Original Article

Study of Plasma Omentin-1 Level in Type 2 Diabetic Patients with and Without Microvascular Complications.

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Abstract:

Background: Adipose tissue produces several hormones and cytokines termed adipokines that have widespread effects on carbohydrate and lipid metabolism. Omentin-1 is a newly identified adipokine that is highly and selectively expressed in visceral adipose tissue relative to subcutaneous adipose tissue. In some recent studies, it was shown to be decreased in obese and in insulin resistant diabetic patients. **Aim:** In this study, intending to increase the knowledge about omentin-1 and its relation with type 2 diabetes mellitus, insulin resistance and obesity, It is planned to point out the relationship between serum plasma omentin-1 level in type 2 diabetic patients with and without microvascular complications. **Subjects & Methods:** The study included 60 type 2 diabetic patients and 30 age matched control subjects. All participants subjected to the following: BMI, WC, nerve conduction velocity, fundus examination and laboratory investigations including: fasting blood glucose, glycosylated hemoglobin, Lipid profile including; Total cholesterol, serum triglycerides, low density lipoproteins cholesterol, high density lipoproteins cholesterol, Blood urea and creatinine. High sensitivity CRP urine analysis for albumin/creatinine ratio. Plasma level of omentin-1. **Results:** Diabetic group with microvascular complications had significantly lower plasma omentin-1 levels than the control group ($p<0.001$). Positive correlations were obtained between high density lipoprotein cholesterol and omentin-1 levels, and negative correlations between body mass index, fasting blood glucose, HbA1c, HS CRP and omentin-1 levels. **Conclusion:** omentin-1 levels were significantly low in diabetic patients with microvascular complications. The data may point toward a role of omentin-1 in insulin resistance and type 2 diabetes mellitus with microvascular complications.

Keywords: Omentin-1, diabetes mellitus, microvascular complications.

Introduction:

The microvascular complications of diabetes may already be present at the day of diagnosis. This may have devastating consequences, including blindness, end stage renal disease and lower limb amputation. The global increase in the prevalence of diabetic microvascular complications and consequently, significant increase in health care expenditure Recently, a new protein omentin (also named omentin-1, intelectin, intelectin-1, endothelial lectin and intestinal lactoferrin receptor) has been identified as a major visceral (omental) fat secretory adipokine. It was then found that omentin-1 is predominantly expressed in visceral but not in subcutaneous adipose tissue, with the omentin-1 mRNA being 150 times higher in the visceral adipose tissue[(1)]. Lean subjects had significantly higher plasma omentin-1 levels than obese and overweight subjects[(2)]. It is interesting to note that the omentin-1 gene is localized on a chromosomal region of 1q22–q23, where it was reported a

presence of linkage to type 2 diabetes in various populations. Visceral obesity is reportedly more pathogenic than subcutaneous obesity in promoting insulin resistance, type 2 diabetes, and microvascular complications. In addition, It has been shown that omentin-1 plasma level are decreased in type 2 diabetic patients. It was found that omentin decreases in vitro migration and angiogenesis in human endothelial cells (EC) induced by human sera, c-reactive protein (CRP) and vascular endothelial growth factor (VEGF). Thus omentin appears to be a 'protective adipokine' that it induces vasodilatation and inhibits EC migration, vascular inflammation and angiogenesis. As well as reducing endothelial dysfunction. As a secretory factor, omentin-1 may be a novel hormone that is likely to act as both an endocrine factor to modulate systemic metabolism, including insulin action in subcutaneous adipocytes, and an autocrine and paracrine factor to regulate visceral adipose biology locally[3,4].

Studies have demonstrated that omentin-1 enhances insulin action by stimulating insulin-mediated glucose uptake by subcutaneous as well as omental adipocytes in vitro[5]. There are few sudies about obesity, diabetes mellitus and omentin-1. Lean subjects had significantly higher plasma omentin-1 levels than obese and overweight subjects[6,7]. Decreased plasma omentin-1 levels were reported in type 1 and type 2 diabetes[8-10] and in patients with impaired glucose regulation[11,12] Keeping in mind that omentin-1 levels may be predictive of the metabolic consequences or co-morbidities associated with obesity and glucose metabolism.

Aim of the Work:

The study was designed to study the changes in the circulating plasma Omentin-1 level in type 2 diabetic patients with and without microvascular complications, determine the relationship of circulating omentin-1 levels with diabetic retinopathy, in subjects with type 2 diabetes and controls and investigate the possible association of Omentin-1 with some anthropometric and metabolic parameters in such diabetic patients.

Subjects and Methods:

Subjects:

The study will enroll ninety age matched subjects selected from outpatient clinic of the diabetes and metabolism unit, Alexandria Main University Hospital. Subjects were divided into 3 groups:

Group (I): will include 30 type 2 diabetic patients with history of microvascular complications (Diabetic Retinopathy, polyneuropathy and/or nephropathy).

