Study of Serum Adipocytokines and Lipid Profile with Leptin/Adiponectin Ratio in First-Degree Relatives of Type 2 Diabetic Patients

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Abstracts: Background: The primary health issues worldwide which silently kill are Type 2 Diabetes Mellitus and obesity with the prevalence range of respectfully. The adipose tissue functions play a critical role mainly in glucose and lipid homeostasis. The expansion of the adipocyte mainly leads to chronic low-grade inflammation by the release of pro-inflammatory cytokines such as adiponectin & leptin and others. The adiponectin has anti-atherogenic, anti-inflammatory properties and is also considered a metabolic hormone which influences the glucose and lipid metabolism. The aim of the study is to study the significance of serum adiponectin [HMW] and serum leptin and its correlation with the Lipid profile and the study of atherogenic index [AI] in the first-degree relatives [FDR] of diabetic family [DF] and non-diabetic family [nDF]. Materials & Methods: Present study is a cross-sectional analytical study conducted on 100 first-degree relatives [FDR] of both diabetic and non-diabetic families, along with their parents 50 type 2 diabetic patients and 50 non-diabetic patients. We have categorized the above study participants as groups with a and b as the diabetic and non-diabetic parents and a1 & b1 as the FDR of diabetic [DF] and non-diabetic family [nDF]. Fasting lipid profile, serum adiponectin [HMW] & serum leptin were analysed in all four groups. Result: Serum adiponectin is found significant with serum triglycerides, serum low-density lipoprotein [LDL], Leptin/adiponectin ratio and Atherogenic index [AI] between a & b and a1 & b1 groups. Conclusion: The serum adiponectin is correlated with serum Total cholesterol, TGL, LDL, Leptin/adiponectin ratio and atherogenic index mainly in the a1 first-degree relatives [FDR] of positive diabetic family history, which can be considered as the biomarker for the future risk of diabetic dyslipidaemia.

Keywords: Adiponectin, First-degree relatives, Leptin. Fasting lipid profile, Atherogenic index [AI], Leptin/Adiponectin ratio.

1. INTRODUCTION

Diabetes mellitus is one of the top global health issues in 2023 with an estimated prevalence of 537 million or 10.5 percent worldwide, in which 74.2 million is seen in India [1]. Most instances of diabetes [about 90%] are Type 2 diabetes mellitus [T2DM]. Type 2 Diabetes Mellitus is most frequently diagnosed in those over the age of 45. Nevertheless, it is becoming more common in children, teenagers, and young adults because of rising obesity rates, inactivity rates, and calorie-dense diets leading to prediabetic state [2]. An individual's risk of developing diabetes is 3–4 times higher among those with a positive family history of diabetes than in those with a negative family history. Several studies conducted in western countries have found a high prevalence of developing pre-diabetes condition, mainly in relatives of type 2 diabetic subjects [3]. Insulin resistance or decreased insulin secretion are characteristics of T2DM, which is frequently accompanied by obesity, diabetic dyslipidaemia which in turn enhances insulin resistance by release of numerous adipocyte-derived proteins like leptin and adiponectin [4]. Leptin and Adiponectin are adipokines that impact the mechanism of insulin sensitivity and inflammation and are the main factors that lead to progression of type 2 diabetes. Leptin is a pro-inflammatory molecule that plays a vital role in glucose and energy homeostasis, and their higher levels in serum directly correlate with insulin resistance [IR] [5]. Adiponectin has been considered as a potential anti-diabetic, anti-inflammatory, and anti-atherogenic factor. Their levels are inversely linked with adiposity and reduced in obesity, insulin resistance, and type 2 diabetes mellitus [6]. The ratio of serum leptin to adiponectin [L/A ratio] has been suggested as a more reliable predictor of insulin resistance than serum leptin or serum adiponectin levels alone, since leptin and adiponectin have opposing effects on glucose and fat metabolism [7]. The present study aims to analyse the serum adiponectin, serum leptin and leptin/adiponectin ratio with fasting lipid profile in type 2 diabetic subjects and their first-degree relatives [FDR-DF] compared with non-diabetic subjects

and their first-degree relatives [FDR-nDF]. To determine the association between the serum adiponectin & serum leptin and hyperlipidaemia between the FDR-DF diabetic family and FDR-nDF.

