



Serum Omentin-1 Concentrations and Biochemical Markers of Chronic Subclinical Inflammation in Obese Subjects

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Abstract

Background: Whilst chronic subclinical inflammation is now considered to be a predisposing risk factor of cardiovascular diseases. The extent by which adipokines induce metabolic abnormalities in humans is not fully resolved. The purpose of this study was to examine the relationship between insulin resistance and serum inflammatory markers in obese subjects.

Methods: One hundred and five subjects without any clinically evident CVD were classified into 3 coronary risk levels according to Framingham risk score. Demographic and anthropometric variables were estimated. Serum levels of lipid profile, blood glucose, insulin, omentin-1 and high sensitivity-Reactive Protein (hs-CRP) were measured in fasting blood samples. Insulin resistance indices were also calculated.

Results: 29% and 62% of the study population were overweight and obese respectively by Body mass index (BMI) measures. Almost half of the study population was considered diabetic. There was a tendency for a fall in serum omentin-1 concentrations with increasing coronary risk with a significant increase in hs-CRP levels in the same direction ($p < 0.05$). Age and fasting blood glucose were found to be independently associated with serum omentin-1 levels. BMI and fasting blood glucose were independent determinants of serum hs-CRP levels.

Conclusions: Omentin-1 might be associated with the development of diabetes mellitus indirectly via insulin activity and obesity. These findings may have important implications for the pathophysiology and therapy of diabetes mellitus by further longitudinal studies.

Keywords: Omentin-1, hs-CRP, Subclinical inflammation, Insulin resistance, Diabetes mellitus, Obesity

Introduction

Adipose tissue is a dispersed endocrine organ, and a source of several hormones, for example leptin, and a number of cytokines known to be involved in systemic inflammation; these include plasminogen activator inhibitor type 1 (PAI-1), interleukin 6 (IL-6), and tumor necrosis factor- α (TNF- α) [1].

Cardiovascular disease (CVD) is now recognized to be a process

involving inflammatory processes, and serum inflammatory markers are considered to be important for the evaluation of cardiovascular risk [2].

It is possible that the relationship between CVD risk and obesity are linked by the increased inflammatory milieu [3]. Obesity related inflammation has also been proposed as a possible mechanism by which obesity increases insulin resistance and leads to diabetes [4].

Whilst chronic subclinical inflammation is now considered to be a predisposing risk factor of CVD [5]. The extent by which adipokines induce metabolic abnormalities in humans is not fully resolved [6].

Omentin-1 is a circulating adipokine that is down-regulated in patients with CVD. Decreased omentin expression was shown to be implicated in a variety of chronic inflammatory diseases [7,8], and has been identified as an adipokine that may improve insulin sensitivity [9], although its circulating levels in obesity have not been adequately studied and its correlation with insulin resistance or obesity is still controversial.

We hypothesized that insulin resistance in obese subjects is associated with higher serum concentrations of inflammatory cytokines and that the association of cytokines with insulin sensitivity may be independent of body fat mass.

The purpose of this study was to examine the relationship between insulin resistance and serum inflammatory markers in obese subjects.

Methods

Subjects

One hundred and five subjects, attending the outpatient clinic in King Abdulaziz University Hospital, who were without any clinically evident CVD were considered for inclusion in this cross-sectional study. All patients gave their written informed consent for participation in the study and the ethics committee at KAUH approved the study protocol.

Exclusion criteria included subjects with liver, kidney, thyroid, malignancy, acute, or chronic infectious or inflammatory diseases. Subjects taking medications, such as, statins and aspirin that could affect inflammatory markers levels were also excluded from the study.

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The Framingham risk score used in this study is a version defined in the ATP III report and is a composite score of traditional cardiovascular risk factors that includes age and sex, systolic blood pressure, total cholesterol, HDL-C, presence of diabetes, and smoking status [10].

Anthropometric measurements

Clinical assessment included anthropometric measurements and blood pressure readings. Data on health status were obtained from medical files and supplemented by the participants' self-reported health-related data. Body weight, height, body mass index (BMI), waist circumference, hip circumference, and waist to hip circumference ratio (WHR) were estimated for all study subjects. Body height and weight were measured using a stadiometer and a standardized balance-beam scale, respectively. Waist circumference was measured at the level of the umbilicus with silent breathing and hip circumference was measured at the inter-trochanteric girth according to the WHO guideline [11] in standing position. BMI was calculated as weight (kg) divided by height (m^2) and WHR was obtained from waist circumference divided by hip circumference. Gender-based waist circumference and WHR cutoffs were employed as a measure of cardiovascular risk [12].

