The relation of omentin gene expression and glucose homeostasis of visceral and subcutaneous adipose tissues in non-diabetic adults

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Received: 13 March 2021 / Accepted: 18 October 2021 / Published online: 5 November 2021 © The Author(s), under exclusive licence to Springer Nature B.V. 2021

Abstract

Background Adipose tissue (AT) is a passive reservoir for energy storage and an active endocrine organ responsible for synthesizing bioactive molecules called adipokines. Omentin is known as an anti-inflammatory adipokine that can modulate insulin sensitivity. The present study aimed to investigate the relationship between omentin mRNA expression and glucose homeostasis of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in non-diabetic adults.

Methods VAT and SAT adipose tissues were collected from 137 adults aged ≥ 18 years hospitalized for abdominal surgery. Before surgery, preoperative blood samples were taken from the participants to measure fasting plasma glucose, insulin, and triglyceride. BMI, HOMA-IR, HOMA-B, and QUICKI were calculated. Insulin levels were measured with Mercodia kits using enzyme-linked immunosorbent assay (ELISA). In order to obtain omentin mRNA expression, real-time PCR was performed.

Results Overall, 91 (66.4%) subjects were healthy [without insulin resistance (IR)], and 46 (33.6%) participants were with IR. In healthy and IR subjects, omentin gene expression was 1.04 and 2.32, respectively in VAT, and 3.06 and 1.30, respectively, in SAT (P > 0.05). After controlling for age and BMI, linear regression analysis indicated a significant positive association of SAT omentin expression with insulin concentration (β = 0.048; 95% CI 0.009, 0.088, P = 0.017) and HOMA-IR (β = 0.173; 95% CI 0.023, 0.323, P = 0.014). Moreover, a negative association of SAT omentin expression with HOMA-B (β = − 0.001; 95% CI 0.002, − 0.001, P < 0.001) was observed.

Conclusion This study's finding confirms a direct association between IR with omentin mRNA levels in SAT. Besides, the indicator of insulin sensitivity had an inverse association with omentin gene expression in SAT. This aspect of research suggests that omentin secretion from SAT has a strong link with insulin regulation.

Keywords Omentin expression · Adipose tissues · Glucose homeostasis · Insulin resistance

Abbreviations

AT  Adipose tissue
VAT  Visceral adipose tissue
SAT  Subcutaneous adipose tissue
WAT  White adipose tissue
BAT  Brown adipose tissue
BMI  Body mass index
PCR  Polymerase chain reaction
CT  Threshold cycle
NF-κB  Nuclear factor-Kb

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Introduction

Adipose tissue (AT) is considered an active endocrine organ due to its role in the body’s homeostasis by secretion of bioactive mediators called adipokines with endocrine, paracrine hormonal functions [1]. It has also been well shown that these bioactive mediators derived from fat cells play a vital role in insulin and energy homeostasis [2]. There are two types of AT in mammals: white adipose tissue (WAT) and brown adipose tissue (BAT). White adipose tissue is classified into two groups: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) [3]. Excessive fat alters AT metabolism and endocrine function, contributing to adipokine levels, affecting insulin sensitivity and regulating energy homeostasis throughout the body [4].

The increased abdominal fat causes the secretion of inflammatory activating peptides, or adiponectin, from adipose tissue [5, 6]. These adipokines have critical effects on glucose and lipid metabolism [7], insulin resistance (IR), diabetes, and so on [8]. Nowadays, novel adipokines related to AT are important research topics. There are various types of adipokines, including adiponectin, resistin, leptin, visfatin, TNFα, and IL-6 [9–11].

