Study of Serum Omentin-1 in Relation to Insulin Resistance in Type II Diabetes Mellitus

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Abstract:
Aim and Objective: Omentin-1 is a novel adipokine expressed in visceral adipose tissue and has been reported to be negatively associated with insulin resistance (IR). The present study aimed at assessing the correlation of serum Omentin-1 with IR in Type II Diabetes mellitus patients as measured by Homeostasis Model Assessment (HOMA-IR). There has been very few reports (if any) from Indian subcontinent on the role of Omentin in IR.
Materials and Methods: It is a case control study, fifty cases of Type II DM patients and equal number of age and sex matched controls were included in the study. Fasting serum Omentin, fasting serum insulin were estimated by ELISA using commercially available ELISA kit and fasting blood sugar by glucose oxidase method by using EM360 autoanalyzer. HOMA-IR score was calculated as HOMA-IR = [Fasting Glucose (mg/dl) × Fasting Insulin (μIU/ml)] / 405. Serum Omentin-1 was correlated with FBS, serum insulin and HOMA-IR using SPSS version-20.
Results: Significant difference was observed in serum Omentin levels between patient and control group(27.57 ± 6.67 vs 49.78 ±4.34ng/ml:p<0.001). Significantly high insulin levels(33.11 ± 13.75 vs 10.96 ±2.4μIU/ml) and high HOMA-IR levels (18.58±11.96 vs 2.85 ± 0.85) observed in patients as compared to controls. Serum Omentin correlated negatively with FBS(p<0.001,r=-.766), insulin(p<0.001,r=-.883) and HOMA-IR(p<0.001,r = -.810) in patient group.
Conclusion: Omentin-1 level was observed to be significantly low in diabetic patients. The negative correlation signifies that when IR worsens the level of serum Omentin-1 decreases. Thus this adipokine holds promise as a therapeutic target in future.
Key words: Omentin-1, insulin resistance, HOMA-IR, Type II Diabetes.

1. Introduction

Type II diabetes mellitus is a quickly growing global metabolic disease characterized by impaired insulin secretion from pancreatic cells and insulin resistance in liver, muscle and adipose tissue, in the presence of appropriate environmental factors, particularly those leading to obesity.[1] The prevalence of diabetes is rising all over the world due to population growth, aging, urbanisation and an increase in obesity and physical inactivity. Unlike in the west, where older persons are worst affected, diabetes in Asian countries is disproportionately high in young to middle-aged adults[2,3]. This would have long lasting adverse effects on a nation's health and economy, especially for developing countries. According to recent estimates by International Diabetes Federation 2014, approximately 387 million people worldwide (prevalence rate of 8.3%) in the 20-79 year age group have diabetes in 2014 and by 2035, 592 million people of the adult population is expected to have diabetes, a jump by 55 percent[4]. The largest increase will take place in the regions dominated by developing economies[4].The number of people with type II DM is increasing in every country. 77% of people with diabetes live in middle and low-income countries. The greatest number of people with diabetes are between 40 to 59 years of age[4]. Estimated global health care expenditure to treat and prevent diabetes and its complications are expected to a total of at least 548.5 billion US $ in 2013[4]. Among the top ten countries in the world by number of people with diabetes in 2013, ages 20 to 79 years, the three countries with the largest number of people with diabetes are China, India and the U.S [4]. India is the second largest country in the world with 65.1 million people affected with diabetes[4]. Roughly 80% of people with diabetes are in developing countries, of which India and China share the largest contribution. It is evident from the above figures that DM is becoming a major public health concern and hence research is important for prevention and treatment of the disease. Recently, a new protein called **Omentin** has been identified as a novel depot-specific adipokine in human adipose tissue, which could have a possible role in modulating insulin action [5]. The study on Omentin-1 and its relation with type II DM, degree of IR is of recent interest and holds therapeutic promises.

Insulin is a key regulator of glucose homeostasis. Insulin resistance is established by genetic and environmental factors. Insulin resistance (IR) leads to impaired glucose tolerance, and plays an important pathophysiological role in the development of diabetes[6]. The insulin resistance (IR) is defined as a diminished physiological response of tissues to insulin action, particularly at the level of muscles and adipose tissues with a consequent compensatory hyperinsulinemia, which initially maintains plasma glucose levels in normal ranges. It is a hallmark of type II diabetes and cardiovascular diseases, and leads to many of the abnormalities associated with metabolic syndrome [7], determination of which has become important at the population level.

