Changes of serum omentin-1 levels in normal subjects, type 2 diabetes and type 2 diabetes with overweight and obesity in Chinese adults

Variations du taux sérique d’omentine-1 chez les sujets normaux et les diabétiques de type 1 avec ou sans surpoids dans une population chinoise adulte

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Abstract

Purpose. – Omentin-1 has been identified as interesting novel adipokines that may modulate insulin action. Its exact biological function is unclear. The aim of this study is to assay the levels of serum omentin-1 in normal subjects and type 2 diabetes mellitus (T2DM) with normal weight, overweight and obesity and to analyze the relationship between serum omentin-1 levels with body mass index (BMI), waist to hip ratio (WHR), glycosylated hemoglobin (HbA1c), plasma glucose, insulin resistance index (HOMA-IR) and serum lipid levels.

Methods. – There are eighty newly diagnosed type 2 diabetes patients, thirty-five type 2 diabetes patients with normal weight, twenty-nine type 2 diabetes patients with overweight, sixteen type 2 diabetes patients with obesity, and forty healthy control subjects were enrolled in this study. The levels of plasma glucose at fasting and 2-hour postprandial blood glucose and fasting serum levels of insulin, omentin-1 and HbA1c were measured. HOMA-IR was calculated.

Results. – Serum omentin-1 levels were found to be significantly decreased in type 2 diabetes patients with normal weight (821.16 ± 312.50 ng/L), in type 2 diabetes patients with overweight (748.00 ± 322.51 ng/L), and in type 2 diabetes patients with obesity (530.44 ± 357.35 ng/L) compared with healthy control subjects (994.71 ± 435.90 ng/L) at P < 0.05. The level of serum omentin-1 was negatively correlated to BMI, HOMA-IR, WHR, fasting insulin (FINS), fasting plasma glucose (FPG), 2-hour postprandial blood glucose (2HPG), triglycerides (TG), and positively correlated to high-density lipoprotein (HDL). BMI was independent related factor that influenced the levels of serum omentin-1.

Conclusion. – Decreased omentin-1 levels may contribute to the development of insulin resistance, T2DM and particularly to obesity in Chinese adults, however, its role in these diseases needs to be fully elucidated.

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Keywords: Omentin; Adipokines; Insulin and diabetes

Résumé

Objectif. – L’omentine-1 a été identifiée comme une nouvelle adipokine qui pourrait moduler l’activité de l’insuline par un mécanisme moléculaire inconnu. L’objectif de cette étude est de mesurer la concentration d’omentine-1 dans le sérum de sujets contrôles et de patients diabétiques de type 1 avec ou sans surpoids et de rechercher une association entre les taux d’omentine-1 sérique avec l’index de masse grasse (IMC), le rapport taille sur hanche (T/H), l’hémoglobine glyquée (HbA1C), la glycémie et l’insulinémie à jeun, l’index HOMA pour évaluer la résistance à l’insuline, et le taux de lipides. Méthodes. – Pour cette étude nous avons recruté 80 nouveaux cas de diabète de type 2 avec surpoids, et 60 nouveaux cas sans surpoids ainsi que 40 sujets en bonne santé. L’omentine-1, l’HbA1C, la glycémie et l’insulinémie à jeun ont été mesurés. Résultats. – La concentration d’omentine-1 était significativement (p = 0.05) abaissée chez les patients diabétiques avec poids normal (821,16 ± 312,50 ng/L) ou avec surpoids (748,00 ± 322,51 ng/L) en comparaison des contrôles sains (994,71 ± 435,90 ng/L).

Abbreviations: BMI, Body mass index; FINS, Fasting insulin; FPG, Fasting plasma glucose; HbA1c, Glycosylated hemoglobin; HDL-c, High-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; 2HPG, 2-hour postprandial blood glucose; LDL-c, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglyceride; WHR, Waist to hip ratio.

