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Relationship between Testosterone Level, Serum Omentin-1 and Insulin Resistance in Obese Men

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Abstract

Background: Adipose tissue besides its role in energy storage produces several hormones and cytokines termed adipokines that have widespread effects on carbohydrate and lipid metabolism. Omentin-1 is a newly identified adipokine that increases insulin sensitivity and is highly and selectively expressed in visceral adipose tissue relative to subcutaneous adipose tissue. *Objective:* The aim of the present work was to evaluate the level of serum omentin-1 and its association with serum testosterone and insulin resistance in obese men. *Subjects and Methods:* The present study included 20 apparently healthy men their mean BMI was (21.51 ± 2.26) kg/m2 and 40 obese men their mean BMI was (33.03 ± 2.41) kg/m2. Blood samples were collected from all subjects and the level of plasma omentin-1, insulin, total and free testosterone, sex hormone-bonding globulin and 17β-estradiol were measured by enzyme linked immunossorbent assay (ELISA). *Results:* Both serum omentin-1 and total testosterone as well as free testosterone were significantly negatively correlated with body mass index, waist circumference, fasting serum glucose, serum insulin and HOMA-IR, and significantly positively correlated with QUICKI and sex hormone-binding globulin. In addition, omentin-1 serum levels correlate positively with free testosterone. *Conclusions:* Obese men showed significantly higher; body mass index, waist circumference, waist to hip ratio, fasting serum glucose, 2hr oral glucose tolerance test, serum insulin, HOMA-IR and estradiol, and significantly lower omentin-1, total testosterone, free testosterone and sex hormone-binding globulin as compared to normal group.

Keywords: omentin-1, testosterone, insulin resistance, obese men.

1. Introduction

Obesity is a worldwide epidemic that continues to grow at an alarming rate. this condition increases the morbidity and mortality associated with both acute and chronic diseases. some of the deleterious consequences of obesity have been attributed to its induction of low-grade chronic inflammatory state that arises from the production and secretion of inflammatory mediators from the expanded pool of activated adipocytes. [1]

The metabolic syndrome is associated with excessive accumulation of central body fat. As well as its role in energy storage, adipose tissue produces several hormones and cytokines termed adipokines that have widespread effects on carbohydrate and lipid metabolism. They appear to play an important role in the pathogenesis of insulin resistance (IR), diabetes, and atherosclerosis.5 Adipose tissue is now hypothesized to be the largest endocrine organ that has widespread effects on carbohydrate and lipid metabolism, secreting a large number of biologically important substances termed adipokines. Furthermore, it is apparent that accumulation of visceral adipose tissue poses a greater cardiometabolic risk than does subcutaneous adipose tissue [2], as removal of visceral but not subcutaneous adipose tissue has been demonstrated to improve insulin sensitivity. [3]

Omentin-1 (also named Omentin, Intelectin-1, Endothelial Lectin HL-1 and Intestinal Lactoferrin Receptor) is a novel fat depot-specific adipokine that was identified from a cDNA library of visceral omental adipose tissue by Yang et al. [4] The mature omentin is a secretory glycoprotein consisting of 295 amino acids and N-linked oligosaccharides, and its basic structural unit is a 120-kDa homotrimer in which 40-kDa polypeptides are bridged by disulfide bonds. Omentin-1 is primarily secreted by stromal vascular cells in visceral adipose tissue, and is expressed to a lesser extent in the heart, lung, and placenta. [5,6] In vitro experiments have revealed that treatment with recombinant omentin-1 enhanced insulin-stimulated glucose uptake in human subcutaneous and omental adipocytes, triggering Akt signaling in both the absence and the presence of insulin. [7] Furthermore, plasma omentin-1 level was inversely correlated with obesity and insulin resistance (IR). [8]

In clinical studies, circulating omentin-1 concentrations have been shown to be decreased in patients with obesity, impaired glucose regulation, polycystic ovary syndrome, type 1 diabetes, and type 2 diabetes. [9-13] Low circulating levels of omentin-1 have also been associated with endothelial dysfunction and cardiovascular disease. [14,15] Given these clinical associations, omentin-1 has garnered attention as a possible contributor to the pathogenesis of the metabolic syndrome. [16,17]

The aim of the present work was to evaluate the level of serum omentin-1 and its association with serum testosterone and insulin resistance in obese men.