The hyperinsulinemic euglycemic clamp is considered to be the gold standard of laboratory methods to confirm the diagnosis of IR, but it is a complex and invasive technique, not suitable for implementation at the population level[8]. Homeostasis model assessment (HOMA-IR) developed by Matthews in 1985 estimated IR by the homeostasis basal fasting concentrations of glucose and insulin [9] and has been proven to be a good equivalent of IR measurements as evidence against clamp euglycemic, the clamp or minimal model hyperglycaemic in different age groups and even in diabetic patients[10]. It is therefore, a non-invasive, fast, inexpensive alternative and reliable way to estimate IR, allowing its applications in large scale epidemiological studies.

Like an endocrine organ, adipose tissues secretes a variety of adipokines, including leptin, adiponectin, visfatin, TNF-α and IL-6[11,12]. These adipokines have widespread effects on carbohydrate and lipid metabolism and appear to play an important role in the pathogenesis of insulin resistance, diabetes, atherosclerosis, vascular endothelial dysfunction and inflammation[13-17]. Recently **Omentin,** a novel fat depot-specific adipokine that was identified from a cDNA library from visceral omental adipose tissue by Yang et.al. in 2003[18].The Omentin gene is located in the 1q22-q23 chromosomal region, which has been linked to type II diabetes in different populations[19-22]. Omentin m-RNA is predominantly expressed in the stromal vascular fraction of visceral adipose tissue and is barely detectable in subcutaneous fat depots and mature adipocytes. There are two highly homologous isoforms of Omentin, Omentin-1 and Omentin-2; Omentin-1 is the major circulating form in human plasma[23].The biological activity of Omentin is not well understood. Recombinant Omentin enhances insulin-stimulated glucose uptake and Akt phosphorylation in human subcutaneous and visceral adipocytes in vitro, but has no effect on basal glucose uptake[5]. Recent studies had shown that Omentin-I plasma levels and gene expression correlated negatively with obesity and insulin resistance and positively with adiponectin and HDL (High Density Lipoprotein) levels.[23,24]

Research on Omentin has generated interest in its biological roles in DM with respect to generation of insulin resistance. As it has been seen that Omentin increases insulin sensitivity, it is supposed to have potential theraputic role. The research on Omentin is very limited from this part of the world. The present work is taken up to identify the role of Omentin in insulin resistance which could add to its role in therapeutic importance.

2. Study Design and Methods

2.1 Subjects

A total of 50 male newly diagnosed type II diabetes from 33-68 yrs of age were recruited from the outpatients attending Endocrinology OPD M.K.C.G Medical College Hospital, Berhampur, Odisha from 1st January 2013 to 1st may 2014. 50 members of age and sex matched healthy subjects formed the control group. Diagnoses were based on the diagnostic criteria of World Health Organisation (WHO) 1999[25]. No subjects had acute or chronic infectious diseases, hypertension, heart failure, stroke, peripheral vascular diseases, hepatic or renal disease or cancer; none of the subjects had taken any medicine affecting blood glucose levels. This study was approved by the institutional ethical committee. Informed consent was obtained from each participant.

2.2 Biochemical measurements

After an 8-12 hr overnight fast, fasting venous blood samples were obtained. Plasma glucose was measured by glucose oxidase method by using EM 360 autoanalyzer from ERBA Transasia using commercial kits from Erba diagnostics. Fasting serum Omentin was measured by using commercially available enzyme-linked immunosorbent assay (ELISA) from EMD Millipore corporation, USA according to manufacture's protocol (HUMAN OMENTIN-1, Cat # EZHOMNTIN1-29K). Intra-assay coefficient of variation was 1.10%, inter-assay coefficient of variation was 2.9%. Insulin levels were assessed by using commercially available ELISA, made by Diagnostic Automation /Cortez Diagnostics, Inc. (Insulin ELISA,Cat #1606Z). A homeostasis model assessment of insulin resistance was calculated as **HOMA-IR= [Fasting Insulin (μIU/ml) X FPG (mg/dl)] /405.**

2.3 Statistical analysis

Data was presented as mean ± SD. The data was analysed by student's t' test for unpaired data. Correlation was derived by Pearson's correlation analysis. A p-value of < 0.05 was considered significant. Statistical analysis was done using SPSS version 20 software.

