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Original Research Article

Adipocytokines, Insulin Sensitivity and Endothelial Dysfunction among offsprings of Type 2 Diabetes Mellitus

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Abstract

Prevention of diabetes and its associated burden has become a major health issue worldwide. The present study was undertaken to assess the changes in insulin sensitivity and endothelial dysfunction well before the onset of diabetes in population with positive family history for diabetes. The objectives of the study is to estimate the levels of serum Adiponectin, Visfatin, Insulin, HOMA IR and platelet derived microparticles P-selectin levels in offspring of type 2 Diabetes mellitus. The healthy volunteers who are aged between 18- 22 years of either sex, were selected based on their family history of diabetes. The study showed a significant decrease in serum Adiponectin and increase in serum Visfatin, Insulin, HOMA IR & P-selectin levels in the offspring of type 2diabetes. The Adiponectin showed a negative correlation with Visfatin, P selectin, Insulin & HOMA IR. Genetic predisposition for diabetes may influence adipocytokine levels which might play a key role in developing diabetes in near future.

Keywords: Adiponectin, Visfatin, P-Selectin, Endothelial Dysfunction, Insulin sensitivity, Type 2 Diabetes mellitus.

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INTRODUCTION

As per International Diabetic Federation, India is so called as diabetic capital of the World with already 50.8 million existing diabetic patients, expected to rise up to 87 million by 2030 [1]. The recent global epidemic of Type-2 Diabetes Mellitus is indicative of the importance of environmental triggers such as rapid changes in lifestyle related to changing patterns and increasing physical inactivity. However, there is strong evidence from twin, family, and epidemiological studies for genetic factors contributing to the etiology of type 2 Diabetes [2].

Many studies have hypothesized that atherosclerotic Cardiovascular disease (CVD) & Diabetes share common antecedents. A syndrome of insulin resistance may constitute this common antecedent, but molecular mechanisms underlying the diverse effects of insulin resistance are not well studied. Subclinical inflammation could be a unifying factor as it is a precursor of CVD, is associated with insulin resistance, and precedes development of type 2diabetes. Inflammatory mediators may be pathogenic by inducing systemic endothelial dysfunction. Identification of endothelial dysfunction as a type 2 diabetes precursor might expand options for the early diagnosis prevention and treatment of Diabetes [3]. The etiology of endothelial dysfunction is complex and involves deregulation of multiple pathways. Endothelial dysfunction (ED) has been implicated in the pathophysiology of different forms of cardiovascular disease, including chronic heart failure, diabetes mellitus, hypertension, coronary heart disease and chronic kidney disease (CKD) [4].

With the recent progress in adipocyte biology it is clear that adipose tissue is not just an energy storage organ but it is an active endocrine organ, secreting number of small protein peptides, or adipokines (namely, leptin, Adiponectin, Visfatin**,** resistin, TNFα, IL-6) [5]. These adipocytokines can act locally within the adipose tissue, but they can also reach distant organs through the systemic circulation, where they can exert a wide range of biological actions, including the regulation of food intake and body

weight, insulin sensitivity, reproduction, immunity, inflammation, or vascular homeostasis [6, 7]. Importantly, an imbalanced adipocytokine production, as observed in clinical metabolic conditions including obesity and type 2 diabetes mellitus, has been associated with adipose tissue inflammation and the pathogenesis of insulin resistance and endothelial dysfunction. Adipose tissue also appears to be a modulator of vascular injury and systemic inflammation. Thus, adipokines link endothelial dysfunction with insulin resistance, a prominent feature in type 2 diabetes mellitus [8].

Adiponectin is a protein exclusively secreted by the white adipose tissue. Adiponectin has a molecular weight of 30 KDa and composed of 244 amino acids. It modulates a number of metabolic processes including glucose regulation and fatty acid metabolism by exerting anti-diabetic, anti-inflammatory and anti-atherogenic effects [9].

Anti-inflammatory and anti-atherogenic properties of adiponectin and the ability to stimulate insulin sensitivity have made Adiponectin an important molecule for physiological and pathophysiological studies with the aim of potential therapeutic applications that suggesting a protective role in diabetes development [10]. The serum adiponectin concentration has a strong genetic component, with heritability estimated at 88%. Recent studies have indicated that Hypo adiponectinemia is caused by interactions of genetic factors such as SNPs (Single Nucleotide Polymorphisms) in the adiponectin gene and environmental factors which may be responsible for insulin resistance, type-2 diabetes and metabolic syndrome [11]. Studies undertaken on different ethnic groups have shown a strong positive association of the adiponectin gene, SNP45 T>G polymorphism with type 2 Diabetes [12, 13].