The present study included 60 apparently healthy men. They were classified into two groups:

The normal control groups consist of twenty men, their mean BMI was (21.51 ± 2.26) kg/m^2 (were chosen from the staff members of MRI), and the obese groups consist of forty men, their mean BMI was (33.03 ± 2.41) kg/m^2 (were recruited from the Chemical Pathology Medicine Department, Chemical Pathology unit MRI).

The following were done for all participants:

1- Clinical examination
- Through history taking: with special stress on family history of diabetes mellitus and any drug intake.
- Complete physical examination. .

2- Anthropometric measurements
- Body mass index (BMI).
- Waist circumference (WC)
- Waist to hip ratio (WHR).

3- Laboratory measurements
- Fasting and 2hr OGTT glucose level by enzymatic method. [18]

- Assessment of insulin resistance (IR) [19] and insulin sensitivity [20] by homeostasis model assessment HOMA score (HOMA-IR = Fasting glucose (mg/dl) × Fasting Insulin (μIU/ml) / 405) and QUICKI respectively.
- Measurement of concentration of insulin [21], omentin-1 [22], total [23] and free [24] testosterone, sex hormone-bonding globulin [25] and 17β-estradiol [26] were measured in serum by enzyme linked immunosorbent assay.

2. Results

2.1 Results of anthropometric parameters

The statistical analyses of range and mean ± SD values of age, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist/hip ratio (WHR) of normal and obese men were shown in table (1).

For normal men (table 3), the mean age was 43.40 ± 5.66 year (range 39.0 – 60.0), the mean BMI was 21.51 ± 2.26 kg/m^2 (range 18.0 – 25.0), the mean WC was 86.35 ± 7.81 cm (range 69.0 – 96.0), the mean WHR was 0.89 ± 0.06 (range 0.79 – 1.13).

Table 1. The statistical analyses of age (year), body mass index (kg/m^2), waist circumference (cm), waist/hip ratio of normal and obese groups

	Normal group (n = 20)	Obese group (n = 40)
Age (year)		
Range	39.0 – 60.0	38.0 – 57.0
Mean ± SD	43.40 ± 5.66	44.73 ± 4.95
p_1		$p_1 = 0.147^*$
BMI (kg/m^2)		
Range	18.0 – 25.0	29.5 – 39.5
Mean ± SD	21.51 ± 2.26	33.03 ± 2.41
p_1		$p_2 < 0.001^*$
WC (cm)		
Range	69.0 – 96.0	99.0 – 121.0
Mean ± SD	86.35 ± 7.81	110.95 ± 6.08
p		$p_2 < 0.001^*$
WHR		
Range	0.79 – 1.13	0.77 – 1.34
Mean ± SD	0.89 ± 0.06	0.95 ± 0.09
p_1		$p_1 = 0.001$

p : p value compared to normal control subjects (independent T test)
p_1 : p value compared to normal control subjects (Mann-Whitney test)
* : Significantly different from normal control group
Significance was considered at the level of $p \leq 0.05$

For obese men (table 3), the mean age was 44.73 ± 4.95 year (range 38.0 – 57.0), the mean BMI was 33.03 ± 2.41 kg/m^2 (range 29.5 – 39.5), the mean WC was 110.95 ± 6.08 cm (range 99.0 – 121.0), the mean WHR was 0.95 ± 0.09 (range 0.77 – 1.34).

Data showed a significant difference in BMI, WC and WHR ($p_1 < 0.05$) and insignificant

difference in age ($p_1 > 0.05$) normal and obese men.

2.2 Biochemical results:

2.2.1 Results of fasting glucose (FG) (mg/dl), 2hrs serum oral glucose tolerance test glucose (2hrs OGTT glucose) (mg/dl), plasma insulin (µIU/ml), homeostasis model assessment insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI):-

The statistical analyses of range and mean ± SD values of FG, 2hrs OGTT glucose, plasma insulin, HOMA-IR and QUICKI of normal and obese men were shown in table (2).

For normal men (table 2), the mean FG was 90.85 ± 6. 91 mg/dl (range 81.0 – 104.0), the mean 2hrs OGTT glucose was 84.17 ± 10.51 mg/dl (range 68.0 – 110.0), the mean plasma insulin was 5.05 ± 1.89 µIU/ml (range 3.00 – 11.17), the mean HOMA-IR was 1.14 ± 0.47 (range 0.61 – 2.56) and the mean QUICKI was 0.38 ± 0.02 (range 0.33 – 0.42).