3. Results

3.1 The Clinical and biochemical parameters of cases and controls :

The study was performed with 50 newly diagnosed type II diabetic males and similar number of age and sex matched control subjects. Table-1 shows the age distribution of controls and cases. The age distribution of the two groups did not show significant difference. In the present study, 68% of cases (34 out of 50 cases) belonged to the age-group of 40-54 yrs. While that in the control group was 56% (28 out of 50 controls). The difference of mean age was insignificant among the two groups (p>0.05).

The biochemical parameters of the cases and control group were shown in Table 2. Fig-1 compares fasting insulin, serum Omentin, insulin resistance (as measured by HOMA-IR) between control and patient group. The mean ± SD of FBS level was 207.12 ±55.56 (mg/dl) in cases while that in the control group was 102.20 ± 10.79(mg/dl). The difference of fasting blood sugar between the two groups was significant (t=13.10, p < 0.001). The mean ± SD of fasting insulin was 33.11 ± 13.75 (µIU/ml) in cases while that in the control group was 10.96 ±2.48 (µIU/ml). The difference of fasting insulin level between the two groups was significant (t=11.20, p < 0.001). The mean ± SD of serum Omentin was 27.57 ± 6.67 (ng/ml) in cases while that in the control group was 49.78 ±4.34 (ng/ml). The difference of fasting Omentin level between the two groups was significant (t=-19.71, p < 0.001). The mean ± SD of HOMA-IR was 18.58 ± 11.96 in cases while that in the control group was 2.85 ± 0.85. The difference of insulin resistance as measured by HOMA-IR between the two groups was significant (t= 9.27, p< 0.001). Thus It was observed that FBS, Fasting Plasma insulin and HOMA-IR levels were significantly higher (p<0.001) in case group as compared to control group and serum Omentin was found to be significantly lower in cases as compared to control group with p-value <0.001.

3.2 Correlation of serum Omentin-1 with fasting blood sugar, fasting insulin, insulin resistance as measured by HOMA- IR in cases and control group :

Table 3 and Fig. 2 show the correlation between serum Omentin with FBS in the cases. Plasma Omentin correlated negatively with Fasting Blood Sugar in cases (r = -0.766, p <0.001), which was statistically significant. Thus, it was observed that as the FBS level rises there is significant fall in serum Omentin level.

Table 4 and Fig.3 show the correlation between serum Omentin with FBS in the controls. Serum Omentin correlated negatively with Fasting Blood Sugar in control group (r = - 0.698, p <0.001) which was statistically significant. Thus it was observed that serum Omentin level decreased with rise of FBS both in cases and control group.

Table 5 and Fig.4 show the correlation between plasma Omentin with Fasting insulin in cases. Serum Omentin correlated negatively with Fasting insulin in cases (r=-0.883, p <0.001) which was statistically significant. Thus it was observed that serum Omentin level decreased with rise of Fasting insulin in cases.

Table 6 and Fig.5 shows the correlation between serum Omentin with Fasting insulin in controls. Serum Omentin correlated negatively with Fasting insulin in control group (r=-0.067, p < 0.001) which was statistically significant. Thus it was observed that serum Omentin level decreased with rise of Fasting insulin in control group.

Table 7 and Fig. 6 show the correlation between serum Omentin with insulin resistance as measured by HOMA-IR in patient group. Serum Omentin correlated negatively with HOMA-IR in cases (r=-0.810, p < 0.001) which was statistically significant. Thus it was observed that serum Omentin level decreased with rise of insulin resistance in diabetic patients.

Table 8 and Fig. 7 show the correlation between plasma Omentin with insulin resistance as measured by HOMA-IR in control group. Plasma Omentin correlated negatively with HOMA-IR in control (r=-0.544, p <0.001) which was statistically significant. Thus it was observed that plasma Omentin level decreased with rise of insulin resistance in control group.