Blood pressure measurements were obtained on each subject following a 10 minute rest period in a seated position using auscultation and a mercury sphygmomanometer. The average of three successive readings of systolic and diastolic pressure was used as the documented blood pressure values.

Biochemical tests

Blood samples were collected from all participants after a 12 hour overnight fasting into plain and EDTA tubes. Fasting blood glucose levels were measured using an automated analyzer (Dimension Vista System, Siemens, Germany) standard enzymatic method. Fasting insulin was measured using an enzyme amplified chemiluminescence assay (Modular E170 immunoassay analyzer, Roche, USA).

The homeostasis model assessment of insulin resistance (HOMA-IR) and the homeostasis model assessment of β -cell insulin secretion (HOMA-IS) were calculated from fasting insulin and glucose levels using the following equations: HOMA-IR = Fasting insulin (μ U/L) \times Fasting blood glucose ($mmol/L$) / 22.5; HOMA-IS = [20 \times Fasting Insulin (μ U/L)] / [Fasting blood glucose ($mmol/L$) - 3.5] [13]. Quantitative insulin sensitivity check index (QUICKI) was calculated by (QUICKI = 1 / [log (fasting insulin) + log (fasting glucose)]) [14].

A residual aliquot of serum from the fasting blood sample on each participant was stored at $-80^{\circ}C$. Serum high sensitive C-reactive protein (hs-CRP) was measured by means of immuno turbidimetric assay (Behring Nephelometer-BNA2, Siemens, USA). Three categories of serum hs-CRP were defined based on the cut-off points for coronary risk stratification, < 1.0 mg/L is considered a low risk, between 1.0 and 2.99 mg/L an intermediate risk, and ≥ 3.0 mg/L a high risk [15].

Serum omentin-1 was measured by ELISA in duplicate using commercially available kits (Biovendor, Germany). The intra-assay CV was 3.2% and inter-assay CV was 4.4%.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation. Categorical variables were expressed as percentage. Kolmogorov-Smirnov test was performed to verify the normal distribution of the data. Logarithmically transformed values were used for the statistical analysis.

ANOVA test for normally distributed parameters or Kruskal-Wallis test for non-normally distributed parameters were used to compare mean values of continuous variables in between the subgroups followed by Bonferroni's test. Categorical variables were compared by χ^2 or Fisher exact tests as appropriate. Correlations between continuous variables were assessed with the use of Pearson

correlation test or Spearman correlation rank test as appropriate. Multiple stepwise regression analysis was performed to determine significant confounding factors for serum hs-CRP and omentin-1 levels. P values < 0.05 were considered to be statistically significant. All the statistical analyses were performed using SPSS version 16 software (SPSS Inc., Chicago, IL, USA).

Results

The study cohort consisted of 105 participants, aged 40 to 78 years, 73% of whom were females and 27% were males. Ten percent were lean, 29% were overweight, and 62% were obese according to their respective BMI classes namely, 18.5-24.9 kg/m^2 , 25-29.9 kg/m^2 ; and ≥ 30 kg/m^2 . Approximately 66% of the male subjects had a waist circumference > 102 cm in comparison with 95% of the female subjects with waist circumference > 88 cm. Alternatively, 43% of males had WHR ≥ 0.95 whereas 97% of females had WHR ≥ 0.80 .

In further analysis the patients were divided into those with low coronary risk ($n = 62$), those with intermediate coronary risk ($n = 25$), and those with high coronary risk ($n = 18$) based on their Framingham score of 10-year CVD risk.

Table 1 provides clinical characteristics of the study participants. Those with low coronary risk had significantly lower body height and WHR values than those with high coronary risk ($p < 0.05$). Additionally, significant differences in age and blood pressure readings existed between the low coronary risk groups versus the remaining groups ($p < 0.05$).

Although no significant differences in mean levels of fasting blood glucose, fasting insulin, and/or insulin resistance indices were found across the subgroups, 44% of the study participants were considered diabetic with fasting blood glucose ≥ 7 $mmol/L$ (**Table 2**).