2. MATERIEL AND METHODS

A cross-sectional study was conducted at ACS Medical College and Hospital, Chennai with 50 type 2 diabetes subjects and their corresponding first-degree relatives [FDR-DF] [n=50] and 50 non-diabetic subjects and their first-degree relatives [FDR-nDF] [n=50]. The known diabetic patients and their first-degree relatives represented as FDR-DF were taken into the study as cases 'a' and 'b' respectively. The research excluded first-degree relatives with prediabetic or diabetic individuals that have been known to exist. The patients who were not diabetic and their first-degree relatives represented as FDR-nDF were taken into control as 'a1' and 'b1' respectively. Using the proforma, details on name, age, gender, and family history of diabetes for cases and controls were obtained.

Overnight fasting blood samples [4 mL] were collected in a plain tube. Serum Lipid profiles were measured in fully automatic analyzer - Beckman Coulter AU480. Atherogenic indexes [AI] were calculated [8]. Serum adiponectin [HMW] and Serum leptin were measured using the ELISA method.

Statistical Analysis: Version 20 of the SPSS programme was used for statistical analysis. Percentages are used to show categorical data. The standard deviation and mean were used to express all other data [SD]. A student's 't' test was used to determine whether there was a significant difference between the groups. The significant relationship between various factors is examined using Pearson correlation analysis. Statistics were considered significant if the p value is less than 0.05.

3. RESULTS

A total of about 200 participants were taken into this cross-sectional study. Among these, 50 type 2 diabetic patients who were on oral glycemic drugs with mean age of 46.4 ± 4.5 were taken into study as group-a [Diabetic Family – DF] and their 50 first-degree relatives of type 2 diabetic patients were taken into study as group-b [first-degree relatives of diabetic patients - FDR-DF]

From the participants, 50 non-diabetic subjects with known no other complications with mean age of 52.5 ± 6.5 were taken into study as group-a1 [non-Diabetic family-nDF] and their 50 first-degree relatives of non-diabetic patients were taken into study as group-b1 [first-degree relatives of non-diabetic patients - FDR-nDF].

The parameters were analyzed in independent t test like Serum fasting lipid profile with serum adiponectin, serum leptin and serum leptin/adiponectin ratio in between the group 'a' & group 'b' and group 'a1' & group 'b1', which is shown in Table-1 and Table-2 respectively.

Table-1 represents the significance [p<0.01] between serum adiponectin, serum leptin, serum leptin/adiponectin ratio with serum total cholesterols, serum triglycerides and serum Low density lipoprotein [LDL] and Very Low-density lipoprotein [VLDL] between the groups a and b. There was no significance [p=0.07] between the group a & b over serum High density lipoprotein [HDL].

Table-1: Demographic and clinical parameter between group *a* and group *b* [diabetic family-DF and non-diabetic family-nDF]

Parameter	Mean of *Group a* Diabetic family [DF]	Mean of *Group b* – non-Diabetic family [nDF]	p value
Age	46.4 ± 4.5	52.5 ± 6.5	

Leptin	0.95 ± 0.3	1.20 ± 0.3	P=0.01
Adiponectin	1.27 ± 0.2	1.6 ± 0.7	P<0.01
Leptin/adiponectin ratio	3.5 ± 1.2	4.4 ± 1.1	P<0.01
Total Cholesterol	209 ± 35	160 ± 16.4	P<0.01
Triglycerides	170 ± 50	135 ± 17.4	P<0.01
HDL	48 ± 9.9	47 ± 5.1	P=0.07
LDL	127 ± 34	85 ± 15.3	P<0.01
VLDL	33 ±10.6	27 ± 3.5	P<0.01
Atherogenic Index [AI]	3.6 ± 1.15	2.9 ± 0.59	P<0.01

Table-2 represents the significance [p<0.01] between serum adiponectin, serum leptin, serum leptin/adiponectin ratio with serum total cholesterols, serum triglycerides and serum High density lipoprotein [HDL], Low density lipoprotein [LDL] and Very Low-density lipoprotein [VLDL] between the groups a1 and b1 of First-degree relatives of diabetic and non-diabetic family.

