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Assessment of sCD36 levels and Lipids in Type II Diabetes Mellitus

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Abstract:
Background: *Cluster determinant 36 (CD36) is a fatty acid translocase which is expressed in variety of cells. Increased expression of CD36 is observed in liver, adipose tissue and skeletal muscle. Non-cell bound CD36 was identified in human plasma and was termed soluble CD36(sCD36) and its level parallels with the increased expression of CD36 observed in various cell types. In diabetes mellitus (DM) the cellular uptake of fatty acids is increased and is associated with insulin resistance and atherosclerosis. Various studies showed elevated sCD36 its association with insulin resistance and atherosclerosis. The aim of the present study is to determine the association of sCD36 with type II DM.* ***Methods:*** *This was a cross-sectional study, and participants were classified as healthy controls and T2DM patients. We estimated FPG, HbA1c, and lipids in them. A quantitative ELISA was used to assess sCD36 levels. Correlation analysis was performed between sCD36 and Triglycerides (TG).* ***Results****: A total of 65 subjects were included, 25 healthy controls and 40 T2DM were included in the study. Elevated levels of sCD36, HbA1c and lipids was observed in cases when compared to controls. Median serum concentrations of sCD36 in healthy controls and type 2 Diabetics are 254 and 462 ng/L respectively and it is statistically significant (p 0.01). The median values for FPG, TG, VLDL in cases were 152.5 (mg/dL), 154.5 (mg/dL) and 31 (mg/dL) respectively and it is significantly higher in cases than controls. But there was no significant association between CD36 & TG.* ***Conclusion:*** *Soluble CD36 (sCD36) identified in human plasma is associated with insulin resistance, Type II DM, atherosclerosis and plasma sCD36 levels reflects its tissue expression. In our study we observed elevated sCD36 levels in type II DM when compared to controls. The findings of our study suggests sCD36 may be used as a marker of insulin resistance.*

Keywords: *sCD36, Type II Diabetes mellitus, HbA1c, Lipids.*

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I. Introduction:

CD36 (cluster of differentiation 36), also known as platelet glycoprotein 4, fatty acid translocase is an integral membrane protein. CD36 consists of 472 amino acids and has an apparent molecular weight of 88,000 Da which is extensively glycosylated. The protein belongs to the class B scavenger receptor family and is expressed in variety of cells i.e. monocytes, macrophages, RBCs, B lymphocytes, capillary endothelial cells, platelets, and adipocytes. CD36 recognizes a different group of primarily lipid ligands, including phosphatidyl serine and a Plasmodium parasite that infects red blood cells. CD36 binds many lipid ligands (anionic or oxidized phospholipids, diacylglycerol, cholesterol) and binds native (High, low and very low density; HDL, LDL and VLDL) and oxidized lipoproteins (ox-LDL and Ox-HDL). Interaction of these ligands with CD36 was shown in many cases to induce CD36-mediated intracellular signaling often initiated by Src tyrosine kinases and involving pathways linked to angiogenesis, inflammation or atherosclerosis.[1-2] Recently Non-cell bound CD36 was identified in human plasma and was termed soluble CD36 (sCD36) (Handberg et al., 2006) and it was found that sCD36 levels parallels the increased CD36 expression observed in multiple cell types and tissues in human and rodent models of insulin resistance and T2 DM (Aguer et al., 2010, Bonen et al.,2004; Griffin et al., 2001; Koonen al., 2007; Luiken et al.,2001; Sampson et al., 2003). Plasma level of soluble CD36 (sCD36) has been strongly implicated in pathological conditions associated with metabolic dysregulation, including obesity, insulin resistance, diabetes, and atherosclerosis in large human trials.[3-5] Soluble CD36 was found to be elevated in type 2 diabetic patients and possibly acted as a marker of insulin resistance and atherosclerosis.

Diabetes is the fastest growing disease. The incidence and prevalence of type2 diabetes is increasing world wide. India currently represents 49 percent of the world's diabetes burden, with an estimated 72 million cases in 2017, expected to almost double to 134 million by 2025, hence estimating the risk of diabetes in the population is more important. As various studies showed plasma CD36 association with type II DM. We have selected this

study to investigate the role of sCD36 in the pathogenesis of insulin resistance and Type II Diabetes mellitus (DM).

II. Materials And Methods:

This was a cross sectional study conducted in a tertiary care hospital. The study group comprises of 25 healthy controls and 40 type II DM. Patients with CKD and abnormal LFT were excluded from the study. Blood samples were collected and following biochemical parameters were measured: Fasting plasma Glucose (FPG), HbA1c, lipid profile and sCD36. FPG was measured using the hexokinase method (AU 680 Beckmann coulter Autoanalyzer). HbA1c was measured by high-performance liquid chromatography (Biorad D10). Total cholesterol was measured by enzymatic cholesterol oxidase peroxidase method, TG levels were measured using the glycerol kinase method. High density lipoprotein cholesterol (HDL-C) was measured using direct enzymatic assays. Low density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula. The sCD36 was measured using ELISA (Sandwich method).