Table –1: Age Distribution of Patients and Control Group

Age Groups	Healthy Controls (n=50)			Type II DM Patients		
	Total No.	Total %	Mean ± SD	Total No.	Total %	Mean ± SD
<40	8	16		6	12	
40-54	34	68	47.9 ± 7.3	28	56	50.06± 9.0
>54	8	16		16	32	

SD = standard deviation, (The p-value between cases and control was 0.0803, i.e >0.05)

Table-2: Comparison of Clinical Parameters in Cases and Control Group

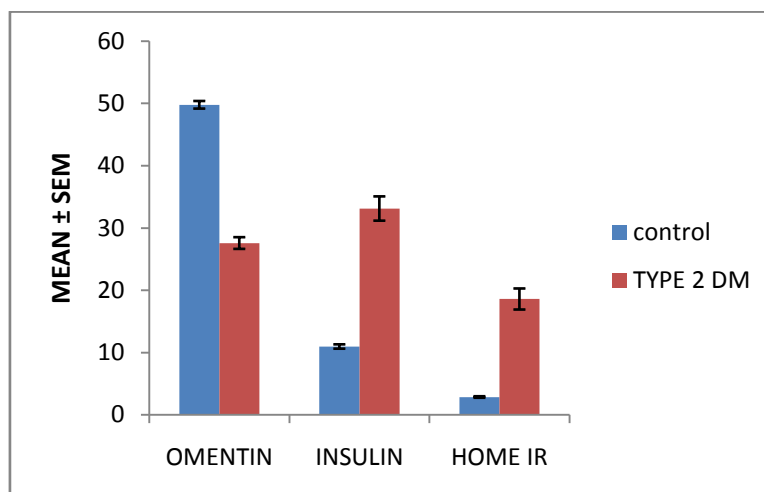| Parameters	Study Group	N	Mean	SD	P-value	t-value
FBS (mg/dl)	Case	50	207.12	± 55.56	<0.001	13.10
	Control	50	102.20	± 10.79		
Fasting Insulin (μIU/ml)	Case	50	33.11	± 13.75	<0.001	11.20
	Control	50	10.96	±2.48		
Omentin (ng/ml)	Case	50	27.57	±6.67	<0.001	-19.71
	Control	50	49.78	±4.34		
HOMA-IR	Case	50	18.58	±11.96	<0.001	9.27
	Control	50	2.85	±0.85		

Fig. 1: Comparison of Plasma Omentin, Insulin & HOMA-IR in Cases and Control group

Table-3: Correlation of Plasma Omentin with FBS in Diabetic Patients

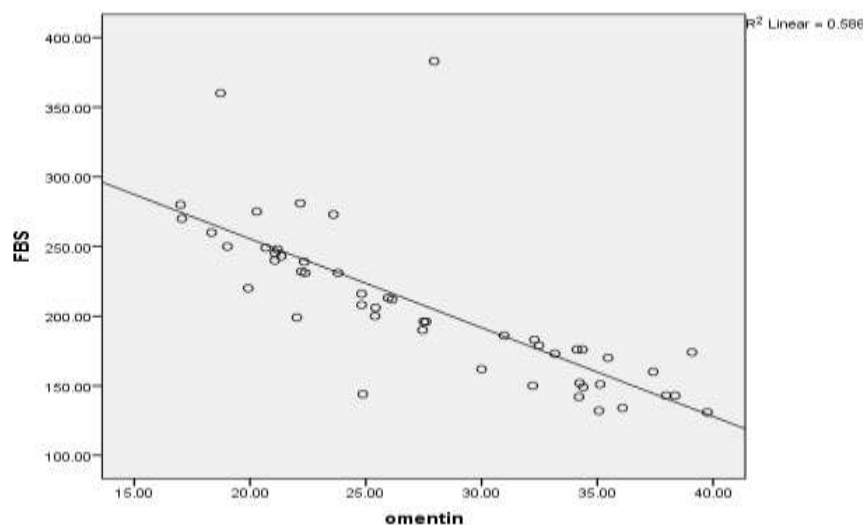| Correlations		Omentin	FBS
Omentin	Pearson Correlation	1	-.766[**]
	Sig. (2-tailed)		.000
	N	50	50
FBS	Pearson Correlation	-.766[**]	1
	Sig. (2-tailed)	.000	
	N	50	50
**. Correlation is significant at the 0.01 level (2-tailed).			