Visfatin (VF) is an Adipokine identified in 2004 [14] and thus named for the suggestion that it would be predominantly produced and secreted in visceral fat. It is identical to pre-B cell colony-enhancing factor (PBEF), described in 1994 as a cytokine produced by lymphocytes, acting on lymphocyte maturation and inflammatory regulation. Visfatin was found to be released predominantly from macrophages rather than from adipocyte in visceral adipose tissue. In this regard, there is sufficient evidence to consider that Visfatin is expressed by the macrophages infiltrating adipose tissue and is produced in response to inflammatory signals [15]. Visfatin may play an important role in regulating insulin sensitivity in the liver [16]. Visfatin exerts insulin-mimetic effects that are dose dependent and qualitatively similar to those of insulin in stimulating muscle and adipocyte glucose transport & inhibiting hepatocyte glucose production. But some of the observations revealed conflicting data regarding the role of Visfatin in regulation of insulin sensitivity in humans [17]. Endothelial dysfunction can readily be assessed by measuring circulating levels of endothelial soluble adhesion molecules [18]. However, prospective data for the relationship between these endothelial adhesion molecules and risk of type 2 diabetes are very limited.

Thus the main objective of the study is to estimate the levels of serum Adiponectin, Insulin, Visfatin & P-selectin levels in offsprings of type 2 diabetes mellitus. To correlate the levels of serum Visfatin and Adiponectin with the BMI (Body Mass Index), Blood glucose, Lipid profile, HbA1c, hsCRP insulin levels & insulin sensitivity.

MATERIAL AND METHODS

It Is a Cross sectional study, participants for the study were the healthy volunteers aged between 18-22years & were selected based on their family history of diabetes and were assigned into two groups. . Group-1, (control group) was those individuals whose both parents are non diabetic & non hypertensive. Group 2, was those individuals whose one or both parents are type-2 diabetic and the study was conducted for 3years. Ethical clearance was taken from the Institutional ethics Committee. A written informed consent was taken from all the participants.

Sample size was calculated with confidence level of 95% with allowable error of 10%. Using Standard deviation as reported by Bose, K. S *et al.*, [19]. The sample size in each group was calculated to be 120.

Inclusion Criteria

Based on the family history of diabetes, the healthy volunteers who are aged between 18- 22 years of either sex, studying at under our institutions namely Govt Medical, Govt Paramedical and Nursing sciences was included in the study.

Exclusion Criteria

Subjects with type 1 diabetes, pre-existing cardiovascular or renal disease and any other acute or chronic inflammatory diseases were excluded.

Sample Collection

Data regarding age, gender, BMI, Blood pressure and other relevant data was collected in the form of questionnaires. 5ml of venous sample & 2ml of EDTA samples was collected in fasting status.

METHODOLOGY

Serum Glucose & Lipid profile was estimated by enzymatic method, Serum hsCRP & HbA1C are measured by turbidometric method using fully automated chemistry analyser Cobas C311 & Serum Insulin by immunoassay method using Cobas e411 immunoassay analyser. Serum Adiponectin,Visfatin

(sincere biotech co, china) and P-Selectin (Boster biotech USA) were analyzed by Sandwich Enzyme linked immunoassay method using commercial kits. Homeostasis model assessment was done using standard formulas [20].

- Homeostasis model assessment insulin resistance (HOMA-IR) is analyzed by formula: Fasting insulin (μU/ml) ×fasting glucose (mg/dl)/22.5.
- The quantitative insulin sensitivity check index [QUICKI] is calculated as 1/log (fasting insulin) +log (fasting glucose).
- Homeostasis model assessment β cell function (HOMA β- cell function) was calculated as HOMA β cell= fasting insulin (μU/ml) ×20/ fasting glucose (mg/dl)-3.5.

Statistical Analysis

The results were expressed as Mean ± Standard deviation. Statistical analysis was performed using SPSS-20 and the test used was Student t- test. To correlate the serum Visfatin, adiponectin and microparticles-P selectin with the insulin sensitivity Pearson's correlation co-efficient was worked out. P value less than 0.05 was considered statistically significant.