Statistical analysis:

Statistical analysis was done using Graph pad prism 7. Normally distributed variables are expressed as mean and SD and that of non normal variables as median and inter quartile range. Comparison between two normally distributed groups is done by unpaired t-test and Mann-whitney U test is used for comparison of non-normally distributed variables. Spearman correlation was performed to determine relationship between sCD36 and TG levels.

III. Results:

A total of 65 patients were enrolled in the study. 25 healthy controls and 40 Type 2 DM. Among 40 cases, 24 (60%) were males and 16 (40%) were females. In the control group of 25 healthy subjects, there were 16 (64%) males and 9 (36%) females. The mean ± S.D age of controls and cases were 46.6±7.69 and 48.15±8.7 years respectively and the difference was not statistically significant.

Figure1. Distribution of males and females in Controls and Cases

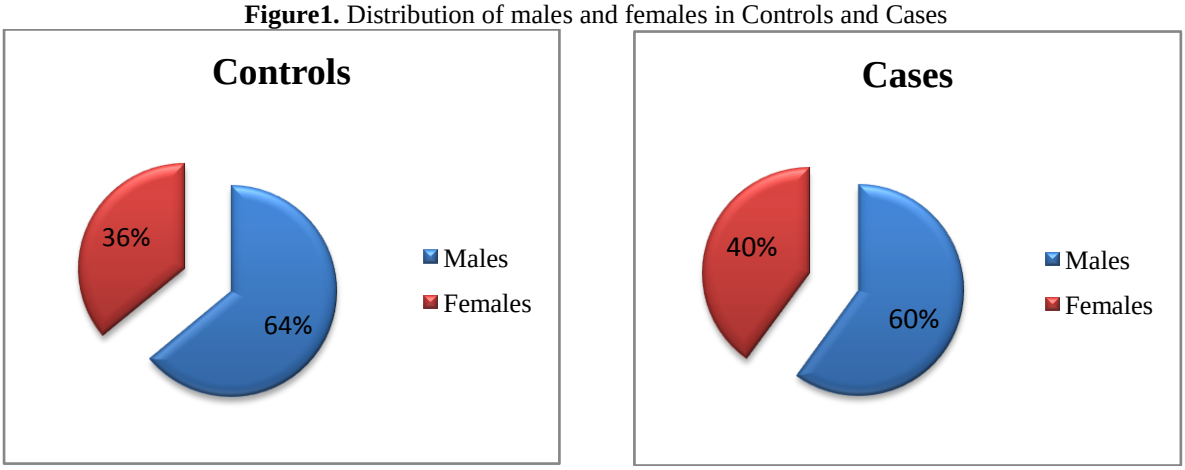


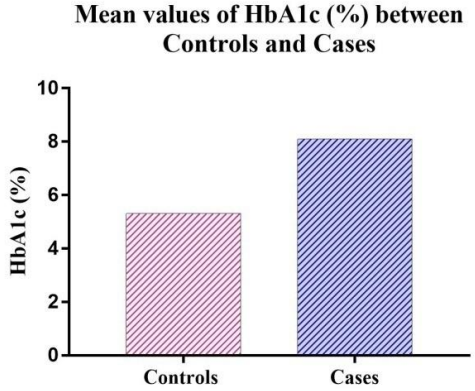
Table 1 Base line characteristics of Controls and Cases

	Controls (n=25) Mean±S.D	Cases (n=40) Mean±S.D	p value
Age (yrs)	46.6±7.69	48.15±8.7	0.46
HbA1c (%)	5.3±0.36	8.28±1.4	<0.0001*
T. Cholesterol (mg/dl)	154.7±37.0	204.6±26.6	<0.0001*
LDL-C (mg/dl)	82.5±27.1	121±28.4	<0.0001*

	Controls (n=25) Median (IQR)	Cases (n=40) Median (IQR)	p value
FPG (mg/dl)	78(73-88)	152.5(120.5-189)	<0.0001*
CD36(ng/L)	254.5(190.7-374.3)	462.7(204.1-658.1)	0.01
TG (mg/dl)	85(63.5-127.5)	154.5(136.3-244)	<0.0001*
HDL-C (mg/dl)	49(45-57)	48(37-53)	0.14
VLDL(mg/dl)	17(12.5-26)	31(27-48.25)	<0.0001*

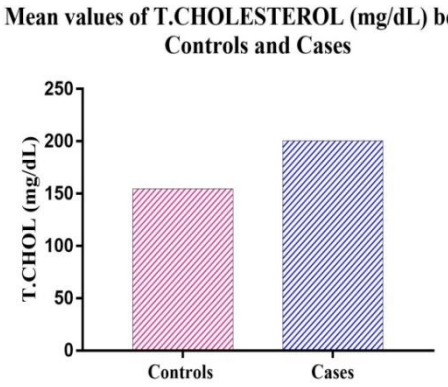
Data presented as mean±SD when it is normal distribution and Median and range when non-normal distribution. *$p<0.05$ is taken as significant. Unpaired t test is done for comparison of two groups for normally distributed parameters and Mann whitney U test for non-normal distributed parameters.