Yang et al. [12] initially investigated the Omentin gene from the VAT cDNA library [12]. Omentin is a secretory protein with 313 amino acids mainly expressed in VAT adipose tissue. This protein, also known as the most potent anti-inflammatory adipokine, acts as a modulator of glucose metabolism by increasing insulin-mediated glucose uptake and stimulating human body fat [12]. Indeed, omentin can increase VAT insulin sensitivity and glucose metabolism through the paracrine and endocrine manner in which protein kinase (Akt/protein kinase B) is activated, thereby increasing insulin signal transduction [13, 14]. This signal is derived from fat cells that directly bind to adiponectin, acting as an insulin sensitizer [15]. Omentin can accelerate insulin-mediated glucose transport and does not affect basal glucose transport [12]. Removal of VAT instead of the SAT has been shown to improve insulin sensitivity [16]. Hence, the focus of studies on the omentin gene expression in AT as the primary source of omentin biosynthesis can be warranted.

Thus far, numerous studies have shown down-regulation of omentin in obesity, type 2 diabetes mellitus (T2DM), and IR [17–21]. A previous study on patients with impaired glucose regulation (IGR), newly diagnosed and untreated T2DM patients, and subjects with normal glucose tolerance (NGT), revealed that omentin levels were adversely correlated with BMI, HOMA-IR, fasting insulin, TNF-α, and IL-6. Moreover, plasma glucose, HOMA-IR, and BMI were independent related factors that influenced serum omentin levels, which was decreased in IGR subjects [19]. Data from another study showed a high expression of omentin mRNA in VAT. On the other hand, the expression of omentin mRNA was decremented in individuals who were obese as well as in a combination of obese/T2D [22].

A few studies evaluate the expression of omentin within VAT and SAT in non-diabetic patients with IR. Hence, this study attempts to examine the expression of the omentin gene expression in VAT and SAT of non-diabetic adults and then compares its expression with glucose homeostasis.

Materials and methods

Study population

This cross-sectional study enrolled 137 adults aged 18–84 years who were hospitalized for abdominal surgery. Participants were divided into two groups according to their IR status, subjects with IR (n = 46) and healthy (n = 91). Participants who had cancer, diabetes mellitus, or received fat-reducing, anti-obesity, and blood sugar drugs were excluded. Moreover, individuals with pregnancy and lactation or hospitalization less than two days before surgery were also excluded.

People's general characteristics, including sex, age, medical history, and history of drug use (hypoglycemic drugs, lipid-lowering drugs, hypertension drugs, heart drugs, hormonal drugs, supplements), were asked and recorded.

Blood samples, anthropometric information, and demographic characteristics were obtained before surgery. About 100 mg of VAT and SAT was also collected during surgery.

Measurement of anthropometric parameters and blood pressure

As described previously, participants' weight, height, and blood pressure were assessed [23, 24]. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m²).
Assessment of Biochemical and glucose homeostasis

Preoperative and fasting venous blood samples were taken from the participants and poured into potassium-EDTA tubes. Fasting plasma glucose (FPG) was measured by the enzymatic method of glucose oxidase. The enzyme colorimetric method with glycerol phosphate oxidase was also used to measure triglycerides (TGs). FPG and TGs were measured using commercial kits (Pars Azmoon Inc., Tehran, Iran). Using enzyme-linked immunosorbent assay (ELISA), insulin levels were measured with Mercodia kits (Uppsala, Sweden) using enzyme-linked immunosorbent assay (ELISA). The intra- and inter-test CVs were 1.7 and 2.3%, respectively.

RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)

Both adipose tissues were isolated by biopsy and collected in RNAlater solution. After transfer to the laboratory, the RNA extraction and quantification were performed using the TRIzol reagent (Invitrogen U.S Cat. No. 15596–026) according to the manufacturer’s protocol. Total RNA purity and quantity were evaluated by NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, USA), and the absorption ratio (260/280 nm) of all samples were within an acceptable range. In order to eliminate genomic traces and increase purity, total RNA was treated with DNase I before the synthesis of complementary DNA (cDNA). The cDNA synthesis kit (BioFact, Korea) was used according to the manufacturer’s protocol. GAPDH gene was also used as a reference gene to normalize omentin gene expression. The sequence of primers is shown in Table 1, which was provided by Nosrati-Oskouie et al. previously [25].