RESULTS

As shown in Table-1, A significant decrease in serum Adiponectin and increase in serum Visfatin, Insulin, & P-selectin levels were observed in the offsprings of type 2 diabetic parents when compared with offsprings of non diabetic parents (control group).

The study showed statistically significant increase in the Triglycerides, LDL cholesterol and HsCRP levels in offspring of type 2 diabetes (Table-1).

The study observed no statistically difference in the mean levels of BMI, Waist hip ratio (WHR) & blood pressure between offsprings of diabetes subjects (cases) and offsprings of non diabetic subjects (control group) P > 0.05. At the same time no statistical difference was observed in, serum glucose and HbA1c levels between the groups (*P* > 0.05).

Table-1: Different parameters among offsprings of non-diabetic and diabetic subjects

Parameter	Group-1(Non Diabetic offsprings)	Group 2(Diabetic offsprings)	p- valve
No. of subjects	104	146	
BMI (kg/m2)	20.32±2.5	22.5±2.6	0.120
WHR	0.78±1.5	0.80±0.8	0.131
Systolic BP(mm of Hg)	108± 6	106±6	0.102
Diastolic BP (mm of Hg)	76±2	78±2	0.103
Glucose(mg/dl)	83.56±5.5	85.34±6.6	0.145
Total Cholesterol mg/dl	124.68±28	125.86±25	0.155
HDL-cholesterol mg/dl	55.9±7.7	44.90±8.6	<0.001
LDL-Cholesterol mg/dl	83.19±2.3	95.6±2.2	<0.001
Triglycerides mg/dl	81.43±28	135±31	<0.001
HbA1c%	4.89±0.44	5.02±0.45	0.134
Hs CRP mg/dl	0.82±0.14	2.12±0.56	<0.001
S.Insulin μIU/mL)	4.67±1.6	8.11±2.92	<0.001
Adiponectin(ng/ml)	32.16±7.34	16.14±3.65	<0.001
P-selectin (pg/ml)	298.57±85.52	419.9±56.25	<0.001
Visfatin(ng/ml)	456±145	857±225	<0.001

P<0.05 statistically significant

Assessment of Insulin Sensitivity

The present study showed statistically significant increase in Homeostasis model assessment insulin resistance (HOMA-IR), Homeostasis model assessment β cell function (HOMA β- cell function) and decrease in quantitative insulin sensitivity check index (QUICKI) with mean standard deviation 2.25±0.45, 245±25 and 0.32±0.12 respectively among offsprings of type 2 diabetes mellitus when compared with non-diabetic offsprings as shown in Table-2.

Table-2: Markers of Insulin sensitivity among offsprings of non-diabetic and diabetic subjects

Parameter	Group-1(Non Diabetic offsprings)	Group 2(Diabetic offsprings)	p- valve
No. of subjects	104	146	
HOMA-IR	1.45±0.23	2.25±0.45	<0.001
HOMA Beta cell	255±20	245±25	<0.001
QUICKI	0.45±0.15	0.32±0.12	<0.001

p<0.05 statistically significant

Correlation of Adiponectin with Endothelial dysfunction markers

The Pearson's correlation showed negative when Adiponectin was compared with glucose, Triglyceride, LDL, hsCRP, Insulin and P-Selectin. There was significant positive correlation between adiponectin with HDL with r value of 0.56 as shown in Table-3.

Table-3: Correlation of Serum Adiponectin in offsprings of diabetic patients with other parameters

Parameters	r-valve	Correlation	p value
Glucose	-0.56	Negative	<0.05
HDL	0.558	Positive	>0.05
Triglycerides	-0.53	Negative	<0.05
LDL	-0.51	Negative	<0.05
hsCRP	-0.57	Negative	<0.05
Insulin	-0.67	Negative	<0.05
P selectin	-0.58	Negative	<0.05

p<0.05 statistically significant

Correlation of Adiponectin with Insulin sensitivity indices

Adiponectin showed negative correlation with HOMA IR and significant positive correlation with quantitative insulin sensitivity check index (QUICKI) & Homeostasis model assessment β cell function (HOMA β- cell function) with the r value of -0.51, 0.65 and 0.60. Indicating prospective role of adiponectin in insulin sensitizing activity in Table-4.

