, in patients afflicted with diabetes type 1 and 2, and in patients with polycystic ovary syndrome. These are all diseases commonly associated with insulin resistance and obesity. The aim of this study was to show and compare the latest information about omentin and its relationships with obesity, diabetes mellitus (DM), metabolic syndrome (MetS), inflammation, cardiac problems, sex hormone imbalances and cancer.

The association of omentin with particular metabolic indexes may suggest that an elevation in omentin level may be seen as being a marker for leanness, while a decreased level will underline possible situations of overweight and obesity along with their comorbidities (diabetes, cardiovascular disease, metabolic syndrome, inflammation and even cancer). However, a challenge for the future is to fully understand the multiple role played by omentin. Thus, more studies in these matter are required.

INTRODUCTION

Adipose tissue, commonly known as “body fat”, accumulates predominantly as visceral and subcutaneous fat. However, adipose tissue is also known to be a very important and active endocrine organ. It is well established that adipocytes (or fat cells) play a vital role in the storage and release of energy throughout the human body. More recently, the endocrine function of adipose has been discovered. In addition to adipocytes, adipose tissue contains numerous other cells that are able to produce certain hormones in response to signals from the rest of the organs throughout

the body. Through the actions of these hormones, adipose tissue plays an important role in the regulation of glucose, cholesterol and the metabolism of sex hormones. Prolonged accumulation of adipose tissue leads to overweight and obesity development, both of which are closely associated with a cluster of metabolic diseases, such as dyslipidemia, hypertension, insulin resistance, type 2 diabetes, and atherosclerosis [13,21,29]. Visceral obesity is especially thought as being the risk factor for the development of obesity-related comorbidities. Now at a point of high interest in the medical field, adipose tissue is not only an energy depot, but also secretes nearly more than 600 cytokines termed ‘adipokines’ [12,16]. Human adipokines are involved in numerous metabolic processes, including the regulation of appetite, energy

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expenditure, insulin sensitivity, inflammation and cardiovascular activity, thus, these could be clinically important as a markers of adipose tissue function and increased metabolic risk [3,12,15,35,37]. The search for novel adipokines linking obesity to related co-morbidities has become a major topic in obesity research. Hence, there is an increasing need to define their function, molecular targets and potential clinical relevance as biomarkers or in the treatment of obesity and metabolic diseases.

Omentin (34 kDa) is a recently identified fat deposition-specific adipokine codified by two genes (1 and 2). It is considered to be highly and selectively expressed in visceral omental adipose tissue (AT). Omentin is predominantly expressed in the AT stromal vascular cells, however, it is also expressed in the heart (epicardial fat), lungs, ovary and placenta, but in these organs, the action of omentin have yet to be established. Omentin/intelectin was initially described in intestinal Paneth cells and has been implicated in the gut defensive mechanisms against pathogenic bacteria [32]. Omentin 1 is the major circulating form of omentin and its biological role is still not well known [49]. In vitro studies show that omentin enhances insulin stimulated glucose uptake in human adipocytes. Moreover, it triggers Akt signaling in both the absence and presence of insulin [32,45]. Lowered levels of omentin are seen in overweight or obese subjects, as well as in individuals with impaired glucose regulation or in diabetes type 2 patients, but also new reports demonstrate the implication of omentin in many chronic inflammatory diseases, eg. Crohn's disease, rheumatoid arthritis, as well as diabetes type 1, and its involvement in endothelial functioning [27,28,42,49].

The aim of this study was to show and compare the newest information about omentin and its relationship with obesity, diabetes mellitus (DM), metabolic syndrome (MetS), inflammation, cardiac problems, sex hormones imbalance and cancer.

OMENTIN IN OBESITY, DIABETES AND METABOLIC SYNDROME

One of the primary defects seen in obesity, is the impaired adipose tissue function being reflected by alternations in the serum circulating adipokines. This may link obesity to inflammation, insulin resistance and cardiovascular disease [3,4,12,35].