Table-2: Demographic and clinical parameter between group *a1* and group *b1* [First-degree relative-FDR and First-degree relatives-nFDR]

Parameter	**Mean of *Group a1* - FDR**	**Mean of *Group b1* – nFDR**	**p value**
Age	30 ± 6.7	28 ± 5.4	
Leptin	1.04 ± 0.23	2.26 ± 0.78	P=0.05
Adiponectin	1.26 ± 0.33	2.59 ± 0.88	P<0.01
Leptin/adiponectin ratio	4.04 ± 1.17	2.14 ± 1.32	P<0.01
Total Cholesterol	197 ± 36	157 ± 13.6	P<0.01
Triglycerides	171 ± 42	138 ± 20.2	P<0.01
HDL	44 ± 9.39	47 ± 5.5	P=0.03
LDL	119 ± 34.8	82 ±13.9	P<0.01
VLDL	33 ± 8.7	27 ± 4.0	P<0.01
Atherogenic Index	4 ± 1.2	2.9 ± 0.6	P<0.01

Serum Adiponectin is highly significant with serum triglycerides in Pearson's correlation with R2 = 0.161 & p < 0.01, which is shown in Figure-2 below. However, when controlling the variable serum adiponectin in partial correlation in relation to serum triglycerides, there is no discernible difference between serum adiponectin and triglycerides, as indicated in Table-3.

Table-3: Partial Correlations of serum adiponectin vs Serum Triglycerides, Serum Low density lipoprotein.

Correlation	**r value**	**p value**
Adiponectin vs TGL	R^2=0.161	p<00.1**
Controlling Adiponectin variable		
Adiponectin vs TGL	R^2=0.150	P=0.302
Adiponectin vs LDL	R^2=0.87	P=0.393

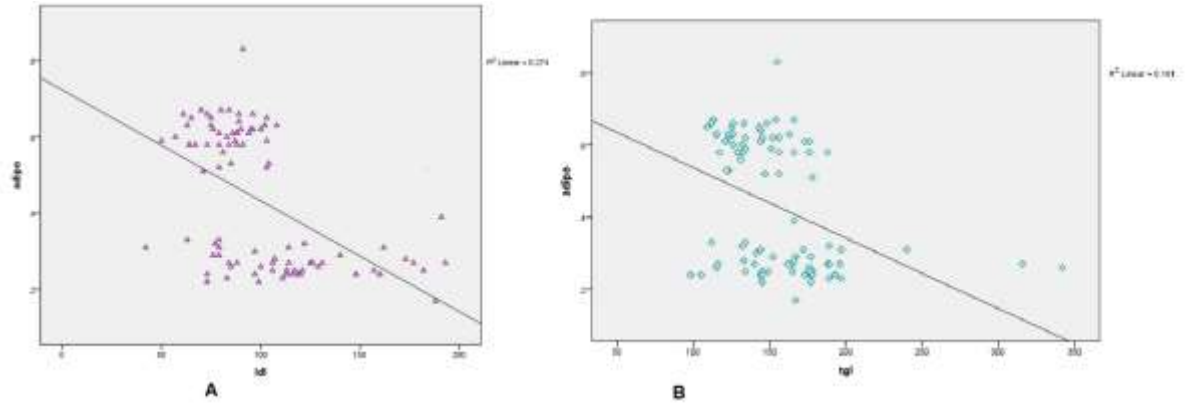

Figure-1-A. Correlation graph between Adiponectin vs LDL, 2-B Correlation graph between Adiponectin vs TGL