Fig. 2: Correlation of Plasma Omentin with FBS in Cases

Table-4: Correlation of Plasma Omentin with FBS in Control Group

Correlations		Omentin	FBS
Omentin	Pearson Correlation	1	-.698[**]
	Sig. (2-tailed)		.000
	N	50	50
FBS	Pearson Correlation	-.698[**]	1
	Sig. (2-tailed)	.000	
	N	50	50
**. Correlation is significant at the 0.01 level (2-tailed).			
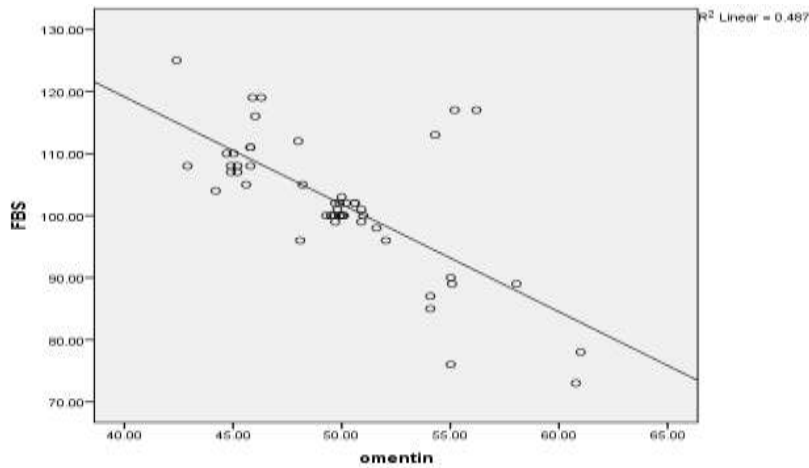
Fig. 3: Correlation of Plasma Omentin with FBS in Controls

Table-5: Correlation of Plasma Omentin with Fasting Insulin in Diabetic Patients

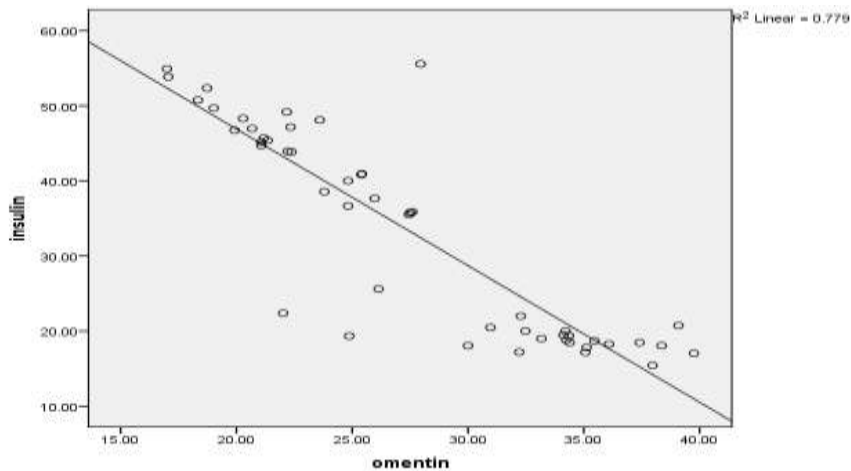| Correlations		Omentin	insulin
Omentin	Pearson Correlation	1	-.883[**]
	Sig. (2-tailed)		.000
	N	50	50
Insulin	Pearson Correlation	-.883[**]	1
	Sig. (2-tailed)	.000	
	N	50	50
**. Correlation is significant at the 0.01 level (2-tailed).			