Most articles published so far have shown an inverse correlation between omentin and obesity. In clinical studies, circulating omentin concentrations have been showed to be decreased in patients with obesity, impaired glucose regulation, diabetes type 1 and 2, as well as in patients with polycystic ovary syndrome. The aforementioned are diseases commonly associated with insulin resistance and obesity [7,10,30,32,33,36]. Additionally, circulating omentin levels were negatively correlated with markers of obesity, among these being: BMI, WHR, HOMA and serum leptin, thus, obesity and possibly leptin, may regulate serum omentin [10,32].

In patients with diagnosed diabetes type 2, as well as impaired glucose tolerance, omentin levels and omental gene expressions were significantly lowered than in healthy

subjects. What is more, a significant increase in serum omentin has been observed after weight loss induced by a hypocaloric diet, and is associated with improvement in insulin sensitivity [20,32]. Regarding anorexia nervosa, levels of omentin were elevated, in comparison to a control and to an obese group. These results might have come about from dieting and excessive physical effort and low estradiol concentration [22]. In a cluster analysis which was oriented for recognition of adipokine, patterns associated with parameters of obesity, glucose metabolism, insulin sensitivity, omentin, progranulin and Nampt (nicotinamide phosphoribosyltransferase or visfatin) were observed, together with significantly higher markers of inflammation. The aforementioned was seen in patients with obesity and insulin resistance, and who were diagnosed DM type 2. In obese individuals with normal glucose metabolism, significant clusters of omentin, HbA1C, resistin and Nampt were observed. This situation suggests that these adipokines may useful indicators in identifying subgroups of obese patients with DM type 2 and with additional disturbances of lipid metabolism [12].

The regulation of omentin secretion in adipose tissue is still not fully understood. According to Tan *et al.* [30], in a study of human omental adipose tissue explants, insulin and glucose decrease the production and expression of omentin mRNA in visceral AT, while hyperinsulinemia strongly reduces the omentin level and secretion into conditioned media. Similarly, prolonged insulin-glucose infusion in healthy subjects gave reduction in circulating omentin. These findings suggest that glucose and insulin, directly or indirectly, regulate the synthesis of omentin. Omentin, in turn, may modulate the metabolism of glucose and insulin sensitivity [22,32,43]. However, further research is needed to clarify the relationship between insulin and omentin.

In the study of Bremer *et al.* [5], serum plasma omentin and subcutaneous adipose tissue were reduced in subjects displaying nascent metabolic syndrome (in individuals without the presence of diabetes and/or cardiovascular disease). In another report focused on analyzing the relationship between omentin circulating levels and components of metabolic syndrome (MetS) in adult patients without diabetes type 2 or cardiovascular disease (CVD), the authors discovered that circulating omentin levels did not differ by metabolic syndrome status nor between men and women. However, men with MetS had significantly lower omentin levels than did men without MetS and women with MetS. It was, hence, postulated that sexual dimorphism in circulating omentin may be a result of differences in the pattern of body fat distribution between men and women, inherent sex differences in adipose tissue gene expression and function, or the impact of sex hormones on omentin regulation [14,18,38,44]. This is in agreement with the work of Luque-Ramirez *et al.* [18], which showed a negative correlation between omentin and free testosterone in normal and overweight subjects. These observations are consistent with situations of androgen excess such as polycystic ovary syndrome, wherein which omentin levels are decreased, and correlate negatively with androgen levels. A study by Vu *et al.* [38], demonstrates that omentin is associated with HDL-C (high density cholesterol), and that sex may

influence patterns of association between omentin levels and components of the MetS phenotype. The physiological mechanisms underlying the relationship between omentin and HDL could be an effect of disturbed insulin signaling and regulation, also altered HDL production, but the underlying problem is thought to be deregulated omentin level and function [38,44]. This finding broadens the role of omentin as an anti-inflammatory adipokine, while the seen association with metabolic indexes (BMI, WHR, HOMA) suggests that higher omentin levels may be looked upon as a marker for leanness or as a positive factor that opposes the obese state and its pathophysiological consequences [14,10,32].