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patients with newly diagnosed and untreated Type 2 diabetes, that subjects with impaired glucose regulation, as well as omentin-1 and omentin-2. The former is the major circu-
lation, it is known that it is exclusively secreted from stromal vascular cells of visceral adipose tissue [10,11]. The omentin gene is located in the 1q22–q23 chromosomal region, which has been linked to Type 2 diabetes in different populations [12–14]. There are two highly homologous isoforms of omentin, omentin-1 and omentin-2. The former is the major circu-
lating form in human blood [15]. Recently, it was found that subjects with impaired glucose regulation, as well as patients with newly diagnosed and untreated Type 2 diabetes, showed a decrease in serum omentin-1 level [16]. The bio-
logical activity of omentin is not well understood. Recent studies showed that omentin-1 plasma levels are lower in type 1 and type 2 diabetes patients [17]. Lean subjects had significantly higher plasma omentin 1 levels than obese and overweight subjects. Plasma omentin 1 levels were inversely correlated with BMI, waist circumference, leptin levels, and insulin resistance as measured by homeostasis model assessment and positively correlated with adiponectin and HDL levels. In addition, higher plasma omentin 1 levels were detected in women compared with men [15,18]. Omentin gene expression are correlated negatively with obesity and insulin resistance and correlated positively with adiponectin and HDL levels [19]. There is a lot of study about omentin-1 with dia-
betes and obesity, but it is not known the change of serum omentin-1 levels in type 2 diabetes patients with abnormal weight. The aim of our study was to determine the serum omentin-1 levels in normal subjects and type 2 diabetes patients with normal weight, overweight and obesity and to analyze the relationship between serum omentin-1 levels with BMI, WHR, HbA1c, plasma glucose, HOMA-IR and serum lipid levels.

1. Introduction

Obesity is an emerging health hazard and contributes to the increased morbidity and mortality worldwide [1]. Increased abdominal/visceral fat is associated with insulin resistance, type 2 diabetes mellitus and cardiovascular complications [2]. A variety of adipokines, including leptin, adiponectin, visfatin, TNF alpha, and IL-6 [3,4] have widespread effects on carbo-
hydrate and lipid metabolism and appear to play an important role in the pathogenesis of insulin resistance, diabetes, obesity, atherosclerosis, vascular endothelial dysfunction, and inflam-
mation [5–9].

Omentin (intelectin, intestinal lactoferin receptor, endothel-
lian lectin HL-1, galactofuranose-binding lectin) is a novel fat depot-specific secretory factor that was identified from a cDNA library from human omental adipose tissue. In addi-
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2. Subjects and methods

2.1. Study population

One hundred and twenty participants (62 men and 58 women, age range 39–89 and 40–86; mean 67.45 and 65.12, respectively) were recruited from the inpatient and outpatient Endocrinology Department in the Yueyang Integrated Traditional Chinese and Western Medicine Hospital of Shanghai University of Traditional Chinese Medicine from March 2011 to May 2012. The control subjects did not have any health problems and were not receiving any medications or dietary supplements. All type 2 diabetic mellitus were newly diagnosed patients. Subjects were classified into four groups: 40 healthy control subjects, 35 type 2 diabetes mellitus with normal weight (BMI < 25 kg/m2), 29 type 2 diabetes mellitus with overweight (25 ≤ BMI < 30 kg/m2), 16 type 2 diabetes mellitus with obesity (BMI ≥ 30 kg/m2). Diag-
oses were based on the diagnostic criteria of World Health Organization (WHO) 1999 [20]. The following exclusion criteria were used for all subjects: having type 1 diabetes, renal or hepatic diseases, acute or chronic inflammatory diseases, cancer, thyroid dysfunction, acute or chronic infection, any haemat-
ologic disorders, the presence of hepatitis C, alcohol or drug abuse; female subjects taking hormonal replacement therapy were also excluded. This study was approved by the Clinical Research Ethics Committee of Shanghai University of Traditional Chinese Medicine, and complied with the Declaration of Helsinki. Informed consent was obtained from each participant.

2.2. Blood sampling

All blood samples were drawn after overnight fasting. Sam-
ple were divided into two aliquots: the first part was collected in Vacutainer tubes (BD Diagnostics, Franklin Lakes, NJ, USA) containing disodium salt (Na2)-EDTA for the assay of HbA1c (mmol/mol and %); the second aliquot of blood was collected in plain Vacutainer tubes for serum preparation used for lipid pro-
file, fasting blood glucose level, insulin, liver enzymes, detection of omentin-1. Thus, serum samples were divided into several aliquots and kept at –80°C for subsequent assay.