Fig. 4: Correlation of Plasma Omentin with Insulin in Cases

Table-6: Correlation of Plasma Omentin with Fasting Insulin in Control Group

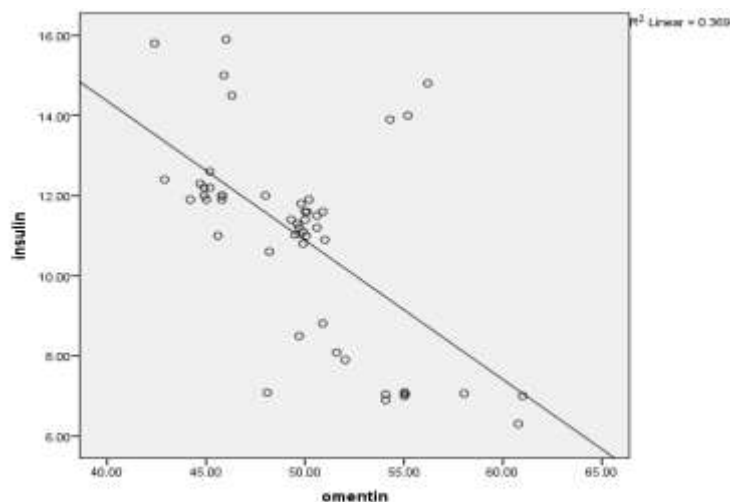| Correlations		Omentin	insulin
Omentin	Pearson Correlation	1	-.607[**]
	Sig. (2-tailed)		.000
	N	50	50
Insulin	Pearson Correlation	-.607[**]	1
	Sig. (2-tailed)	.000	
	N	50	50
**. Correlation is significant at the 0.01 level (2-tailed).			

Fig. 5 Correlation of Plasma Omentin with Insulin in Controls

Table-7: Correlation of Plasma Omentin with Homa-IR in Diabetic Patients

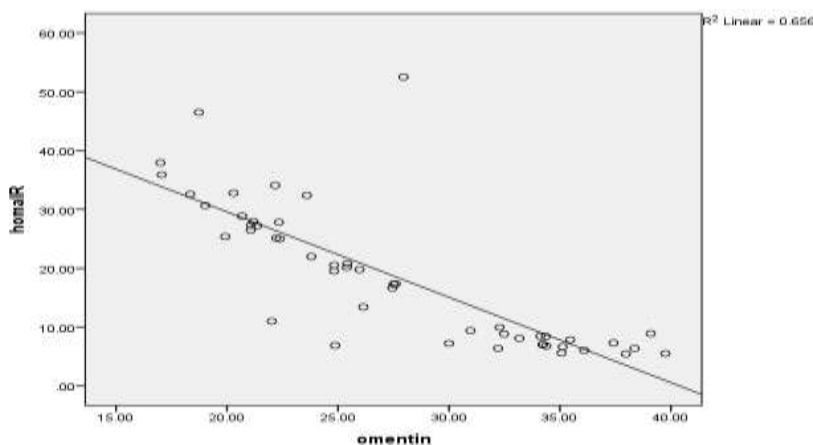| Correlations		Omentin	homaIR
Omentin	Pearson Correlation	1	-.810[**]
	Sig. (2-tailed)		.000
	N	50	50
homaIR	Pearson Correlation	-.810[**]	1
	Sig. (2-tailed)	.000	
	N	50	50
**. Correlation is significant at the 0.01 level (2-tailed).			

Fig. 6 Correlation of Plasma Omentin with HOMA-IR in Cases

Table-8: Correlation of Plasma Omentin with Homa-IR in Control Group

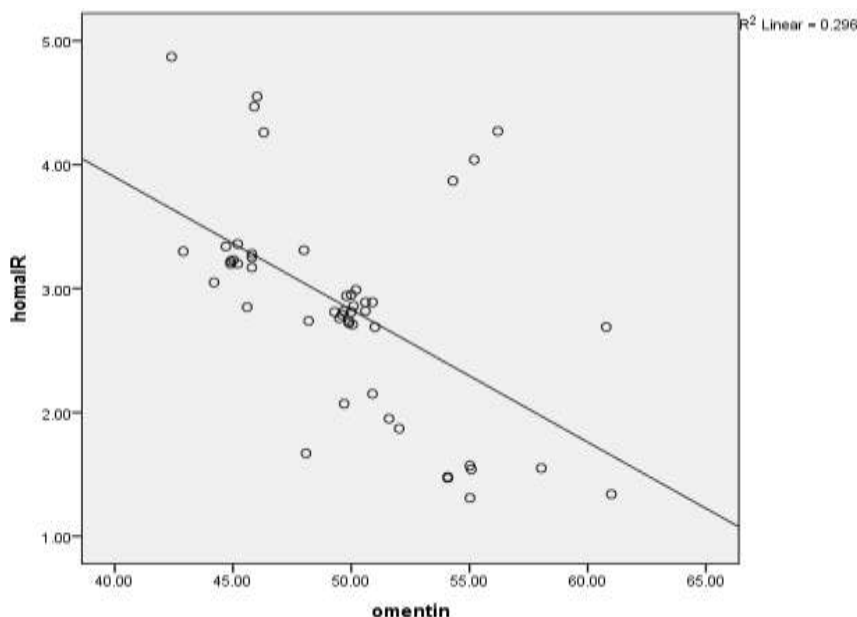| Correlations			
		Omentin	homaIR
Omentin	Pearson Correlation	1	-.544[**]
	Sig. (2-tailed)		.000
	N	50	50
homaIR	Pearson Correlation	-.544[**]	1
	Sig. (2-tailed)	.000	
	N	50	50
**. Correlation is significant at the 0.01 level (2-tailed).			