Table 1: Clinical characteristics of the study participants ($N = 105$).

	Low coronary risk	Intermediate coronary risk	High coronary risk	<i>p</i>
Gender (F:M)	62 (56:6)	25 (18:7)	18 (3:15)	< 0.0001
Age (years)	54.1 \pm 0.8	60.2 \pm 1.7	60.4 \pm 2.1	< 0.0001
SBP (mmHg)	126.8 \pm 2.1	144.3 \pm 3.7	154.4 \pm 4.9	< 0.0001
DBP (mmHg)	76.4 \pm 1.4	85.3 \pm 2.7	85.6 \pm 3.9	< 0.01
Body weight (Kg)	83.8 \pm 2.2	82.8 \pm 3.9	86.2 \pm 5.6	NS
Body height (cm)	159.2 \pm 0.9	158.5 \pm 1.6	164.6 \pm 1.9	< 0.05
BMI (Kg/m^2)	33.1 \pm 0.8	32.9 \pm 1.4	31.6 \pm 1.6	NS
BMI Cut-off levels				
Normal (18.5-24.9 kg/m^2)	4 (7)	3 (12)	3 (17)	
Overweight (25-29.9 kg/m^2)	18 (29)	7 (28)	5 (28)	NS
Obese (≥ 30 kg/m^2)	40 (65)	15 (60)	10 (56)	
Waist circumference (cm)	106.6 \pm 1.4	107.7 \pm 3.3	108.6 \pm 3.1	NS
Hip circumference (cm)	116.4 \pm 1.6	116.2 \pm 4.2	112.4 \pm 2.6	NS
WHR	0.92 \pm 0.0	0.94 \pm 0.0	0.96 \pm 0.0	< 0.05
TC (mmol/L)	4.66 \pm 0.13	5.04 \pm 0.25	4.70 \pm 0.34	NS
HDL-C (mmol/L)	1.21 \pm 0.04	1.15 \pm 0.05	1.06 \pm 0.04	NS
LDL-C (mmol/L)	2.69 \pm 0.11	3.01 \pm 0.23	2.93 \pm 0.29	NS
TG (mmol/L)	1.67 \pm 0.11	1.94 \pm 0.14	1.58 \pm 0.16	NS
FBG (mmol/L)	7.2 \pm 0.3	7.9 \pm 0.5	7.3 \pm 0.6	NS
FBG Cut-off levels				
Normal (< 6.1 $mmol/L$)	30 (48)	9 (36)	3 (17)	
IGT (6.1 - < 7 $mmol/L$)	7 (11)	3 (12)	6 (33)	NS
DM (≥ 7 $mmol/L$)	25 (40)	13 (52)	9 (43)	
Fasting insulin (μU/ml)	16.4 \pm 1.2	17.9 \pm 4.0	18.8 \pm 3.2	NS
HOMA-IR	5.64 \pm 0.7	7.05 \pm 2.1	6.02 \pm 1.1	NS
HOMA-IS	133.8 \pm 15.6	93.1 \pm 13.6	121.4 \pm 19.0	NS
QUICK-I	0.31 \pm 0.0	0.31 \pm 0.0	0.31 \pm 0.0	NS

Data are given as the mean \pm SD or as the number of subjects with percentages given in parentheses, as appropriate. Categorical data are compared by χ^2 test, continuous variables are compared by Kruskal Wallis test.

BMI: Body mass index, DBP: Diastolic blood pressure, FBG: fasting blood glucose, HOMA-IR: Homeostasis model assessment insulin resistance index, HOMA-IS: homeostasis model assessment of β -cell insulin secretion, NS: non-significant, SBP: Systolic blood pressure, WHR: waist- hip ratio.