For obese men (table 2), the mean FG was 96.83 ± 9. 65 mg/dl (range 63.0 – 110.0), the mean 2hrs OGTT glucose was 101.63 ± 15.90 mg/dl (range 81.0 – 141.0), the mean plasma insulin was 10.97 ± 5.61 µIU/ml (range 3.95 – 28.67), the mean HOMA-IR was 2.61 ± 1.35 (range 0.87 – 6.08) and the mean QUICKI was 0.33 ± 0.02 (range 0.29 – 0.39).

Data showed a significant difference in FG, 2hrs OGTT glucose, insulin levels, HOMA-IR and QUICKI ($p_1 < 0.05$) between normal and obese men.

Table.2. The statistical analyses of fasting glucose (FG) (mg/dl), 2hrs serum oral glucose tolerance test glucose (2hrs OGTT glucose) (mg/dl), plasma insulin (µIU/ml), homeostasis model assessment insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) in normal and obese groups

	Normal group (n = 20)	**Obese group (n = 40)**
FG (mg/dl)		
Range	81.0 – 104.0	63.0 – 110.0
Mean ± SD	90.85 ± 6. 91	96.83 ± 9. 65
p		$p = 0.017^*$
2hrs OGTT glucose (mg/dl)		
Range	68.0 – 110.0	81.0 – 141.0
Mean ± SD	84.17 ± 10.51	101.63 ± 15.90
p		$p < 0.001^*$
Insulin (µIU/ml)		
Range	3.00 – 11.17	3.95 – 28.67
Mean ± SD	5.05 ± 1.89	10.97 ± 5.61
p		$p < 0.001^*$
HOMA-IR		
Range	0.61 – 2.56	0.87 – 6.08
Mean ± SD	1.14 ± 0.47	2.61 ± 1.35
p		$p < 0.001^*$
QUICKI		
Range	0.33 – 0.42	0.29 – 0.39
Mean ± SD	0.38 ± 0.02	0.33 ± 0.02
p		$p < 0.001^*$

p : p value compared to normal control subjects (independent T test)

* : Significantly different from normal control group

Significance was considered at the level of $p \leq 0.05$

2.3. Results of serum omentin–1 (ng/l):-

The statistical analyses of range and mean ± SD values of serum omentin–1 of normal and obese men were shown in table (3).

For normal men (table 3), the mean omentin–1 was 84.20 ± 36.43 ng/l (range 51.78 – 202.89).

For obese men (table 3), the mean omentin–1 was 66.39 ± 30.24 ng/l (range 40.75 – 189.08).

The data showed a significant difference in omentin–1 ($p < 0.05$) between normal and obese men.

Table 3: The statistical analyses of serum omentin–1 (ng/l) of normal and obese groups

p_1 : p value compared to normal control subjects

	Normal group (n = 20)	**Obese group (n = 40)**
Omentin-1 (ng/L)		
Range	51.78 – 202.89	40.75 – 189.08
Mean ± SD	84.20 ± 36.43	66.39 ± 30.24
p_1		$p_1 = 0.002^*$

(Mann-Whitney test)

* : Significantly different from normal control group

Significance was considered at the level of $p \leq 0.05$

table 4. The statistical analyses of Results of serum total testosterone (TT) (ng/ml), serum free testosterone (FT) (Pg/ml) serum sex hormone binding globulin (SHBG) (nmol/l) and serum estradiol (E2) (Pg/ml) of normal and obese groups

	Normal group (n = 20)	**Obese group (n = 40)**
TT (ng/ml)		
Range	2.42 – 10.26	2.39 – 6.64
Mean ± SD	6.86 ± 2. 11	4.37 ± 1. 11
p		$p < 0.001^*$
FT (Pg/ml)		
Range	28.48 – 82.36	6.70 – 63.42
Mean ± SD	57.10 ± 12.68	44.95 ± 11.93
p		$P = 0.001^*$
SHBG (nmol/l)		
Range	22.20 – 136.00	11.80 – 42.20
Mean ± SD	56.45 ± 29.82	26.75 ± 7.53
p_1		$p < 0.001^*$
E2 (Pg/ml)		
Range	13.90 – 54.14	23.0 – 52.10
Mean ± SD	31.12 ± 9.65	37.49 ± 6.62
p		$p = 0.004^*$

p : p value compared to normal control subjects (independent T test)

p_1 : p value compared to normal control subjects (Mann-Whitney test)