OMENTIN AND INFLAMMATION

Obesity-induced metabolic disturbances is associated with inflammatory status. Expression analysis of macrophage and nonmacrophage cell populations isolated from adipose tissue reveals that adipose tissue macrophages are responsible for almost all of proinflammatory cytokines [21,40]. Moreover, in recent studies, alternations in the function of the innate immune system are often recognized as being an intrinsic link to metabolic pathways [21,25]. In addition, proinflammatory cytokines such as TNF α and IL-6, have been reported to be negatively associated with circulating omentin concentrations [14,21,24,41].

The main findings of cross sectional studies of humans with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT), of the association between circulating omentin and vascular function, indicate that omentin level is associated with obesity-associated metabolic dysfunction, and with proinflammatory markers such as IL-6 and CRP. What is more, it also contributes independently to the variance of endothelium-dependent vasodilation after controls were put in place for adiposity, age and inflammation [21]. The influence of omentin upon endothelium is triggered by the inhibition of ICAM-1 and VACAM-1 expression via the interruption of the NF- κ b signaling pathway and the suppression of adhesion of monocytes to TNF- α activated endothelial cells [14,48]. Such effects and linkages could be a useful marker of endothelial function, as it is associated with endothelial dependent vasodilation, not only in insulin glucose tolerant subjects with systolic blood pressure and BMI disorders, but also in normal glucose tolerant subjects [21].

Moreover, the paucity of omentin may be important in the pathogenesis of transmural intestinal inflammation in Crohn's disease patients, wherein expression of omentin mRNA is decreased [14,26]. Omentin has been also implicated in the gut defensive mechanisms against pathogenic bacteria such as *Escherichia Coli* [14,26]. Reduced omentin concentrations in the synovial fluid of patients with rheumatoid arthritis was also reported [14,28,41,43]. Moreover, it is thought that decreased omentin expression in the omental endothelial cells in subjects with visceral obesity, could reflect the dysfunction of these cells as induced by the obesity-associated proinflammatory state and by oxidative stress [8,21]. Omentin plausibly may have an anti-inflammatory role in several proinflammatory states, and it could

be important in modulating the proinflammatory elements in the visceral AT where it is mainly expressed [32]. However, further study in this matter is required.

OMENTIN AND CORONARY ARTERY DISEASE (CAD)

Low levels of omentin have been observed in patients with cardiovascular disease and endothelial dysfunction [17,38,44]. In the report of Zhong *et al.* [49], omentin levels were also seen to be lower in patients with coronary artery disease and acute coronary syndrome than in controls or in situations of stable angina pectoris. They also found that omentin concentration was independently associated with the prevalence of coronary artery disease (CAD). A possible explanation for this discovery might be the induction by omentin endothelium-dependent relaxation via endothelium-derived NO, through the phosphorylation of eNOS. This has been observed in work involving the isolated aortas of rats [42,49]. Thus, omentin could have a part in CAD development - at least in part through its effect on the regulation of coronary contractility (which is usually already impaired) [34,49]. Not without significance is the influence of omentin on insulin sensitivity. Herein, decreased omentin levels may contribute to development of CAD by modulating insulin action.

OMENTIN AND POLYCYSTIC OVARY SYNDROME (PCOS)

Akbarzadeh *et al.* [1] reported that there is no significant difference in omentin and vaspin plasma level in patients with normal BMI displaying the polycystic ovary syndrome (PCOS), in comparison to non-PCOS patients. However, in the study of Tan *et al.* [30], patients with PCOS had lower omentin levels. Similarly, Mahde *et al.* [19] observed significant decreases in plasma omental adipokines level in obese woman with PCOS, when compared to a control group. The differences in BMI between obese PCOS patients and non-obese patients provides an explanation for the discrepancy between the study results. Adipokine changes in PCOS are rather the consequences of fat cell accumulation, but not the direct effect of PCOS itself in obese PCOS [1]. Additionally, Tan *et al.* [31], in his next study, reported that in PCOS patients, changes in CRP were predictive for fluctuations in circulating omentin levels after metformin treatment. This is further evidence of the relationship of omentin to an inflammatory status.