Table 2: Correlation analysis of measures of body fat and insulin resistance with serum hs-CRP and omentin-1 levels in the study participants (N = 105). Significant correlations are shown in bold font.

	hs-CRP (mg/L)		Omentin-1 (ng/ml)	
	r	p	r	p
Age (years)	-0.058	0.556	0.261	0.007
SBP (mmHg)	0.136	0.169	-0.106	0.281
DBP (mmHg)	-0.012	0.906	-0.049	0.620
Body weight (Kg)	0.340	< 0.0001	-0.112	0.257
Body height (cm)	-0.120	0.224	-0.049	0.621
BMI(Kg/m²)	0.394	< 0.0001	-0.055	0.580
Waist circumference (cm)	0.236	0.015	0.061	0.541
Hip circumference (cm)	0.282	0.004	0.00-	0.981
WHR	0.110	0.266	-0.037	0.706
FBG (mmol/L)	0.269	0.006	0.260	0.008
Fasting insulin (μU/ml)	0.101	0.311	-0.024	0.812
HOMA-IR	0.069	0.484	0.233	0.018
QUICK-I	-0.183	0.064	-0.233	0.018

BMI: Body mass index, DBP: Diastolic blood pressure, FBG: fasting blood glucose, HOMA-IR: Homeostasis model assessment insulin resistance index, HOMA-IS: homeostasis model assessment of β -cell insulin secretion, NS: non-significant, SBP: Systolic blood pressure, WHR: waist- hip ratio.

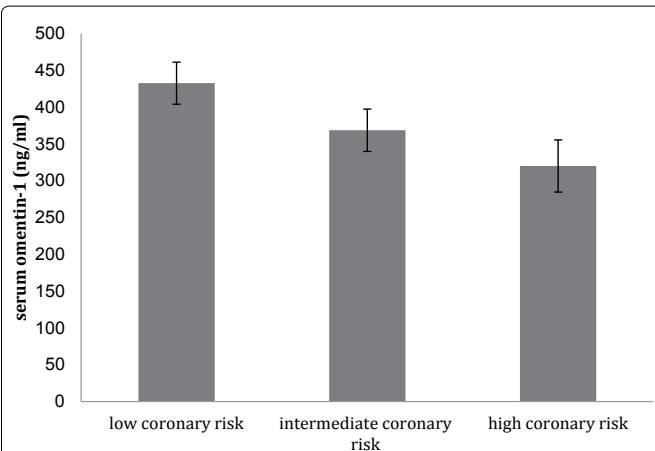


Figure 1(a): Mean values \pm SD of serum omentin-1 levels of the study participants (N = 105) stratified by their Framingham scores of 10-year CVD risk.

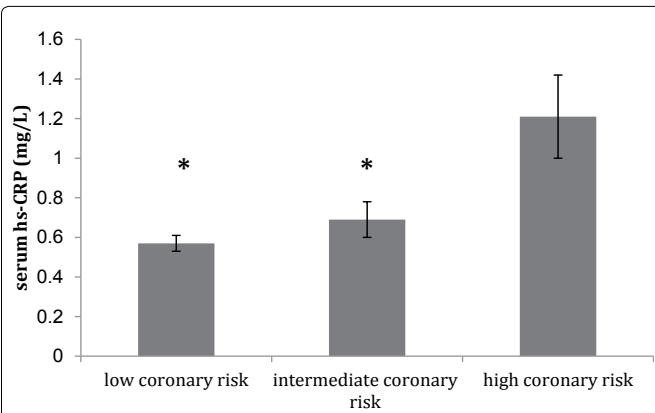


Figure 1(b): Mean values \pm SD of serum hs-CRP levels of the study participants (N = 105) stratified by their Framingham scores of 10-year CVD risk. (*p < 0.05 vs. high coronary risk group).

Notably, there was a trend for a lower mean serum omentin-1 concentration with the increasing coronary risk as shown in [Figure 1a](#), though this did not reach statistical significance. Furthermore, this was accompanied by a significant increase in serum hs-CRP levels ($p < 0.05$) between subjects with low, intermediate, and high coronary risk ([Figure 1b](#)).

[Table 2](#) shows correlation analysis of the measures of body fat and insulin resistance with serum hs-CRP and omentin-1 levels. There were significant associations between circulating omentin-1 levels

Table 3: Multiple regression analysis of omentin-1.

Independent variables	β	95% CI limit of β		p
Total R² = (0.127)² = 11%				
Age	0.245	1.510	10.891	0.01
FBG	0.254	5.150	33.101	0.008

95% CI: 95% confidence interval, FBG: fasting blood glucose

Table 4: Multiple regression analysis of hs-CRP.