Fig. 7 Correlation of Plasma Omentin with Insulin in Controls

4. Discussion

The current study was conducted in the Department of Biochemistry in collaboration with the department of Endocrinology, MKCG Medical College and Hospital, Berhampur, Odisha, India to evaluate the level of plasma Omentin and correlate it with the levels of fasting blood sugar, fasting insulin and insulin resistance as measured by HOMA-IR in newly detected diabetic patients in south Odisha.

In recent studies, role of various adipokines have been highlighted in the aetiopathogenesis of diabetes mellitus. Recently, **Omentin** a novel depot-specific adipokine in human adipose tissue has been identified in last one and half decade only, which could have a possible role in modulating insulin action[5]. Omentin was identified as a 35-kDa protein with 313 amino acids, named after its preferred expression in omental (visceral) rather than subcutaneous fat tissue[18]. Omentin, the fat depot-specific protein is synthesized by visceral stromal cells, but not by adipocytes[18]. It has been proposed to increase insulin sensitivity in human adipocytes [5].There are two other homologs of Omentin which has been identified, but it is the Omentin -1 which is the major circulating form of Omentin[23]. In vitro studies have shown that Omentin has an insulin sensitizing effect on adipocytes in both visceral and subcutaneous adipose depot through increased insulin signal transduction by activation of Akt/ Protin Kinase B (Akt/pkb)[5]. It also enhances insulin–stimulated glucose uptake in human adipocytes[5]. It has been shown that plasma Omentin levels were inversely correlated with BMI, Waist circumference, leptin, resistin, insulin and insulin resistance as measured by homeotstatis model assessment and positively correlated with adiponectin and high-density lipoprotein (HDL-cholesterol) [23,24]. In vitro studies have shown that administration of glucose and insulin to human omental adipose tissue resulted in a dose-dependent reduction of Omentin-1 expression[5]. Furthermore, prolonged insulin glucose infusion in healthy individuals significantly decreased the serum Omentin-levels. These findings suggest that Omentin has a paracrine or endocrine role in modulating insulin sensitivity. There have been very few reports from Indian subcontinent on the role of Omentin in IR. So the present study may help in assessing the correlation of plasma Omentin-1 with insulin resistance in Type II DM patients.

The present study included 50 newly diagnosed diabetic male patients and 50 healthy age and sex matched controls. Various parameters studied among these groups were Fasting blood sugar, Fasting serum insulin, plasma Omentin and insulin resistance as measured by HOMA-IR.

In the present study the mean ± SD of plasma Omentin level in the patient group was 27.57±6.67 ng/ml while that in the control group was 49.78±4.34 ng/ml. The difference was significant (p<0.001). There was significant decrease in plasma Omentin-1 level in cases as compared to control group. Plasma Omentin level correlated negatively with FBS among patients with a 'r' value of -0.766. However the correlation was less observed among the control group with a 'r' value of -0.698.

In a study by Jose maria et al. [26], 2010, the level of serum Omentin (ng/ml) among lean, overweight, obese were 53.7 ± 16.9, 45.2 ± 16.8, 40.1 ± 15.5 respectively. They also found plasma Omentin-1 levels among normal glucose tolerance group and impaired glucose tolerance group were 47.5 ± 18.1(ng/ml) and 44.1 ± 15(ng/ml) respectively. The serum Omentin-1 levels were found to be significantly low in obese and impaired glucose tolerance group.