The Quantitative Reverse Transcripase-PCR (qRT-PCR) amplification was performed in a 20 μl reaction volume by the SYBR Green master mix (Biofact, South Korea) was done using the Rotor-Gene 6000 device (R Corbett Research, Sydney, Australia). The following thermal cycling included initial denaturation (5 min at 95 °C), followed by 45 cycles of 30 s at 95 °C, 30 s at 60 °C, and 30 s at 72 °C. For each gene, samples were run in duplicate for inter-assay control with the GAPDH reference gene and the non-template control (NTC). Relative expression of the omentin gene in each sample calculated by the 2−ΔCT method based on its threshold cycle (Ct), the reference gene was used to normalize CT [26]. All qPCR laboratory steps were written according to the MIQE guidelines [27].

We used the following formulas to calculate HOMA-IR, HOMA-B, and QUICKI:

HOMA-IR = \(\frac{\text{fasting insulin} \mu\text{U/mL}}{} \text{fasting glucose mmol/1))}/22\). HOMA-IR stands for the evaluation of the homeostatic model of IR.

Participants with HOMA-IR ≥ 3.2 were categorized in the IR group.

HOMA-B = \(\times\text{fasting insulin} \mu\text{U/mL/fasting glucose (mmol/ml)} - 3.5\). HOMA-B stands for insulin sensitivity.

QUICKI = \(1/(\log[\text{fasting insulin} \mu\text{U/l}]\log[\text{fasting glucose mg/dl}] + \log [\text{fasting glucose mg/dl}]\)). QUICKI stands for quantitative insulin sensitivity check index.

RNA later solution was removed, and samples were placed in liquid nitrogen and then stored at -80 °C. We extracted total RNA from both adipose tissues using the TRIzol reagent (Invitrogen U.S Cat. No. 15596–026) according to the manufacturer’s protocol. The quantity and purity of RNA were evaluated by NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, USA), and the absorption ratio (260/280 nm) of all samples were within an acceptable range. In order to eliminate genomic traces and increase purity, total RNA was treated with DNase I before the synthesis of complementary DNA (cDNA). The cDNA synthesis kit (BioFact, Korea) was used according to the manufacturer’s protocol. GAPDH gene was also used as a reference gene to normalize omentin gene expression. The sequence of primers is shown in Table 1, which was provided by Nosrati-Oskouie et al. previously [25].

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HOMA-B = \(\times\text{fasting insulin} \mu\text{U/mL/fasting glucose (mmol/ml)} - 3.5\). HOMA-B stands for insulin sensitivity.

QUICKI = \(1/(\log[\text{fasting insulin} \mu\text{U/l}]\log[\text{fasting glucose mg/dl}] + \log [\text{fasting glucose mg/dl}]\)). QUICKI stands for quantitative insulin sensitivity check index.

Table 1 Sequences and information of Omentin and GAPDH primers for PCR reaction

| Genes    | Primers’ sequences 5′–3′ | Length | Tm    | GC%  | product length (pb) |
|----------|--------------------------|--------|-------|------|---------------------|
| Omentin  | F: AGGAGCTCTCTGTACCCAAG  | 20     | 58.14 | 55   | 119                 |
|          | R: TAGCTCATCTGTACCCATC  | 21     | 56.05 | 47.62|                     |
| GAPDH    | F: CTGCTCTCTCTGTACGCAGT  | 21     | 61.76 | 57.14| 100                 |
|          | R: CGGTGACTCCGCACCTGCAC | 20     | 60.67 | 60   |                     |

Statistical analysis

The normal distribution of variables was evaluated by histogram and Kolmogorov–Smirnov test. Data analysis was carried out by Statistical Package for Social Sciences software (SPSS) (Chicago IL. Ver. 15). P < 0.05 was considered statistically significant. Continuous variables were reported as mean ± standard deviation (SD). As plasma TGs and insulin were skewed, we reported median and inter-quartile ranges. T-test and \(\chi^2\) tests were used to compare demographic data, anthropometrical, and plasma biochemical parameters.
between IR and healthy subjects. Linear regression was performed to determine the association of glucose homeostasis and omentin expression in VAT and SAT, and standardized β (STZβ), after adjusting for BMI and sex.