Group (II): will include 30 newly diagnosed type 2 diabetic patients without complications.

Group (III): will include 30 healthy subjects as a control.

Methods:

All subjects included in the study were subjected to the following:

- History taking including an interview questionnaire comprising the following items: Diabetic history, screening for microvascular complications, history of renal disease (dialysis or transplantation), of laser photocoagulation, of numbness, prickling sensation or burning pain at leg or feet, screening for macrovascular complications & screening for associated risk factors: History of hypertension & Smoking status with calculation of smoking index.
- Physical examination: Anthropometric measurements including height and weight measurements then calculation of body mass index (BMI), Waist circumferences, Vital signs, Sensory function: a) Superficial sensation b) Deep sensation.
- Fundus examination: Retinal blood vessels fluorescein angiography

- Nerve conduction velocity.
- Laboratory investigations including: Fasting blood glucose, Glycosylated hemoglobin (HbA1c), Lipid profile including, Total cholesterol, Serum triglycerides, Low density lipoproteins cholesterol, High density lipoproteins cholesterol, Urine analysis for albumin/creatinine ratio, Blood urea and creatinine, High sensitivity CRP by immunoturbidemetric method & Plasma level of Omentin-1by ELISA technique

Results:

The study was performed on 90 subjects 73 of them were males and 17 were females presented to outpatient clinic, internal medicine department, Alexandria main university hospital.

Table (I) Comparison between the three studied groups according to fundus exam

	Micro-vascular complication (n = 30)		Newly diagnosed (n = 30)		Control (n = 30)		χ^2	^{MC}p
	No.	%	No.	%	No.	%		
Fundus Exam								
Normal	0	0.0	24	80.0	30	100.0		
Non prolifertive diabetic retinopathy	20	66.7	6	20.0	0	0.0	83.048*	<0.001*
Prolifertive diabetic retinopathy	10	33.3	0	0.0	0	0.0		
Sig.bet. Grps	p_1 <0.001*, p_2<0.001*, p_3= 0.024*							

χ^2:value for Chi square
MC: Monte Carlo test
Sig. bet. grps was done using Fisher Exact test or Monte Carlo test
p_1: p value for comparing between Micro-vascular complication and Newly diagnosed
p_2: p value for comparing between Micro-vascular complication and Control
p_3: p value for comparing between Newly diagnosed and Control
*: Statistically significant at p ≤ 0.05

Table (II) Comparison between the three studied groups according to plasma omentine.1

	Micro-vascular complication (n = 30)	Newly diagnosed (n = 30)	Control (n = 30)	F	P
Plasma Omentine.1					
Min. – Max.	0.57 – 0.61	0.61 – 0.71	0.71 – 3.43		
Mean ± SD	0.59 ± 0.01	0.66 ± 0.03	1.05 ± 0.71	11.096*	<0.001*
Median	0.59	0.65	0.79		
Sig.bet. Grps	p_1= 0.516, p_2<0.001*, p_3<0.001*				

F: F test (ANOVA), Sig. bet. grps was done using Post Hoc Test (LSD)
p_1: p value for comparing between Micro-vascular complication and Newly diagnosed
p_2: p value for comparing between Micro-vascular complication and Control
p_3: p value for comparing between Newly diagnosed and Control
*: Statistically significant at p ≤ 0.05

Table (III) Correlation between Plasma omentine.1 with different parameters in each group

		Plasma omentine.1		
		Micro vascular complication	**Newly diagnosed**	**Control**
Age	**R**	-0.158	0.213	0.040
	P	0.406	0.259	0.835
Duration	**r_s**	-0.256	0.132	-
	P	0.173	0.485	-
Weight	**R**	-0.565*	0.115	-0.067
	P	0.001	0.543	0.724
BMI	**R**	-0.781*	0.181	-0.148
	P	<0.001	0.337	0.436
WC	**R**	-0.541*	-0.546*	-0.231
	P	0.002	0.002	0.220
SBP	**R**	0.129	0.267	-0.111
	P	0.495	0.154	0.558
Fundus exam	**r_s**	-0.537*	0.212	-
	P	0.002	0.260	-
Nerve conduction velocity	**r_s**	-0.269	0.240	-
	P	0.151	0.201	-
FBS	**r_s**	0.161	-0.487*	-0.047
	P	0.394	0.006	0.806
HbA1C	**R**	0.095	-0.166	-0.367*
	P	0.617	0.381	0.046
Urea	**r_s**	0.098	0.004	-0.246
	P	0.606	0.985	0.190
Creatinine	**R**	-0.223	-0.013	-0.162
	P	0.236	0.944	0.391
Alb/Creat ratio	**r_s**	-0.393*	-0.078	0.253
	P	0.031	0.681	0.178
HS-CRP	**r_s**	-0.589*	-0.513*	0.352
	P	0.001	0.004	0.056
LDL	**R**	-0.296	-0.012	-0.153
	P	0.112	0.952	0.419
HDL	**R**	0.454*	0.621*	0.088
	p	0.012	<0.001	0.643
TG	**r_s**	-0.196	-0.228	0.260
	p	0.298	0.225	0.165
Cholesterol	**r**	-0.610*	-0.800*	-0.036
	p	<0.001	<0.001	0.850

r: Pearson coefficient

r_s: Spearman coefficient

*: Statistically significant at $p \leq 0.05$

Discussion:

How omentin-1 levels are influenced by glucose levels and vice versa glucose levels by omentin-1 levels warrant elucidation[8-10]. Decreased omentin-1 levels were reported in subjects with impaired glucose regulation, type 1 and type 2 diabetic[13] individuals. In this study, diabetic patients had statistically significant lower omentin-1 levels than control subjects. Between the three groups of diabetic and control groups the lowest omentin-1 levels were found in diabetic patients with microvascular complications. The results demonstrated that omentin-1 levels decreased in diabetic individuals and decreased further when diabetes mellitus was combined with microvascular complications. The serum omentin-1 level in diabetic retinopathy group was significantly lower than that of the newly diagnosed diabetic group (P<0.001). Statistical significant difference was found between control group and diabetic retinopathy group (P<0.001). Statistical significant difference was found between control group and newly diagnosed diabetic patients group (P = 0.024) In agreement with our results, Hideyuki Yamawaki, Naoya Tsubaki found that omentin-1 inhibits TNF-α induced vascular cell adhesion molecule (VCAM)-1 expression via preventing the activation of P38 and JNK at least in part through inhibition of superoxide production. Omentin plays an anti-inflammatory role through inhibition of TNF-α induced superoxide production in vascular smooth cells [14,15].

The serum omentin-1 level in diabetic neuropathy group was significantly lower than that of the newly diagnosed diabetic group (P<0.001). Statistical significant difference was found between control group and diabetic neuropathy group (P<0.001). Statistical significant difference was found between control group and newly diagnosed diabetic patients group (P = 0.002).

The serum omentin-1 level in diabetic nephropathy group was significantly lower than that of the newly diagnosed diabetic group (P<0.001). Statistical significant difference was found between control group and diabetic nephropathy group (P<0.001). Statistical significant difference was found between control group and newly diagnosed diabetic patients group (P = 0.001). Ho Ra1, Ji Han Yoo2, found that albuminuria is a marker of endothelial dysfunction and may influence on alterations in microvasculature of retina and kidneys[16].

The serum omentin-1 level was significantly lower in the newly diagnosed type 2 diabetic group (P<0.001). the results of G. Gürsoy study goes hand in hand with our results who proved the same result.

A significant negative relation was found between serum omentin-1 and body mass index and waist circumference in diabetic patients . Celia M. de Souza Batista,1,2 Rong-Ze Yang,1 Mi-Jeong Lee found that Central obesity and the accumulation of visceral fat are risk factors for the development of type 2 diabetes and cardiovascular disease[17-19]. Omentin is a protein expressed and secreted from visceral but not subcutaneous adipose tissue that increases insulin sensitivity in human adipocytes[20].

A significant negative relation between serum omentin-1 and fasting blood sugar and blood glucose and HbA1c in diabetic patients with microvascular complications.

A significant negative relation between serum omentin-1 and high sensitive CRP in diabetic patients with microvascular complication.

A significant positive relation between serum omentin-1 and HDL-cholesterol in diabetic patients microvascular complications. In concordance with our results G. Gürsoy study demonstrated that omentin-1 levels decreased in diabetic individuals and decreased further when diabetes mellitus was combined with insulin resistance[21,22]. They also found positive correlation between omentin-1 and age, HDL-C levels.

For the time being, it is difficult to say whether high glucose and insulin levels are the cause or the result of low omentin-1 levels and with which mechanisms they effect omentin-1 levels. Further studies are needed.

Conclusion:

The study showed that omentin-1 levels are lower in type 2 diabetics with microvascular complications. Since type 2 diabetes mellitus is closely related to visceral adipose tissue

amount and diabetes has declared to be a state of inflammation it was reasonable to further investigate the role of omentin-1 in type 2 diabetic patients. According to the study, it may be said that glucose and insulin levels as well as insulin resistance may have a repressive effect on omentin-1 levels. Decreased omentin-1 levels may contribute to the underlying pathophysiology of microvascular complications of diabetes mellitus. Future studies probably with bigger sample size will be required to address the link of omentin-1 with metabolic disturbances such as obesity, insulin resistance and microvascular complications .

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