OMENTIN AND END STAGE RENAL DISEASE (ESRD)

Regarding, chronic renal disease, atherosclerosis, inflammation and raised cardiovascular risk in this group of patients is predicted by a rise in the number of certain biomolecules. There is not a lot of data, but in some of such studies, end stage hemodialysis patients evidence higher levels of omentin than do controls. This situation seems to be quite controversial [2], and it requires further investigation.

OMENTIN AND CANCER

Obese individuals are known to be at higher risk of developing gastrointestinal cancers than are normal weight individuals. Indeed, according to the International Agency for Cancer and Research (IACR), there is sufficient evidence to state that there is a causal link between situations of being overweight and obese, and being afflicted with cancer of the colon. However, the basic mechanism of this relationship is still incompletely uncovered [6,11]. Adipocytokines are protein factors that demonstrate a number of important systemic complex interactions and an influence upon a large number of diverse organ systems. Studies show that circulating visfatin and omentin levels differed significantly between patients with colorectal cancer (CRC) and controls [11]. In such work, a decrease in level of adiponectin was recognized as a strong risk factor for early colorectal cancer [11,23]. Omentin, a newly identified adipocytokine in human adipose tissue, is inversely related to degree of obesity, and is down regulated by insulin and glucose level. It has been realized that omentin enhances Akt phosphorylation/activation in the absence of insulin [11,39], and a novel understanding of the role played by omentin in angiogenesis through the Akt signaling pathway has been advanced [31,32]. Moreover, Akt signaling is now believed to play a crucial role in carcinogenicity. There is sufficient evidence that the PI3K/Akt-Nos Ras pathway may be also be involved in colorectal cancer-tumor development. Since omentin enhances Akt phosphorylation/activation, it can be hypothesized that omentin, by promoting the activation of the Akt signaling pathway, and, in turn, modulating eNOS, may contribute towards the pathogenesis of CRC [11,32,45].

Beyond the aforementioned, an association between prostate cancer and anthropometric measures, such as adiposity and body mass index (BMI), has been reported. This work implies that obesity or being overweight carries a significant risk for becoming afflicted with prostate cancer. It is now thought that factors including insulin, IGF-1, and adipocytokine levels may play significant roles in the association of prostate cancer with obesity and other malignancies. Such work has revealed that omentin level was found to be statistically higher in patients with prostate cancer, but without association between the omentin and Gleason score of PCa (prostate cancer). This result suggests that increased body weight could be a factor in the etiology of PCa [9,36].

Zhang and Zou [46] have reported that omentin promotes apoptosis in hepatocellular carcinoma cells, and they have argued that omentin could be a candidate anticancer agent. Their study incorporated 69 colon cancer patients in whom their obesity was believed to play a significant role in the etiology. The work of Zhang and Zou demonstrated that significantly higher levels of omentin are seen in colon cancer patients than a control population [11]. Similarly, Uyeturk *et al.* [36], in a study of PCa patients, observed significantly higher omentin levels, but without any relationship with the aggressiveness of the cancer. Omentin known to be over-expressed in malignant pleural mesothelioma, whereas it is consistently present in ovarian carcinoma, human hepatocellular carcinoma, colon and gastric cancers. Hence, omentin

levels are thought to have potential screening and therapeutic implications [14,47].

SUMMARY

In summary, plasma omentin is a very interesting adipokine with multiple interactions. Research has revealed that its level is inversely related to degree of obesity, and correlates negatively with BMI, leptin, WHR and HOMA, while it correlates positively with HDL and adiponectin. Furthermore, an increase of omentin concentration runs in parallel with an increase in insulin sensitivity [7,14,20]. In addition, an association with named metabolic indexes may suggest that the elevation of omentin level may be seen as a marker for leanness. Omentin also plays an inhibitory role on the inflammatory state of vascular endothelial cells and may be associated with coronary artery disease [43,49]. These findings may have important implications for the pathophysiology and therapy of CAD. Due to such findings, there is an emerging necessity to perform wide-scale in vivo and in vitro studies to elucidate the various roles of omentin, not only in cardiovascular disease development, but also in cancer, renal, ovary, as well as inflammatory diseases. Finally, its potential therapeutic role for cardiovascular complications of obesity, and the identification of omentin receptors, are worthy of future study.

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