**Results**

**Study participants**

In IR and healthy subjects, the mean (SD) age of participants were 36.2(10.8) and 43.1(14.1) years, respectively. As presented in Table 2, participants with IR were younger than healthy groups (P = 0.001). It is apparent from this table that BMI, insulin, TG, and FPG concentration in IR subjects were significantly higher when compared with healthy ones (P < 0.05).

**Omentin gene expression in VAT and SAT**

From the data in Fig. 1, we can see that VAT omentin mRNA expression has increased in IR compared to healthy individuals. Further, a slight decrease in the expression of omentin in SAT was observed. However, these differences were marginally significant.

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**Table 2** Demographic, anthropometric and serum biochemical parameters of the studied population

| Variables          | Healthy (n=91) | Insulin resistance (n=46) | P value |
|--------------------|----------------|---------------------------|---------|
| Age (years)        | 43.1±14.1      | 36.2±10.8                 | <0.001  |
| Female (%)         | 73.8           | 77.8                      | 0.637   |
| Body mass index (Kg/m²) | 33.6±10.5     | 40.1±8.4                  | <0.001  |
| Insulin (µU/mL)    | 5.7 (3.0–9.3)  | 23.5 (20.2–28.0)          | <0.001  |
| Triglycerides(mg/dl) | 84.5 (66.0–144.5) | 119.5 (80.5–155.8)     | 0.020   |
| Fasting plasma glucose (mg/dL) | 83.7±16.2 | 99.7±21.4                  | <0.001  |
| HOMA-IR            | 1.3±0.8        | 6.2±3.2                   | <0.001  |
| HOMA-B             | 85.5 (39.4–141.9) | 251.5 (198.1–382.1)      | 0.764   |
| QUIKI              | 0.16±0.2       | 0.13±0.0                  | <0.001  |

**Table 3** Association between Omentin gene expression in VAT and SAT and glucose homeostasis

| Visceral | Insulin resistance | P value | Subcutaneous | Insulin resistance | P value |
|----------|--------------------|---------|--------------|--------------------|---------|
| β (95% CI)| STZ β              |         | β (95% CI)   | STZ β              |         |
| Fasting plasma glucose | 0.023 (−0.003, 0.049) | 0.139 | 0.077 | −0.002 (−0.024, 0.021) | −0.011 | 0.891 |
| Insulin   | −0.033 (−0.080, 0.014) | −0.115 | 0.171 | 0.048 (0.009, 0.088) | 0.200 | 0.017 |
| HOMA-IR   | −0.083 (−0.259, 0.094) | −0.076 | 0.356 | 0.173 (0.023, 0.323) | 0.287 | 0.014 |
| HOMA-B    | −0.000 (−0.001, 0.001) | −0.003 | 0.974 | −0.001 (0.002, −0.001) | −0.436 | <0.001 |
| QUICKI    | 15.82 (−6.57, 38.22) | 0.129 | 0.165 | −7.47 (−26.79, 11.85) | −0.071 | 0.446 |

Adjusted for sex and body mass index
Omentin gene expression status and glucose homeostasis

The β coefficient for the relationship between omentin gene expression and glucose homeostasis parameter are presented in Table 3. After controlling for sex and BMI, linear regression analysis indicated a significant positive association of omentin gene expression in SAT with insulin concentration (β = 0.048; 95% CI: 0.009, 0.088, P = 0.017). There was also a significant positive correlation between omentin mRNA levels and HOMA-IR (β = 0.173; 95% CI: 0.023, 0.323, P = 0.014). However, in SAT, omentin gene expression was negatively associated with HOMA-B (β = -0.001; 95% CI: 0.002, -0.001, P < 0.001). Glucose homeostasis indices had no significant association with VAT omentin gene expression.