* : Significantly different from normal control group

Significance was considered at the level of $p \leq 0.05$

2.4. The correlation among the studied clinical and biochemical parameters

Our results revealed that HOMA-IR was negatively correlated with QUICKI (r = -0.935**, p = 0.001), omentin-1 (r = -0.389**, p = 0.002), TT (r = -0.384**, p = 0.002), FT (r = -0.382**, p = 0.003) and SHBG (r = -0.498**, p = 0.001), and positively correlated with BMI (r =0.682**, p = 0.001), WC (r =0.559**, p = 0.001), WHR (r =0.285**, p = 0.027), FG (r =0.316*, p = 0.014) and SI (r =0.987**, p = 0.001), as illustrated in table (5).

Also, serum omentin-1 was found to be negatively correlated with BMI (r = -0.423**, p =

0.001), WC (r = -0.300**, p = 0.020), FG (r = -0.334**, p = 0.009) and SI (r = -0.375**, p = 0.003), and positively correlated with QUICKI (r = 0.403**, p = 0.001), FT (r = 0.447**, p = 0.001) and SHBG (r = 0.275*, p = 0.034), as illustrated in table (5).

In addition, serum TT was negatively correlated with BMI (r = -0.595**, p = 0.001), WC (r = -0.594**, p = 0.001), FG (r = -0.262*, p = 0.043) and SI (r = -0.368**, p = 0.004), and positively correlated with QUICKI (r = 0.440**, p = 0.001), FT (r = 0.392**, p = 0.002) and SHBG (r = 0.646**, p = 0.001), as illustrated in table (5).

Moreover, serum FT was negatively correlated with BMI (r = -0.393**, p = 0.002), WC (r = -0.446**, p = 0.001), WHR (r = -0.399**, p = 0.002) and SI (r = -0.366**, p = 0.004), and positively correlated with QUICKI (r = 0.348**, p = 0.006) and SHBG (r = 0.287**, p = 0.026), as illustrated in table (5).

Table 5. Correlation of plasma RBP-4 levels with clinical and biochemical parameters

		BMI	WC	WHR	FG	SI	HOMA-IR	QUICKI	Omentin-1	TT	FT	SHBG	E2
BMI	r	1.000	0.798**	0.329*	0.441**	0.672**	0.682**	-0.676**	-0.423**	-0.595**	-0.393**	-0.504**	0.213
	p		.000#	.010#	.000#	.000#	.000#	.000#	.001#	.000#	.002#	.000#	.102
WC	r	0.798**	1.000	0.605**	0.276*	0.554**	0.559**	-0.644**	-0.300*	-0.594**	-0.446**	-0.503**	0.325*
	p	.000#		.000#	.033#	.000#	.000#	.000#	.020#	.000#	.000#	.000#	.011#
WHR	r	0.329*	0.605**	1.000	0.052	0.296*	0.285*	-0.264*	-0.224	-0.222	-0.399**	-0.194	0.141
	p	.010#	.000#		.692	.022#	.027#	.041#	.085	.089	.002#	.138	.282
FG	r	0.441**	0.276*	0.052	1.000	0.183	0.316*	-0.412**	-0.334**	-0.262*	-0.078	-0.315*	-0.022
	p	.000#	.033#	.692		.162	.014#	.001#	.009#	.043#	.551	.014#	.870
SI	r	0.672**	0.554**	0.296*	0.183	1.000	0.987**	-0.916**	-0.375**	-0.368**	-0.366**	-0.465**	0.075
	p	.000#	.000#	.022#	.162		.000#	.000#	.003#	.004#	.004#	.000#	.567
HOMA-IR	r	0.682**	0.559**	0.285*	0.316*	0.987**	1.000	-0.935**	-0.389**	-0.384**	-0.382**	-0.498**	0.050
	p	.000#	.000#	.027#	.014#	.000#		.000#	.002#	.002#	.003#	.000#	.702
QUICKI	r	-0.676**	-0.644**	-0.264*	-0.412**	-0.916**	-0.935**	1.000	0.403**	0.440**	0.348**	0.485**	-0.183
	p	.000#	.000#	.041#	.001#	.000#	.000#		.001#	.000#	.006#	.000#	.161
Omentin-1	r	-0.423**	-0.300*	-0.244	-0.334**	-0.375**	-0.389**	0.403**	1.000	0.148	0.447**	0.275*	-0.194
	p	.001#	.020#	.085	.009#	.003#	.002#	.001#		.259	.000#	.034#	.138
TT	r	-0.595**	-0.594**	-0.222	-0.262*	-0.368**	-0.384**	0.440**	0.148	1.000	0.392**	0.646**	0.073
	p	.000#	.000#	.089	.043#	.004#	.002#	.000#	.259		.002#	.000#	.580
FT	r	-0.393**	-0.446**	-0.399**	-0.078	-0.366**	-0.382**	0.348**	0.447**	0.392**	1.000	0.287*	-0.057
	p	.002#	.000#	.002#	.551	.004#	.003#	.006#	.000#	.002#		.026#	.663
SHBG	r	-0.504**	-0.503**	-0.194	-0.315*	-0.465**	-0.498**	0.485**	0.275*	0.646**	0.287*	1.000	-0.153
	p	.000#	.000#	.138	.014#	.000#	.000#	.000#	.034#	.000#	.026#		.243
E2	r	0.213	0.325*	0.141	-0.022	0.075	0.050	-0.183	-0.194	0.073	-0.075	-0.153	1.000
	p	.102	.011#	.282	.870	.567	.702	.161	.138	.850	.663	.243	