2.3. Clinical and biochemical measurements

All subjects were screened with regard to medical history (i.e., date of birth, smoking, alcohol consumption, and medi-
cal treatments). Height and weight (with light-weight clothing and without shoes), waist and hip circumferences and seated
blood pressure were determined by the same observer. BMI was calculated as weight (kg) divided by the square of height (m). WHR was calculated waist to hip ratio. Plasma glucose was measured by the glucose-oxidase method. HbA1c was determined using an automated high performance liquid chromatography (HPLC) method (Bio-Rad Variant II, America). Total serum cholesterol (TC) was measured through the reaction of cholesterol esterase/cholesterol oxidase/peroxidase, using a Hitachi 747. high-density lipoprotein cholesterol (HDL-c) was quantified after precipitation with polyethylene glycol at room temperature. Low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald formula. Total serum triglycerides (TG) were measured through the reaction of glycerol/phosphate/oxidase and peroxidase. Serum omentin-1 concentrations were measured using manual omentin-1 (human) detection set (Elisa) (JRDUN Biotechnology (shanghai) Co., Ltd, China). The intra-assay coefficients of variation were 4.7%; inter-assay coefficients of variation were 6.8%. The detection limit of the assay ranged 20 to 800ng/L. The antibodies used in this kit are specific to measurement of natural and recombinant human omentin-1. Insulin levels were assessed using a commercially available chemical luminescence method kit (Siemens Healthcare Diagnostics Inc., USA). A homeostasis model assessment of insulin resistance (HOMA-IR) described by Matthews et al. [21] was used with HOMA-IR index = fasting insulin (mU/mL) × fasting glucose (mmol/L)/22.5.

2.4. Statistical analysis

The IBM statistical package for social sciences (SPSS) statistics version 19.0 (IBM Corp., Chicago, IL, USA) was used for data analysis. Data are presented as means ± SD. Before analysis, data were tested for normality of distribution using the Shapiro–Wilks test. Comparison between two independent mean groups for parametric data was performed using Student’s t-test. However, comparison between two independent groups for non-parametric data was carried out using the Wilcoxon rank-sum test. More than two groups were compared by Anova using least significant difference as a post hoc test to compare individual groups. Any skewed data were further analysed by Kruskal–Wallis and Mann–Whitney U-test. Multiple stepwise regression analysis was performed to determine significant confounding factors for serum omentin-1 levels. Finally, the ranked Spearman correlation test was performed to study the possible association between two variables for non-parametric data. P-value less than 0.05 was considered statistically significant.

3. Results

The characteristics of our study subjects are given in Table 1. Age, gender, distributions were similar among the four groups. The levels of fasting plasma glucose (FPG), postprandial 2 hour glucose (2 hPG), fasting insulin (FINS), HbA1c, TG, BMI, WHR, and the HOMA-IR were higher in diabetic groups than normal subjects (P<0.05). During the diabetic groups, the levels of HbA1c, TG, BMI and WHR were higher in overweight group than normal weight group. The levels of FPG, FINS, HbA1c, TG, BMI, WHR, and the HOMA-IR were higher in T2DM with obesity group than T2DM with normal weight group (P<0.05). The levels of FINS, TG, BMI, WHR, and the HOMA-IR were higher in T2DM with obesity group than overweight group (P<0.05). However, the levels

<table>
<thead>
<tr>
<th>Factor</th>
<th>Groups</th>
<th>Normal subject</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal weight</td>
<td>Overweight</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Age (year)</td>
<td>65.65 ± 12.91</td>
<td>65.09 ± 10.723</td>
<td>68.38 ± 8.71</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>(20/20)</td>
<td>(20/15)</td>
<td>(15/14)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.01 ± 1.14</td>
<td>23.35 ± 1.00</td>
<td>26.51 ± 1.22</td>
</tr>
<tr>
<td>WRH</td>
<td>0.86 ± 0.03</td>
<td>0.91 ± 0.08</td>
<td>0.98 ± 0.04</td>
</tr>
<tr>
<td>FPG (mM)</td>
<td>4.81 ± 0.41</td>
<td>7.78 ± 3.25</td>
<td>7.96 ± 1.88</td>
</tr>
<tr>
<td>2hPG (mM)</td>
<td>5.87 ± 0.80</td>
<td>13.67 ± 4.73</td>
<td>13.27 ± 4.00</td>
</tr>
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<td>FINS (mU/L)</td>
<td>7.06 ± 1.84</td>
<td>10.96 ± 6.87</td>
<td>12.68 ± 9.43</td>
</tr>
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<td>HOMA-IR</td>
<td>1.53 ± 0.49</td>
<td>3.59 ± 2.33</td>
<td>4.65 ± 3.84</td>
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<td>HbA1c (%)</td>
<td>5.45 ± 0.37</td>
<td>7.94 ± 1.98</td>
<td>8.67 ± 1.98</td>
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<tr>
<td>TG (mM)</td>
<td>1.03 ± 0.35</td>
<td>1.54 ± 0.59</td>
<td>2.19 ± 0.65</td>
</tr>
<tr>
<td>TC (mM)</td>
<td>4.24 ± 0.89</td>
<td>4.24 ± 0.95</td>
<td>4.41 ± 0.72</td>
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<tr>
<td>LDL-c (mM)</td>
<td>2.57 ± 0.61</td>
<td>2.63 ± 0.92</td>
<td>2.88 ± 0.65</td>
</tr>
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<td>HDL-c (mM)</td>
<td>1.33 ± 0.29</td>
<td>1.10 ± 0.25</td>
<td>1.14 ± 0.27</td>
</tr>
<tr>
<td>Omentin-1 (ng/L)</td>
<td>994.71 ± 435.89</td>
<td>821.16 ± 312.50</td>
<td>748.00 ± 322.51</td>
</tr>
</tbody>
</table>