Discussion

Omentin is a novel anti-inflammatory adipokine with insulin-sensitive effects related to obesity, IR, and T2D. Indeed, omentin is a secretory factor that can increase insulin sensitivity through Akt protein kinase B in visceral and subcutaneous adiposity, thereby increasing glucose uptake in human adipocytes via the GLUT4 carrier and glucose metabolism [12]. In addition, increasing insulin sensitivity, which is modulated by omentin, TNF-α, one of the IR stimulators, can be suppressed by activating NF-κB cells [28, 29]. Further, omentin up-regulates the expression of adiponectin, which can induce insulin sensitivity [29], which seems to provide a better predictor of IR in obese individuals [30].

Seeking to find the expression of omentin in adipose tissues such as VAT and SAT and its relation with glucose hemostasis may help find novel therapeutic strategies for patients with IR. The present study was designed to determine the omentin mRNA level in adipose tissues of patients with IR compared to healthy subjects. The results of this study indicated a slight increase and decrease of mRNA expression in VAT and SAT, respectively, in patients with IR compared to healthy subjects, which was not statistically significant. Moreover, it is interesting to note that a direct association was found between insulin concentration and HOMA-IR with omentin gene expression in SAT. In contrast, HOMA-B (the indicator of insulin sensitivity) had an inverse association with omentin expression in SAT.

Commonly, it has been argued that omentin, directly and indirectly, has a connection with IR. Some studies have revealed that omentin levels were reduced in patients with impaired glucose tolerance and obesity [15, 19]. Indeed, the findings of our study can support the previous reports.

A growing number of studies examining omentin have generated contradictory findings. In an investigation, Tan et al. found that plasma omentin-1 levels, omentin-1 mRNA, and protein expression in VAT of overweight women with PCOS were decremented than healthy subjects. Furthermore, they showed that insulin and glucose substantially dose-dependently led to decreased omentin-1 mRNA expression and protein levels. Therefore, it is suggested that insulin and glucose are directly or indirectly involved in omentin regulation [20].

Our previous study indicated a significant lower omentin gene expression in VAT of obese participants compared to non-obese ones; while, no difference was found in SAT [31]. Additionally, in evaluating the association between plasma fatty acids, pattern and omentin mRNA levels in adipose tissues of adults aged ≥ 18 years, no significant difference in omentin gene expression between SAT and VAT was found [25]. Run-Ce Cai et al. indicated high expression of omentin mRNA level in omental adipose tissue and low level of it in the overweight/obese individuals and decreased further when overweight/obesity was combined with T2D in patients with benign diseases undergoing the selective abdominal operation. Moreover, they showed that omentin expression was positively correlated to serum omentin level, obese indexes, IR, and lipid metabolism parameters [22]. Besides, in contrast to the current findings, some studies on children demonstrated a significant reduction of serum omentin-1 concentration in obese subjects compared to controls (non-obese ones) and in obese with metabolic syndrome cases compared to controls (obese without metabolic syndrome) [32, 33]. There are two possible explanations for this difference; first, these studies were conducted on overweight and obese subjects, but our study was based on two groups: IR and insulin-sensitive as a healthy group. Second, different antibody affinities in test kits can justify inequalities.

Several studies supported the role of omentin in insulin sensitivity [15, 20]. In a systematic review by As Habi A. et al., among available observational studies, serum omentin level was significantly lower in T2DM and impaired glucose tolerance (IGT) in adolescent and adult populations, but not in T1DM ones [34]. However, according to the Hossein-Nezhad. study, no significant relation was observed between circulating omentin-1 with fasting insulin and IR [35], but it was associated with visceral obesity, which is also in contrast with our findings.