r :Pearson coefficient **r_s** : Spearman coefficient

** . Correlation is significant at the 0.01 level (2-tailed).

* . Correlation is significant at the 0.05 level (2-tailed).

: Statistically significant at $p \leq 0.05$

3. Discussion

Over the last two decades, the prevalence of overweight or obesity in the world has increased at an accelerating and alarming rate. Obesity is closely linked to a wide array of pathophysiologic consequences including insulin resistance (IR), type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia and atherosclerosis.[27] The association of obesity with T2DM has been recognized for decades, and the major basis for this link is the ability of obesity to engender IR. But not all obese have IR or diabetes, not all fat deposits contribute to this disease.[27] Banerji

and his colleagues discovered that fat distribution in the body is important for the progress of the disease. [28] Thus, visceral fat in central or visceral obesity, mainly composed of omental and mesenteric fat and retroperitoneal fat,[29] is more important in relation to IR than subcutaneous fat and the reduction in visceral fat can increase the sensitivity of insulin.[28,29] In clinical studies waist circumference and waist-to-hip ratio are closely correlated with visceral fat content.[30,31] In the present study, BMI, WC and WHR were significantly higher in obese group as compared to normal group.

In the present study, it was noticed that glucose and the two proxy parameters of IR,[32-34] SI and HOMA-IR, were significantly higher in obese than in normal group and significantly positively correlated with WC,WHR and BMI. This result is expected and confirmed by Kahn and his colleagues, who reported that obesity is a major cause of IR.[35]

As for the mechanism linking obesity and IR, FFAs role is preferentially considered because it has ever been suggested to be a main underlying cause of IR. In obesity, FFAs released from visceral fat to the liver via portal vein are more than those released from subcutaneous fat,[36] which could decrease the sensitivity of insulin in the liver and exert dysfunction in the liver via several mechanisms, including stimulation of gluconeogenesis and / or fatty acid oxidation. [27] So FFAs have been suggested to be a main underlying mechanism of IR in obesity. [37]

FFAs are not sufficient to account for the mechanism from obesity to IR. However, further studies were done demonstrating that visceral obesity affects the release of certain cytokines from macrophages infiltrating into the fat, particularly increasing the release of tumor necrosis factor-α (TNF-α), IL-6, resistin and plasminogen activator inhibitor-1. Elevated TNF-α in adipose tissue is known to contribute to IR along with IL-6, a cytokine that is elevated in both obesity and T2DM. IL-6 reduces insulin sensitivity by inhibiting insulin receptor signal transduction in tissue. [38,39

Therefore we hypothesis that adipocytokines may be a bridge connecting obesity and IR, and visceral fat in obesity also could be a primer for IR.