Table-4: Correlation of Serum Adiponectin with Insulin sensitivity markers in offsprings of diabetic parents

Parameters	r-value	Correlation	P value
HOMA IR	-0.51	Negative	<0.05
QUICKI	0.65	Positive	>0.05
HOMAβ-cell function	0.60	Positive	>0.05

p<0.05 statistically significant

Correlation of Visfatin with endothelial dysfunction markers

The Pearson's correlation showed positive when Visfatin was compared with glucose, Triglyceride, LDL, hsCRP, Insulin, and P-Selectin was 0.50, 0.58, 0.53, 0.63, 0.67, and 0.64 respectively. There was significant negative correlation between Adiponectin with HDL with r value of- 0.68 & -0.60 respectively in Table-5.

Table-5: Correlation of Serum Visfatin with different parameters in offspring of diabetic parents

Parameters	r-valve	correlation	P value
Glucose	0.50	Positive	>0.05
HDL	-0.601	Negative	<0.05
Triglycerides	0.580	Positive	>0.05
hsCRP	0.624	Positive	>0.05
Insulin	0.615	Positive	>0.05
P selectin	0.642	Positive	>0.05
Adiponectin	-0. 68	Negative	<0.05
LDL	0.532	Positive	>0.05

p<0.05 statistically significant

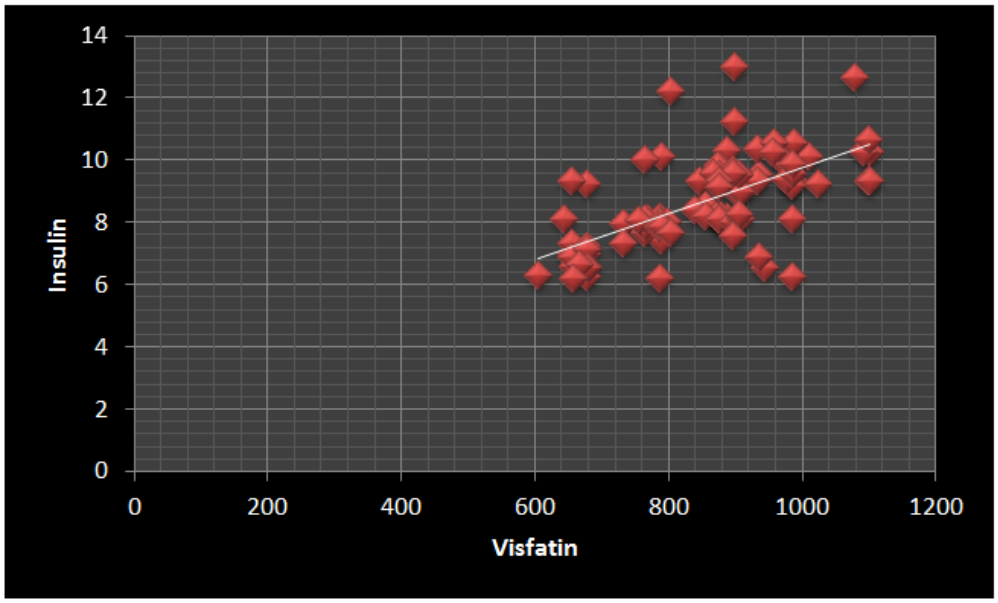
Correlation of Visfatin with Insulin sensitivity indices

We observed Visfatin showed positive correlation with HOMA IR, and negative correlation with quantitative insulin sensitivity check index (QUICKI) Homeostasis model assessment β cell function (HOMA β- cell function) with the r value of 0.561, -0.591 and -0.551 in Table-6.

Table-6: Correlation of Visfatin with Insulin sensitivity markers among offsprings of type 2 Diabetes mellitus

Parameters	r-value	Correlation	p-value
HOMA IR	0.561	Positive	>0.05
QUICKI	-0.591	Negative	<0.05
HOMA β- cell function	-0.551	Negative	<0.05

p<0.05 statistically significant



Graph-1: Scatter diagram showing positive co-relation between Visfatin and Insulin levels among offsprings of type 2 diabetes mellitus

DISCUSSION

Type 2 diabetes mellitus has been suggested to be a disease of the innate immune system responsible for an ongoing cytokine-mediated acute phase response and low-grade chronic inflammation, which may be involved in the atherosclerosis, exhibited in diabetes mellitus patients [21]. Therefore, it is important to determine whether signs of an activated innate immune system are present before the onset of type 2 diabetes mellitus. In this study we intend to assess the changes in endothelial functions and insulin sensitivity status well before the onset of diabetes in offsprings of type 2 diabetes subjects who are genetically risk for developing Diabetes mellitus.