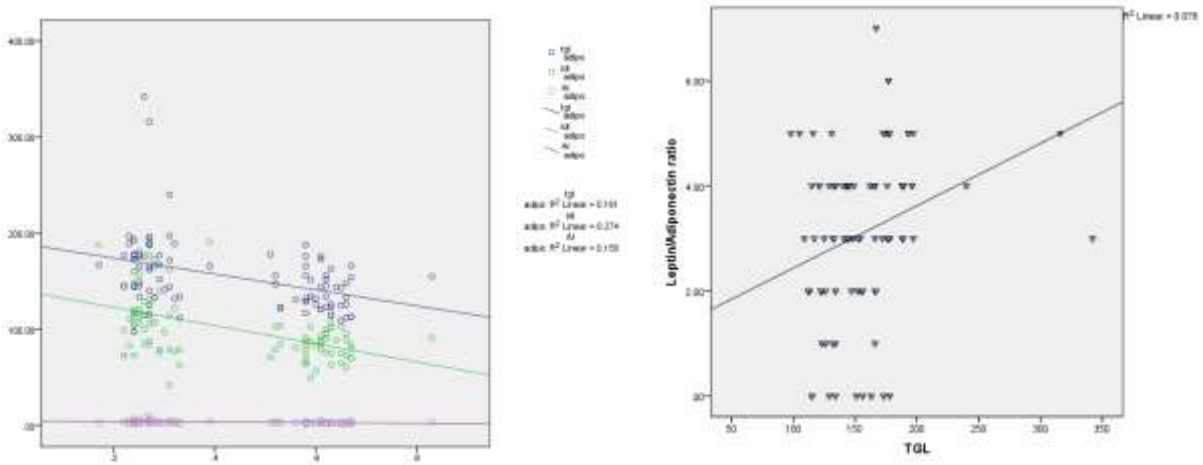

Figure -2A [left] & 2B [right]: Correlation graph between Adiponectin and serum Triglycerides [TGL], serum Low density lipoprotein [LDL], Atherogenic index [AI], Leptin/Adiponectin ratio

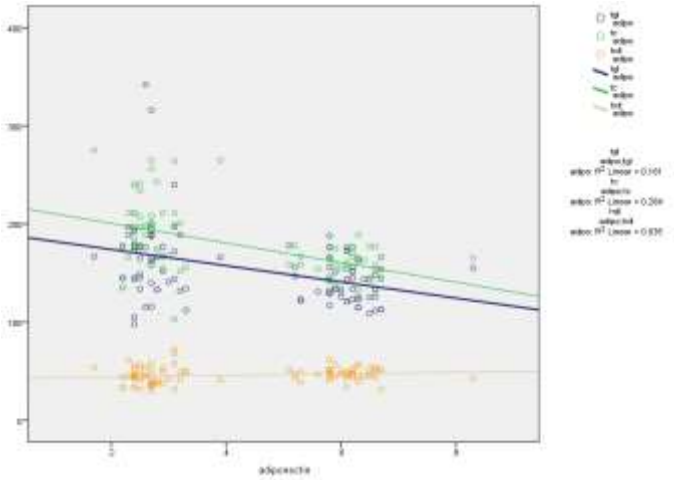

Figure: 3. Pearson's correlation of serum adiponectin with serum Total cholesterol, TGL and HDL

While analysing the Pearson's correlation between First-degree relatives of diabetic [FDR-DF] and First-degree relatives of non-diabetic patients [FDR-nDF], it was found to be negative correlation between serum adiponectin and serum Total cholesterol [r=0.284] and serum Triglycerides [TGL] [r=0.161]. A positive correlation was shown with high density lipoprotein [HDL] [r=0.035].

4. DISCUSSIONS

Prediabetic condition is rapidly increasing in the first-degree relatives [FDR] with positive family history of diabetes in India. Nowadays, the incidence rate of diabetes was found to be high in patients with impaired glucose tolerance [IGT] compared with Normoglycemic patients [NGT] [9]. In our previous study similar results were analysed where among the first-degree relatives of diabetic family and 44% were found to be prediabetic compared with control [10]. Similar study conducted by the Centre for Cardiometabolic Reduction in South Asia [CARRS] in Delhi and Chennai, it was observed that the incidence of type 2 diabetes mellitus among adults aged 20 to 44 was 14.2 in men and 14.8 in women per 1000 people [n=6676] [11]. As per the study analysed by Vijaykumar et al; positive family history of diabetes is a non-modifiable risk factor that can significantly increase the likelihood of developing diabetes in first-degree relatives [FDR], along with prevalence of dyslipidaemia, hypertension, and other metabolic disease [12]. In our previous study analyzed earlier, most of the diabetic patients were found to have high BMI leading to obesity [10], which explains the close association between type 2 diabetes and obesity coining the term "diabesity". Diabesity is a pathophysiological condition, due to development of insulin resistance [IR] in the obese person, which leads to metabolic comorbidities [13]. The secretory protein like adipocytokines such as adiponectin and leptin also have an important role in the development of IR in obese persons [14].

The present data of our findings shown in table 2, [i] the serum adiponectin and serum leptin levels are significantly lower when compared between group a1 and b1 among the first-degree relatives of both DF and nDF. [ii] The fasting lipid profile such as serum total cholesterol, serum triglycerides, serum low-density lipoprotein [LDL] were elevated and was found significant, but showed negative correlation between both groups. The Serum HDL had a positive correlation between the FDR of diabetic family and non-diabetic family. [iii] The Atherogenic index [AI] is significantly higher in the first-degree relatives of DF.