When visceral fat accumulates, just like a primer, in visceral obesity it should begin to display unhealthy effect which begin to take place in the body. In addition to it, as one of physiological regulation mechanisms of the body, most of the adipocytokines from the visceral fat reduce the visceral fat volume. Actually, on the contrary, with a change in the serum adipocytokine level and an imbalance of them in the body for a long term, it will become a pathological condition and various kinds of effects may leads to the formation of new pathogenesis and new therapeutic approach to IR. [27]

White adipose tissue is a major secretory and endocrine organ that secretes ~ 30 biologically active peptides and proteins that can be grouped either adipose derived hormones (for example leptin, adiponectin, and resistin) or adipokines (immune modulating agents) such omentin. [40]

Omentin is recently discovered novel adipokine. [41] Its physiological role in human remain largely unknown. [22] The goal of this study was to evaluate the levels of serum omentin-1 and its association with serum testosterone and IR in obese men. Therefore we planned to analyze the relationship of serum omentin-1 with some parameters of adiposity (WC,WHR, BMI), IR parameters (glucose, SI, HOMA-IR), and hormonal profile (TT, FT, β-estradiol, SHBG).

In the present study, it was found that serum omentin-1 levels in obese group, were lower than normal subjects. Additionally serum omentin-1 concentration were negatively correlated with WC and BMI. The data suggests that some aspects of obesity negatively regulates omentin-1 expression and release into the circulation. This result is in agreement with the report of De Souza Batista, [42] demonstrating that obesity is an important factor to induce the omentin-1 reduction.

Although the data clearly supports the regulation of omentin-1 by obesity, omentin-1

may also be regulated by inflammation. Other studies have shown that omentin-1 expression is altered in inflammatory states.[43,44] Obesity itself is associated with low levels of chronic inflammation, which may contribute to the regulation in the role of omentin-1 in human physiology. [45,46]

Furthermore, the lower omentin-1 levels observed in this study may suggest the dysregulation of omentin-1 in biosynthesis or in response to hyperglycemia and hyperinsulinemia in obese group. Tan and his colleagues [47] reported that insulin and glucose significantly and dose-dependently decreased omentin mRNA expression and omentin protein production in omental adipose tissue explants, and that hyperinsulinemia significantly reduced serum omentin-1 levels in healthy subjects. It may be that serum glucose and insulin levels regulate omentin-1 synthesis directly or indirectly.

In the current study, a negative significant correlation of omentin-1 levels with glucose, insulin and HOMA-IR index, and positive correlation with QUICKI were observed. Previous in vitro studies demonstrated that omentin-1 increases insulin signal transduction by activating the protein kinase B [48] and enhances insulin-mediated glucose transport in adipocytes.[49] We speculate that the decreased serum omentin-1 concentration observed in obese group may cause a reduction of insulin-stimulated glucose uptake in visceral and subcutaneous adipocytes or other insulin sensitive tissues. Accordingly we can predict that lack of omentin-1 may contribute to IR.

Obesity has been associated with various endocrine abnormalities both in men and women. [50,51] in this study, it was noticed that the reproductive hormonal profile of obese men deviate from what is considered the norm. TT, FT and SHBG were significantly lower in obese as compared to normal group whereas β-oesteradiol was higher. Moreover, TT, FT and SHBG were negatively correlated with anthropometric indices (BMI and WC), and FT negatively correlated with WHR. These results are supported by other studies. Allan et al [52] demonstrated that changes in visceral fat appeared to be a function of changes in serum testosterone levels, and prospective studies [53] confirm that lower androgen predict central adiposity in men. Furthermore, longitudinal epidemiological data demonstrate that relatively low testosterone levels are a risk factor for development of visceral obesity. [54]

Testosterone is a lipophilic hormone, its transportation in blood requires binding to plasma proteins, primarily sex hormone binding globulin (SHBG). [55] The reduced level of SHBG concentration reduced in this study and its inverse relation to visceral obesity (BMI, WC) can explain the significant reduction of circulating testosterone in obese subjects. the cause of reduced SHBG is thought to be due to higher circulating insulin concentration detected in obese subjects as basal secretion of SHBG by cultured human hepatoma cell line (HepG2) was greatly reduced by the physiological concentration of insulin.[56-58] Previous studies showed that, in vivo diazoxide treatment, resulting in decreased insulin levels, produces a significant increase in SHBG, [59] whereas SHBG levels decrease actually during hyperinsulinemic euglycemic clamp studies together, these intervention studies suggest that insulin negatively regulates hepatic production of SHBG. [60]