Data are shown as means ± SD. T2DM: type 2 diabetes mellitus; n: number of subjects; BMI: body mass index; WHR: waist to hip ratio; FPG: fasting plasma glucose; 2 h PG, postprandial 2 hour glucose; FINS: fasting serum insulin; HOMA-IR: Homeostasis Model Assessment insulin resistance index; HbA1c: glycosylated hemoglobin; TG: triglyceride; TC: total cholesterol; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.

a P<0.05 T2DM with normal weight, overweight and obesity group compared with normal subject.
b P<0.05 T2DM with overweight and obesity group compared with T2DM with normal weight.
c P<0.05 T2DM with obesity group compared with T2DM with overweight.
of HDL and omentin-1 were highest in normal subjects and lowest in T2DM with obesity group. During the diabetic groups, the levels of HDL and omentin-1 were inversely to the bodyweight, and there were significant differences in obesity group compared with other groups. No significant differences in TC and LDL were detected in these four groups (Table 1). Bivariate correlation analysis indicated that serum omentin-1 concentrations were negatively correlated with BMI, WHR, and HOMA-IR and levels of FINS, FPG, 2 hPG, TG (P < 0.05, Table 2). Multiple stepwise regression analysis showed that BMI were independently related factors that influenced serum omentin-1 levels (Y = 1564.57 – 29.83 × BMI, Table 2).

4. Discussion

Omentin-1 is a newly discovered adipokine. Recent studies showed that omentin-1 plasma levels and gene expression are correlated negatively with obesity and type 2 diabetes. We demonstrated that serum omentin-1 levels significantly decreased in type 2 diabetes patients compared to normal controls, and were further reduced in type 2 diabetes patients with overweight and obesity compared to those with normal weight. The serum omentin-1 levels were negatively correlated with FPG, 2hPG, FINS, and HOMA-IR. Recently, omentin-1 was identified as a polypeptide hormone, which enhances insulin-stimulated glucose uptake and Akt phosphorylation in human adipocytes in vitro [11]. Our findings confirm that patients with type 2 diabetes and patients with Type 2 diabetes with obesity demonstrated decreased omentin-1 serum levels. Decreased serum omentin-1 levels observed in Type 2 diabetes may cause a reduction of insulin-stimulated glucose uptake in visceral and subcutaneous adipocytes or other insulin-sensitive tissue [16].

This may contribute to the state of insulin resistance observed in type 2 diabetes.

Our data are agreement with that of Tan et al. These results suggest that omentin-1 is important for glucose metabolism. In vitro, omentin-1 increases insulin signal transduction by activating the protein kinase B and enhances insulin-mediated glucose transport in adipocytes [11]. Other studies have suggested that omentin-1 levels were correlated with obesity [15]. In this study, the serum omentin-1 level was lowest in type 2 diabetes patients with obesity. The serum omentin-1 levels were negatively correlated with BMI and WHR. Multiple regression analysis showed that BMI was independent risk factor influencing serum omentin-1 levels, but the mechanism is not well understood. Tan et al. reported that insulin and glucose significantly and dose-dependently decreased omentin-1 mRNA expression and omentin-1 protein production in omental adipose tissue explants and that hyperinsulinemia significantly reduced plasma omentin-1 levels in healthy subjects [19]. It may be that plasma glucose and insulin levels regulate omentin-1 synthesis directly or indirectly. Omentin-1 can modulate insulin sensitivity and glucose metabolism [11], so we speculate that changes in serum omentin-1 concentration may influence the level of glucose or insulin, but our hypothesis must be confirmed.

In conclusion, decreased omentin-1 levels are associated with increasing obesity and insulin resistance. Therefore, omentin-1 levels may be predictive of the metabolic consequences or co-morbidities associated with obesity. The mechanism and physiological role of omentin-1 in glucose metabolism is not well understood. Further investigation is needed to determine whether omentin-1 can act as a link between obesity and diabetes. Omentin-1 circulates in blood and whether decreased serum omentin-1 levels act as a predictor of development of insulin resistance and diabetes should be further investigated.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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