The possible explanation for the hypoadiponectinemia was due to the insulin resistance and obesity seen in first-degree relatives [FDR] of the Diabetic family [DF]. This reflects the inverse function of adiponectin in the development of insulin resistance, which is supported by Lago et al, where reduced secretion of adiponectin and decreased phagocytosis of apoptotic cell leads to inflammation [15]. Adiponectin is associated with anti-atherogenic and anti-diabetes effect such as increasing insulin sensitivity, thus the decreased adiponectin induces the insulin resistance in the individuals [16]. Elevated triglycerides and cholesterol were found significant when compared between the first-degree relatives of both groups a1 and b1. The serum cholesterol and serum triglycerides levels are higher in the first-degree relatives of the diabetic family [DF].

In Figures 1A and 1B, serum adiponectin was correlated with serum low-density lipoprotein [LDL], serum triglycerides [TGL], and serum high-density lipoprotein [HDL]. There was positive correlation between serum HDL & serum adiponectin with r=0.03. There was a negative correlation seen between serum adiponectin and serum TGL, LDL with r=0.27 and r=0.16 respectfully. This negative correlation between serum adiponectin and serum TGL & serum LDL in type 2 diabetic patients seen in similar study done by Vineetha et al [r=-0.63, r=-0.29] and Mukherjee et al [r=0.76, r=0.71] respectfully [17,18]. The adiponectin functions by activating AMP activated protein kinase pathway which decreases the synthesis of TGL and increases the fatty acid oxidation and controls the insulin signalling which increases the insulin sensitivity. In contrast, hypoadiponectinemia influences the increases in TGL and LDL levels. This leads to the cause of diabetic dyslipidaemia in the prediabetic individuals and increases the risk of coronary artery disease [CAD] [18].

In Fig-2A, atherogenic index [AI] graph and in Table -2, AI were found significant and correlated with serum adiponectin with r=0.15. The AI level was elevated in the diabetic family of first-degree relatives [FDR] compared to FDR to nDF. This elevated AI is one of the cardiovascular risks among the positive family history of diabetes, which is similar to the study done by Saeed et al [19]. In Fig-2B, the leptin/adiponectin ratio was correlated with serum triglycerides with r=0.07. As per the study done by Vega and Grundy et al, the leptin/adiponectin ratio is negatively correlated with serum triglycerides [20]. The Leptin/adiponectin ratio is considered as the emerging marker of adipose tissue dysfunction and predicts the risk of cardiometabolic disease clinically in the individuals [21]. Studies suggest that the impact of leptin/adiponectin ratio is correlated with BMI, fat mass, waist circumference and inversely correlated to adiposity which suggested the obesity-related abnormalities in the secretion of leptin & adiponectin [22]

While performing the partial correlation [table-3], between the serum adiponectin and serum triglycerides and serum low-density lipoprotein in first-degree relatives of DF patients, the serum adiponectin which was found statistically significant becomes the causative factor for the elevation of serum triglycerides and serum low-density lipoprotein in the first-degree relatives of Diabetic family history. By lowering blood levels of LDL and TGL, which in turn lowers the synthesis of pro-inflammatory molecules and atherogenic responses, adiponectin levels have been demonstrated to diminish atherogenic reactions.

The increased levels of LDL and the presence of oxidized LDL in the circulation increases atherogenic potential, triggering immune cell activation, foam cell formation, and plaque formation in arterial walls, causing inflammation, endothelial dysfunction, and oxidative stress causing atherogenic dyslipidaemia [23]. In 2A, the Atherogenic index [AI] was found to be significant and correlates [r=0.15] with serum adiponectin when compared between the first-degree relatives of DF and nDF. As a result, hypoadiponectinemia invariably increases the Atherogenic index in first-degree relatives of DF, potentially increasing their future risk of cardiometabolic disease.

CONCLUSION

Despite the fact that the precise aetiology of diabetic dyslipidaemia is unknown, decades of research have shown that it is impacted by a number of complicated genetic and environmental variables, including a family history of diabetes, abdominal obesity, a sedentary lifestyle, and aberrant lipid metabolism. The serum adipocytokines mainly the adiponectin has found to be a biomarker in diagnosing the diabetic dyslipidaemia in the first-degree relatives [FDR] of the diabetic family [DF] and also predicting the cardiometabolic risk in future.

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