Independent variables	β	95% CI limit of β		p
Total R² = (0.207)² = 19.2%				
BMI	0.369	0.157	0.446	< 0.0001
FBG	0.227	0.102	0.816	0.012

95% CI: 95% confidence interval, BMI: body mass index, FBG: fasting blood glucose

and age, fasting blood glucose, HOMA-IR, and QUICK-I. However, there were no association between serum hs-CRP and omentin-1 levels. Serum hs-CRP levels were significantly associated with anthropometric measurements including body weight, BMI, waist and hip circumferences, and fasting blood glucose.

When multiple regression analysis was performed to determine which variables were independently associated with serum omentin-1 levels, age and fasting blood glucose remained significant ([Table 3](#)). [Table 4](#) shows that BMI and fasting blood glucose were independent determinants of serum hs-CRP levels.

Discussion

Several adipokines have been proposed to be linked directly to insulin resistance and obesity [1]. Measurement of their serum levels may be an early marker for atherosclerosis risk. Serum hs-CRP levels have been used as a marker of subclinical inflammation which is expected to identify subjects at early stages of CVD [16]. Independent roles of these risk factors in the development of atherosclerosis are not, however, fully understood.

Dysregulated production of adipocytokines is linked to the pathogenesis of cardiovascular risk factors such as diabetes mellitus [17]. The main findings of this present study are that fasting blood glucose was independently associated with hs-CRP ($\beta = 0.227$, $p < 0.05$) as well as omentin-1 ($\beta = 0.254$, $p < 0.01$) in the study subjects. Our data indicates that obesity and inflammation are closely associated with glucose metabolism impairment [18]. It has previously been proposed that obesity is causally linked to a chronic low-grade inflammatory state, which contributes to the development of metabolic dysfunction [6,19].

It is unclear why omentin-1 and hs-CRP levels were not correlated with each other, but adipose tissue is known to secrete several adipokines that have important roles in the initiation of insulin resistance or endothelial dysfunction [20,21]. Therefore, measurement of visceral adipose mass and/or levels of other adipokines in future studies could help elucidate why these two markers did not correlate together in our study.

Levels of inflammatory cytokines (like TNF- α and IL-6) were found to be increased in obese and diabetic subjects [22]. Serum omentin-1 levels have been shown to be associated with obesity-related metabolic and vascular complications [23]. Overall, overweight and obesity were highly prevalent among the study population. In the current study, BMI was only an independent correlate of hs-CRP level ($\beta = 0.369$, $p < 0.0001$).

Serum omentin-1 levels were previously reported to be significantly reduced in obese compared with lean individuals in one study [24] but were similar between these groups in another study [25]. No association was observed between omentin-1 levels and measures of body fat ([Table 2](#)). It was suggest that obesity negatively regulates omentin expression [26]. Insulin resistance has been shown to be associated with pro-inflammatory states [27]. Inflammatory cytokines may contribute to the regulation of omentin-1 levels [28]. Many studies have shown that omentin-1 levels are negatively

correlated with BMI, waist circumference, fasting insulin, and HOMA-IR index [24,29]. However, in the current study estimates of insulin resistance were derived using the HOMA-IR and QUICK-I, and were significantly related to serum omentin-1 values ($r = 0.233$, $p < 0.05$; $r = -0.233$, $p < 0.05$ respectively).

The Framingham risk score is a conventional means of predicting coronary risk in the general population [30]. Therefore, adipocytokines levels association with the presence and extent of coronary risk could independently predict the future risk of atherosclerotic diseases. Despite the lack of statistical difference in serum omentin-1 levels among the study population as stratified by the Framingham coronary risk score, there seems to be a tendency for a fall in serum omentin-1 concentrations with increasing coronary risk (Figure 1a). Several biomarkers, such as hs-CRP, have been shown to enhance Framingham risk score algorithms and were associated with increased cardiovascular risk [31]. Consequently, determination of circulating levels of novel markers like omentin-1 could have additional value in the prediction of future risk of CVD.

Conclusion

Our findings suggest that omentin-1 might be associated with the development of diabetes mellitus indirectly via insulin activity and obesity. These findings may have important implications for the pathophysiology and therapy of diabetes mellitus. However, due to the nature of the current study design, which does not allow us to infer causality between obesity and inflammation, omentin-1, longitudinal studies are warranted.

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