Hong-yan Pan et al. [27] in the year 2010 had similar serum Omentin-1, among normal glucose tolerance and impaired glucose tolerance groups with values of 18.85±3.23 ng / ml in the former group and 16.22±4.08 in the later group. In their study serum Omentin-1 levels correlated negatively with plasma glucose levels. Our study results had a similar pattern of relation between serum Omentin-1 and fasting Plasma glucose levels.

Similarly Tan et al., 2008a[28] ; Tan et al., 2008b [29]; Souza –Batista et al., 2007 [23]; Cai et al., 2009 [30];Pan et al., 2010 [31]; also found in their studies that plasma Omentin-1 levels decreased in diabetic patients and negatively correlated with plasma glucose levels.

In another study of M. Urbanova, T Dostalova et al. [32], it was detected that serum concentration of Omentin significantly decreased in both obese and type II DM patients relative to control subjects. However, this group failed to find any significant relationship of baseline serum Omentin-1 to fasting glucose levels.

These results suggest that Omentin is important for glucose metabolism. It has been observed that in vitro, Omentin increases insulin signal transduction by activating protein kinase B and enhances insulin–mediated glucose transport in adipocytes. It is possible that the decreased serum Omentin-1 levels observed in patients with impaired glucose regulation may cause a reduction of insulin stimulated glucose uptake in visceral and subcutaneous adipocytes or other insulin sensitive tissues; this way contributes to insulin resistance and development of diabetes.

In the present study the fasting serum insulin level (μU/ml) was found to be high in patient group (31.11±7.75) as compared to control group (10.96±2.48) and the difference was significant. Thus there was some degree of insulin resistance in the patient group. Also, the serum Omentin level decreased with the rise in fasting insulin level both among the controls and patients.

Our data are in concordance with that of previous studies by M. Urbanova et al.[32], G. Gursoy et al.[33], Celia M. De Souza Batista et al. [23], Bee K. Tan et al. [28], Arassh Hossein Nezhad et al.[34], where it has been shown that fasting plasma insulin level correlated negatively with plasma Omentin-1 levels. This finding suggests that plasma Omentin-1 could play an important role in the pathogenesis of insulin resistance in type II DM.

In the present study, the insulin resistance as measured by Homostasis model assessment score (HOMA-IR) was 18.58 ±11.96 in diabetic patients, while in the control group it was 2.85±0.85. And the different was significant (p<0.001). Plasma Omentin-1 level correlated negatively with HOMA-IR both in patients and control group, which is more marked in patient group with a 'r' value of (-.810) as compared to control group ('r' value of -.544).

M Urbanova, I Dostalova et al. [32] have found that fasting insulin (μIU/ml) among Type II DM group was 37.8±4.43 and HOMA-IR index among Type II DM was 11.6±2.19. Our study also corroborates with their findings with fasting insulin (μIU/ml) and HOMA-IR among patient groups being 33.11±13.75 and 18.58 ±11.96 respectively.

It has been reported by Maria Luisa et al. [35] that the HOMA-IR score as a measure of IR was found to be 2.04 to 2.33 among healthy adults. G. Gursoy, N. G. Kirnap et al. [33] reported that the HOMA-IR among healthy adults was 2.2±0.8. Bee K Tan et al. [28]reported that it was 1.8 ±0.6. In our study, the HOMA-IR in the control group was 2.85 ±0.85 which is similar to the findings by the above groups. Serum Omentin was negatively correlated with fasting insulin level and HOMA-IR both in cases and in patient group. This suggests that Omentin has a role in insulin resistance. DM is characterised by a state of insulin resistance which was also

found in the present study where the level of fasting insulin was significantly higher among the patient group as compared to controls.

Thus the present study highlighted the role of Omentin in glucose homeostasis, serum insulin level and indirect measure of IR as calculated by HOMA-IR. Several adipokines hold promise as therapeutic candidates to improve IR in type II DM. Omentin discovered only about one and half a decade ago joins the league of potential therapeutic molecules in the treatment of DM.

5. Summary and Conclusion

The fasting insulin level was found be high among the cases. HOMA-IR score as a measure of insulin resistance was observed to be high in the cases. Serum Omentin level decreased in TYPE II DM cases. Serum Omentin correlated negatively with fasting blood sugar, fasting insulin and HOMA-IR in cases. However large multicentric study regarding the role of Omentin in improving insulin resistance in type II DM is required to assess its potential role as a therapeutic molecule.

Acknowledgement

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