It has been suggested that the increase in adipose tissue in obese may results in increased release of pro-inflammatory cytokines such as TNF-α and IL-1.[61] Cytokines inhibit testosterone production primarily through actions on the testis. TNF-α inhibit steroidogenesis in Leydig cells at the transcriptional level. It has been suggested that NF-kB, a nuclear factor activated by TNF-α, inhibits the transactivation of orphan nuclear receptors that mediate the expression of steroidogenic-enzyme genes. [62] IL-1 has also been found to inhibit cholesterol side chain cleavage by cytochrome P450 in Leydig cells. [63]

Although it is well established testosterone biosynthesis is regulated primarily by pulsatile secretion of LH, there is compelling evidence that Leydig cell steroidogenesis is also modulatedby circulating and / or locally produced hormones. [64] Insulin receptors are present on Leydig cells, and insulin stimulate testosterone production in Leydig cell cultures. [65] These in vitro data seem

to be at variance with the demonstration in our study that high insulin levels are inversely correlated with serum testosterone levels. However, we hypothesized that IR states such as obesity, Leydig cell steroidogenesis is impaired because of target organ resistant to insulin action.

In addition, obese group have been shown to have elevated levels of β-oestradiol than normal group. This estrogen excess is explained by over activity of the aromatase cytochrome P450 enzyme, which is expressed at high levels in white adipose tissue and is responsible for a key step in the biosynthesis of estrogen. [66] An increase in β-oestradiol concentration would lead to the suppression of hypothalamic gonadotropin-releasing hormone and pituitary gonadotropin secretion. [67] Thus would result in the reduction of testosterone secretion by Leydig cells.

Furthermore, it was found that total and free testosterone correlate negatively with insulin and HOMA-IR and positively with QUICKI, this results is consistent with that reported by Tsai et al [33] and Pilleloud et al. [68]

One mechanism by which testosterone via androgen receptor might facilitate insulin sensitivity is by regulating the expression of insulin dependent proteins, and dose-dependent effects of testosterone on insulin receptor substrate-1 (IRS-1) and glucose transporter-4(GLUT-4) have been documented in cell models. [69,70] Thus the low levels of testosterone may throw light on the possibility of decreasing insulin sensitivity in obese subjects.

Moreover, previous studies demonstrated that testosterone correlate positively with genetic and functional mitochondrial indices of increased insulin sensetivity in human skeltal muscle, [68,71,72] and in male rats castration increases IR by decreasing muscular glucose uptake. [73] Recent microarray studies in mice have shown that testosterone regulates skeltal muscule genes involved in glucose metabolism in ways that would be expected to decrease systemic IR. [74,75] In view of these studies it could predicted that decreased levels of testosterone detected in our data may cause mitochondrial dysfunction leading to decreased lipid oxidation, ectopic TG accumulation and ultimatly to IR.

Also, testosterone inhibits lipoprotein lipase enzyme (LPL) in abdominal adipose tissue, leading to decreased TG uptake in central fat depots. [76] This low testosterone levels detected in the present study may predispose to viseral obesity, leading to dysregulation of fatty acid metabolism, which in turn promotes IR.

In obese men, hypoandrogenism is an early marker of glucose metabolism and insulin alteration, which may progress toward a metabolic syndrome, or to an overt diabetes.

The results of the present study revealed that testosterone which is positively correlated with insulin sensitivity may be considered as one of the contributing factor for the development of IR in obese subjects. Moreover, reduced levels of omentin-1 observed in this study may also be attributed to hyperinsulinemia, and its correlation with FT may point to the possible effect of FT on circulating omentin-1 levels.

4. Conclusion

- As compared to normal group, body mass index, waist circumference, waist to hip ratio, fasting serum glucose, 2hr oral glucose tolerance test, serum insulin and HOMA-IR and estradiol were significantly higher, while omentin-1, total testosterone, free testosterone and sex hormone-binding globulin were significantly lower in obese subjects.
- Both serum omentin-1 and total testosterone as well as free testosterone were significantly negatively correlated with body mass index, waist circumference, fasting serum glucose, serum insulin and HOMA-IR, and significantly positively correlated with QUICKI and sex hormone-binding globulin. In addition, omentin-1 serum levels correlate positively with free testosterone.
- Serum omentin-1 levels was significantly decreased in obese men, omentin-1 could be used as a biological marker for insulin resistance in obese. In addition the close relationship between serum omentin-1 levels and free testosterone levels may suggest that

the regulation of omentin-1 might be dependent on free testosterone levels.

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