The mean age in Controls and Cases are 46.6 and 48.15 yrs respectively and there is no significant difference between the two groups (p=0.46). Significant difference between means were noted for HbA1c (p<0.0001), T.Cholesterol (p<0.0001) and LDL-C (p= <0.0001). Overall medians for FPG ,sCD36, TG, VLDL in the cases were 152.5 (mg/dL), 462.7(ng/L), 154.5 (mg/dL and 31 (mg/dL),respectively and it is significantly higher in cases than controls. There was no difference in HDL-C levels between the groups.

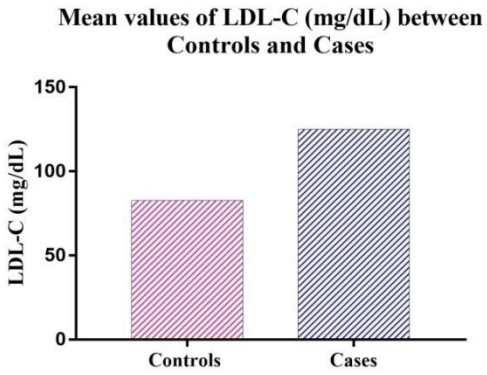


(Fig 2)

The mean HbA1c in Controls and Cases are 5.3 and 8.28 (%) respectively and it is significantly (p<0.0001) higher in cases than controls. (Fig 2)



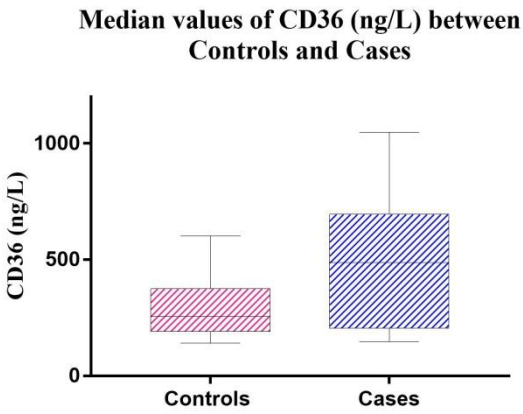
(Fig 3)



(Fig 4)

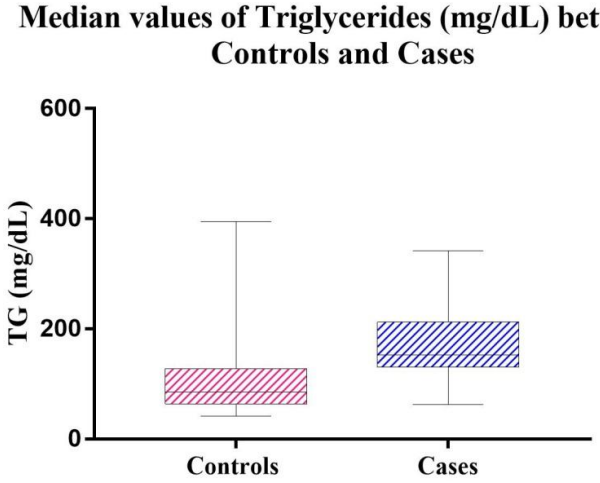
The mean T. Cholesterol in Controls and Cases are 154 and 209 (mg/dL) respectively and it is significantly (p<0.0001) higher in cases than controls. (Fig 3)

The mean LDL-C in Controls and Cases are 82 and 121 (mg/dL) respectively and it is significantly (p<0.0001) higher in cases than controls. (Fig 4)



(**Fig 5)**

The median sCD36 levels in Controls and Cases are 254 and 462 (ng/L) respectively and it is significantly (p 0.01) higher in cases than controls. (Fig 5)



(Fig 6)

The median TG levels in Controls and Cases are 85 and 154 (mg/dL) respectively and it is significantly ($p < 0.0001$) higher in cases than controls. (Fig 6)