The study showed a significant decrease in serum Adiponectin and increase in serum Visfatin, Insulin, & P-selectin levels in the offspring of type 2 diabetes with mean and standard deviation of 16.14±3.65ng/ml, 857±225ng/ml, 8.11±2.92 µIU/ml, and 419.93±56.25pg/ml respectively when compared with non diabetic offsprings with mean and standard deviation of 32.16± 7.34ng/ml, 456±145ng/ml, 4.67±1.60 µIU/ml, & 298.57±85.52pg/ml respectively in Table-1.

The study showed statistically significant increase in the Triglycerides, LDL and HsCRP levels in offspring of type 2 diabetes with mean and standard deviation 135±31 mg/ml, 95.6±2.2mg/ml, 2.12±0.56mg/ml respectively. We in this study observed no statistically difference in the mean levels of BMI, WHR & blood pressure between offsprings of type 2 diabetes population and non diabetic offsprings (control group) $P > 0.05$. At the same time no statistical difference in serum glucose, cholesterol and HbA1c between groups was observed ($P > 0.05$). Table-1. The results were in agreement with the studies done by Bose' *et al*., [20] Zaid Al-Hamodi [22], Nabila A. Abdella [23]. In the present study, irrespective of BMI & WHR we observed decrease in adiponectin levels in study group which may be due to higher visceral fat than subcutaneous fat.

The present study showed statistically significant increase in Homeostasis model assessment insulin resistance [HOMA-IR], and decrease in Homeostasis model assessment β cell function (HOMA β- cell function) & quantitative insulin sensitivity check index (QUICKI) with mean standard deviation 2.25±0.45, 245±25 and 0.32±0.12 respectively among offsprings of type 2 diabetes mellitus when compared with non-diabetic offsprings as shown in Table-2 with $p<0.05$. The results were in agreement with the studies done by Nabila A. Abdella [23], Shereen Aleidi [24].

The Pearson's correlation showed negative when Adiponectin compared with glucose, Triglyceride, LDL Cholesterol, hsCRP, Insulin and endothelial microparticles P-Selectin was -0.56, -0.53,-0.51,- 0.57, -0.67 and -0.58 respectively. There was significant positive correlation between adiponectin with HDL with r value of 0.55. Findings from the studies indicate a positive correlation between circulating adiponectin levels and HOMA- beta cell functions and quantitative insulin sensitivity check index (QUICKI) independent of BMI. This finding is consistent with some previous studies [23, 24].

These results have potential implications in evolving the hypothesis which triggers, developing diabetes in genetically high risk population. The novel observation signifies impact of adiponectin on Insulin Resistance (IR) and blood glucose homeostasis in offsprings of type 2 diabetes population may have

clinical relevance. As per Kadowaki, *et al*., [25] the human adiponectin gene has been localized to chromosome3p27 which has susceptibility locus for the metabolic syndrome, which could suggest an influence of abnormal synthesis of adiponectin in initiation or perpetuation of metabolic syndrome in genetically high risk population. Study done by Lihn *et al*., [26] observed negative correlation of adiponectin levels with visceral adiposity and lower gene expression in visceral fat compared to subcutaneous fat in both lean and obese humans. Offsprings of type 2 diabetes subject may have higher visceral than subcutaneous fat, which might have led to decreased adiponectin levels. Irrespective of BMI we observed overall decrease in adiponectin levels in study group that were correlated with IR. The hypoglycemic effect of adiponectin was also supported by Berg *et al*., [27]. In their study on administration of recombinant adiponectin they observed reduction in serum glucose in normal and diabetic rodents without stimulating insulin secretion and by Fu Y etal they observed adiponectin over expression increased insulin's ability to maximally stimulate glucose uptake by 78% through increased GLUT-4 gene expression [28, 29].

It is also shown that plasma adiponectin regulates TG rich lipoprotein metabolism and lipid metabolism regulatory enzymes. Based on findings from several previous studies, Adiponectin can increase the insulin activities, improve the glucose tolerance and plays an important role on fatty acid oxidation by stimulating the activity of peroxisome proliferation activated receptor α ligand (PPARα) in both skeletal muscle and liver. Thus treatment with PPARα agonists such as rosiglitazone increases adiponectin gene expression and levels of HDL can be improved. Adiponectin regulates HDL concentration by reducing HDL catabolism and inhibiting hepatic lipase activity. Adiponectin reduces TG storage in skeletal muscle by increasing fatty acid oxidation through AMP kinase activity [30].