Although the exact mechanisms of omentin in stimulating insulin sensitivity are uncertain, studies suggested that omentin may oppose the effect of proteases that are overexpressed in IR states. According to reports, omentin plasma levels were reduced in obese subjects, diabetic patients, and people with chronic inflammatory diseases compared to healthy ones [5, 18, 36, 37]. Moreover, a negative correlation was observed between plasma omentin levels and anthropometric indices, including BMI and waist circumference, fasting insulin and HOMA. Likewise, we have found an inverse association between omentin mRNA levels and HOMA-B. Decreased omentin gene expression may contribute to the underlying pathophysiology of IR syndrome, and regulation of omentin-1 production in adipose tissue is probably multifactorial.
Aliasghari F. et al. suggested that omentin levels might reduce in patients with non-alcoholic fatty liver disease (NAFLD), while there was evidence of increased levels of omentin in patients with NAFLD [38, 39]. Furthermore, increased omentin levels had a strong link with the glucose pathway by stimulating phosphorylation of Akt in muscle tissue of Wistar rats and with IL-6 in serum, suggesting that omentin is likely to have anti-inflammatory and protective action in experimental diabetes [40]. Moreover, studies showed that mRNA and protein expression of omentin was higher in epicardial (EAT) adipose tissue when compared to paired SAT in patients with coronary heart disease (CHD) and coronary atherosclerosis (CAD) [41, 42]. Besides, omentin-1 mRNA levels in EAT of patients with CHD had an inverse correlation with anthropometric features such as BMI and waist circumference [42]. It seems omentin-1 gene expression is more active in EAT than subcutaneous fat and CAD, which could be considered an independent predictor of mRNA expression and serum levels of omentin-1.

In accordance with previous studies, omentin seems to be independent of SAT but more associated with VAT [12, 28] because VAT is the most abundant source of secretory omentin [12]. Although omentin is secreted by visceral fat, it is decreased in obese cases and related metabolic risks such as IR and glucose intolerance [15]. However, our results advocate some earlier studies regarding the differences in the expression of omentin in VAT and SAT, but the relation of omentin expression in SAT of IR subjects and glucose hemostasis was more noticeable compared with VAT of cases with IR. Therefore, it is likely that such connections exist between omentin expression in SAT and insulin regulation rather than its expression in VAT.

We had some limitations in our study as follows: we used samples from patients who had already been admitted to the hospital for surgery instead of using a random sampling method for patient selection, and the nature of the cross-sectional design used in this study had no basis to prove causation, allowing for conclusions only regarding the association between the factors analyzed.

Conclusion

This cross-sectional study extends our knowledge of omentin gene expression in adipose tissues and its relation with glucose hemostasis, confirming previous findings and contributing additional evidence suggesting that glucose hemostasis may strongly associate omentin mRNA levels in SAT. Given the beneficial properties of this adipokine and its protective role in preventing IR and inflammation, a future comprehensive study can determine whether these associations are causal and the mechanisms underlying omentin expression in SAT and IR.

Acknowledgements We would like to thank the hospital staff, study assistants, and coordinators that took part in this research.

Authors’ contributions A.D., M.Z. and EY conceptualized and designed the study, analyzed and interpreted the data, prepared the manuscript and approved the final manuscript as submitted. G.A. and P.M. entered data, drafted the initial manuscript, and approved the final manuscript as submitted. R.A. and M.H. critically revised the manuscript and approved the final manuscript as submitted. S.M.F drafted the initial manuscript and approved the final manuscript as submitted. A.Kh. biopsied the patients during the abdominal surgery and approved the final manuscript as submitted.

Funding Not applicable.

Declarations

Conflict of interest The authors declare they have no conflict of interest.

Ethical approval The study’s protocol was approved by the Research Institute for Endocrine Sciences (RIES) of Shahid Beheshti University of Medical Sciences (NO: IR.SBMU.ENDOCRINE.REC.1395.279), and the study was conducted in accordance with the Declaration of Helsinki and RIES institutional guidelines. All participants consciously signed the written consent form approved by the committee.

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