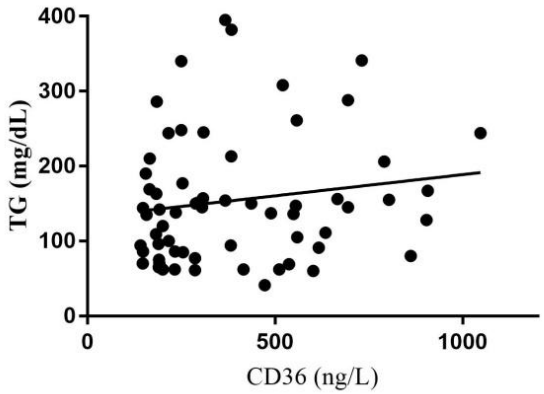


Fig 7. Correlation between CD36 and TG

There was no correlation between CD36 and TG levels (r=0.16 ; p=0.2). (Fig 7)

IV. Discussion:

Type 2 diabetes mellitus (T2DM) is the more common type of diabetes and is characterized by insulin resistance resulting from defects in the action of insulin on its target tissues (muscle, liver, and fat). Increased free fatty acids levels, inflammatory cytokines from adipose tissue and oxidative factors have been implicated in the pathogenesis of diabetes. Type II diabetes is associated with raised TG, LDL-C and low HDL-C levels. In our study we found that FPG and HbA1c between the controls vs cases were 78mg/dL vs 152 mg/dL and 5.3% vs 8.2% respectively with $p<0.0001$. Serum CD36 were analysed and the levels were elevated in the study group (462 ng/L) when compared to the controls (254 ng/L) with $p=0.01$. Serum triglyceride levels of study group (154 mg/dL) were significantly higher than healthy subjects (85 mg/dL) with $p<0.0001$. Circulating lipids influence risk of developing type II DM. The cause for dyslipidemia is decreased activity of lipoprotein lipase due to insulin resistance. Triglyceride levels positively correlate with risk of type2 DM and specifically with beta cell dysfunction of pancreas.[6-7] Correlation analysis was performed for serum CD36 levels and TG, but there was no significant association between CD36 & TG ($r=0.16$, $p=0.2$).

CD36 has been implicated in the uptake of long chain fatty acids into liver, muscle and adipose tissue. Its main role is to coordinate cellular events involved in uptake and processing of fatty acids. Obesity, type II DM there is enhanced expression of CD36 on cellular membrane[8-10] which leads to increased fatty acid influx and impairs insulin sensitivity and thus contribute to the development of type 2 DM. Increased expression of CD36 was observed on adipocytes, monocytes and macrophages[11] and it was

positively correlated with the pro-inflammatory cytokine interleukin 6 levels.[12] Insulin resistance, dyslipidemia, low grade inflammation and fatty liver stimulate CD36 expression in monocytes and macrophages in adipose tissue, liver, and arteries which lead to elevated plasma sCD36. Macrophage infiltration and low-grade inflammation in abdominal obesity, all these leads to dyslipidemia and lipid peroxidation and hepatic steatosis. CD36 expression levels are tissue specific and regulated by a variety of factors. Some of these factors are inter-related, such as plasma lipids and insulin resistance as well as inflammation, oxidative stress and insulin resistance. Most factors that influence CD36 expression also predispose to atherosclerosis and thus increasing the risk of atherosclerosis in DM. However, the exact mechanism of its various functions are not clearly understood. Elevated levels of CD36 were found to be implicated in the pathogenesis of metabolic disorder as seen in Diabetes mellitus. Markedly elevated sCD36 levels were reported by Handberg et al. where the levels of this marker were raised 4.5 times in type 2 diabetes when compared to healthy controls. Glintborg et al(.2008) and Handberg etal (2006) also observed elevated CD36 levels in Obese non diabetic individuals and women with polycystic ovarian syndrome[13] as these conditions were associated with insulin resistance. Thus conditions associated with insulin resistance like type II DM, PCOS and obesity there is enhanced recruitment of CD36 on the cell membrane[8-10] thus resulting in increased cellular uptake of fatty acids. Increased fatty acid influx impairs insulin sensitivity in the skeletal muscle and liver and could be the cause for the development of type II DM.[14]

V. Conclusion:

CD36 also known as fatty acid translocase expressed in variety of cells has been implicated in insulin resistance and atherosclerosis. sCD36 which is the free form or non -cell bound form is recently observed in plasma and its levels in plasma parallels with tissue expression. Insulin resistance, low-grade inflammation and hepatic steatosis stimulateCD36 expression in monocytes and macrophages in adipose tissue, liver and arteries which leads to elevated plasma sCD36. In our study we found that CD36 levels are increased in type2 DM when compared to normal healthy control group. The results of this study suggests that sCD36 may be helpful in assessing insulin resistance. Further large scale studies are required to validate the utility of this marker.

LIMITATIONS: Some limitations of the present study should be acknowledged. Small sample size, we should have measured plasma insulin and included pre diabetics in our study.

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