Adiponectin has been suggested to have anti-inflammatory and anti-atherogenic properties. In our study adiponectin negatively correlated with inflammatory marker hsCRP and endothelial microparticles P-selectin levels (Graph-1). Indeed, hypoadiponectinaemia is associated with impaired endothelium dependent vasodilation and reduced blood flow in humans. Both adiponectin receptor subtypes are expressed in human vascular endothelial cells, indicating a possible direct effect of adiponectin on these cells [31]. Both AMPK and PKB signalling pathways have been proposed to mediate adiponectin-stimulated NO production and angiogenesis in cultured endothelial cells .Adiponectin has also been shown to inhibit the expression of cell adhesion molecules, including ICAM-1, VCAM-1 and P-selectin [32], in addition to class A1 macrophage scavenger receptors, causing markedly decreased up take of oxidized LDL (low-density lipoprotein) and inhibition of foam cell formation [33]. Such effects may well underlie the anti-thrombotic and anti-atherogenic effects of adiponectin. Variation in serum adiponectin concentrations has been proposed to have a strong heritable component in both a predominantly northern European and Pima Indian populations [34].

Hence to summarize, adiponectin plays an important role in glucose metabolism by its favorable effect on insulin sensitivity. Adiponectin exerts potent insulin-sensitizing action through fatty acid oxidation, increased energy consumption, and stimulation of insulin secretion. There is strong accumulating evidence from several prospective studies that showed low adiponectin levels as a predictor of the incidence of Type 2DM.

The present study showed statistically increased levels of serum Visfatin in offsprings of type 2 diabetes patients and positively correlated with the serum Glucose, Triglycerides, LDL, Insulin, hsCRP, P-selectin levels, which is consistent with studies of Fahmida Kabir & Shatha Abdul [35, 36]. The cause for increase in circulating visfatin levels in hyperglycemia is not clear until now, but it may be due to oxidative stress, increased apoptosis, or destruction of B lymphocytes. The increased level of visfatin can down-regulate the insulin receptors and eventually aggravate HOMA-IR, which shows that visfatin may play an important role in the occurrence of IR [37]. The present study shows positive association of Visfatin with HOMA IR and negatively correlated with HOMA-beta cell function and QUICKI in graph 2. The findings are in agreement with Fahmida Kabir etal. Shatha Abdul Wadood AL- Shammaree.

Some studies failed to find a relation between visfatin and IR in T2DM [38] while many studies reported the presence of significant association with IR [39, 40].

Visfatin an adipocytokine with proinflammatory property induces the secretion of inflammatory cytokines such as IL-8, TNF-α and IL-6 [41]. A previous study indicates that HOMA-IR is a contributing factor for coronary artery stenosis, while increased levels of visfatin and MMP-9 (Matrix Metallo Proteinase-9) are found to contribute to the development and complication of atherosclerosis [42]. In the present study, the plasma concentrations of visfatin significantly correlated with HsCRP, and P selectin in genetically risk population. Furthermore, visfatin which affects not only the metabolism of glucose and lipid, but also the function of endothelial cell and promotes angiogenesis, participates in the process of inflammation and plays an important role in atherosclerosis [43].

CONCLUSIONS

The present study showed altered serum levels of Adipocytokines such as Adiponectin and Visfatin in offspring of Diabetes, responsible for endothelial dysfunction and insulin resistance. Serum adiponectin was significantly decreased in offsprings of type 2 diabetes and positively correlated with altered lipid parameters, insulin levels, HOMA IR and endothelial derived microparticles P-selectin. Serum Visfatin a hormone of visceral fat was significantly increased in offsprings of type 2 diabetic subjects irrespective of BMI. Genetic predisposition for diabetes may influence adiponectin gene expression leading to decrease in its plasma concentration, which might play a key role in developing diabetes in near future. Atherosclerosis is a process that starts at an early life, which in turn is responsible for insulin resistance in offspring. Therefore the present study has an impact on early intervention by life style modification in Diabetic offsprings which in turn could retard the progression of diabetes in them in future. Dietary and physical activity intervention, an established strategy of the prevention for type 2 diabetes, can increase circulating adiponectin levels. The present data may help to understand the biological mechanism whereby lifestyle modification retards the onset of diabetes. Additional Prospective studies and Randomized control Trials are warranted to examine whether increasing circulating levels of adiponectin can decrease the Progression of type 2 Diabetes.

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Conflict of Interest: None

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