Section: Biochemistry

Original Research Article

STUDY OF FREE FATTY ACID LEVELS AND INSULIN RESISTANCE PATTERN IN TYPE II DIABETES MELLITUS

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ABSTRACT

Background: Type II Diabetes Mellitus (T2DM) is characterized by insulin resistance (IR). Improved risk prediction and understanding of the pathogenesis underlying Insulin Resistance are crucial for the management of T2DM. The etiology of Insulin Resistance is multifactorial. Fatty acids (FAs) may have a key role in the development of Insulin Resistance and T2DM [(1-3)]. However, the long-term effect of FAs on T2DM has yet to be fully elucidated Elevated FA concentrations in obesity are thought to arise from an increased adipose tissue mass. It is also argued that the process of fatty acid mobilization from adipose tissue is normally suppressed by insulin. **Aim:** The study aiming to estimate average Free fatty acid levels and correlate insulin resistance in Type II Diabetes Mellitus patients with the free fatty acid level.

Materials and Methods: This cross-sectional study includes 290 Type II Diabetes Mellitus patients aged above 30 years, attending Medicine OPD of Dr. B.R. Ambedkar Medical College and Hospital, Bangalore. Patient's serum Free fatty acid, serum Insulin and FBS are estimated; Insulin resistance is calculated and correlated with free fatty acid levels.

Results: In our study Insulin resistance is positively correlated with increase in FBS and serum Insulin levels, whereas serum Free fatty acid levels are negatively correlated with Insulin resistance.

Conclusion: This study establishes Insulin resistance with increase in Insulin levels and FBS. With increase in Free fatty acid Insulin resistance is negatively correlating, suggesting further studies with larger sample size.

Keywords: Free fatty acid, Insulin, Insulin resistance.

INTRODUCTION

Here is a widespread acceptance in the literature that plasma Non-Esterified Fatty Acids (NEFA), also called Free Fatty Acids (FFA), can mediate many adverse metabolic effects, most notably insulin resistance. Elevated NEFA concentrations in obesity are thought to arise from an increased adipose tissue mass. It is also argued that the process of fatty acid mobilization from adipose tissue, normally suppressed by insulin, due to insulin resistance—further increases lipolysis due to stimulation of Hormone sensitive lipase there by leading to a vicious cycle.[1] Although we have also accepted this model for many years, recently there has been a steady accumulation of data, both in literature and from our own research, that has forced us to realize that this simple is not always true. Here we review the background to the idea of "fatty acids as metabolic villains," together with data from the literature and from our own studies, which tend to show another side to the fatty acids/insulin resistance story.[2]

Circulating lipids and FFA may reflect an individual's lifestyle (e.g., diet and exercise) and their gene and protein activity, all of which may affect the development of Insulin Resistance and T2DM.

In a normal condition, when insulin binds to the insulin receptor it inactivates the enzyme hormone sensitive lipase (HSL) involved in the hydrolysis of TG to glycerol and FFA. In an insulin resistant state, there is an increase in the activity of HSL releasing free fatty acids into circulation to the liver. In the liver, hepatocytes take up the fatty acids and channel them into secretory pathways. The enzyme lipoprotein lipase in the blood vessels hydrolyses monoglycerides and FFA. As this cycling process continues, FFA also increases

Fat mobilization is suppressed rapidly by insulin. Plasma NEFA concentrations therefore fall after any meal that contains carbohydrates, which stimulate insulin release. Spill over fatty acids somewhat reduce this effect but do not override it. Circadian profiles of plasma NEFA concentrations therefore show the highest concentrations after an overnight fast, with suppression after each meal.[3]

Deleterious effects of free fatty acids (FFA), on insulin sensitivity are observed in vivo studies in Humans. Mechanisms include impaired insulin signaling, oxidative stress, inflammation, and mitochondrial dysfunction, but the effects on insulin secretion are less well known.

Miles J.M et al suggests relationship of increased FFA with insulin resistance, secretion and mainly with the incretin effect in Humans.[5] Narrative review increased endogenous or administered FFA induce insulin resistance FFA effects on insulin secretion are debatable; inhibition and stimulation have been reported, depending on the type and duration of lipids exposition and the study subjects. Chronically elevated FFA seems to decrease insulin biosynthesis, glucose-stimulated insulin secretion and β-cell glucose sensitivity.[6]

Lipids infusion decreases the response to incretins with unchanged incretin levels in volunteers with normal glucose tolerance. In contrast, FFA reduction by acipimox did not restore the incretin effect in Type-II Diabetes Mellitus, probably due to the dysfunctional β-cell.[4,9] Possible mechanisms of FFA excess on incretin effect include reduction of the expression and levels of GLP-1 (glucagon like peptide-1) receptor, reduction of connexin-36 expression thus the coordinated secretory activity in response to GLP-1, and GIP (glucose-dependent insulinotropic polypeptide) receptors downregulation in islets cells. Increased circulating FFA impair insulin sensitivity. Effects on insulin secretion are complex and controversial.

Deleterious effects on the incretin-induced potentiation of insulin secretion were reported.[7] Glucose and free fatty acids (FFA) are essential nutrients that are both partly regulated by insulin. Impaired insulin secretion and insulin resistance are hallmarks of aberrant glucose disposal, and Type II Diabetes Mellitus (T2DM).[8,12]

Excessive adiposity leads to hyperinsulinemia and insulin resistance, a major risk factor for diabetes mellitus and a cluster of related diseases collectively known as the metabolic syndrome.[12] It is commonly accepted that hyper insulinemia is consequent to resistance to insulin action in glucose metabolism, leading to increased glycaemia, which in turn stimulates the pancreatic β-cell to release insulin to avoid a more severe hyperglycemia.

However, a major limitation of this model is that marked hyperinsulinemia can be observed in subjects with normal glycemic control, suggesting that high blood glucose may not be the driver of hyperinsulinemia in these subjects.[13] Along this line of reasoning, it has been proposed that hyperinsulinemia itself may be a cause of the resistance to insulin action in glucose metabolism instead of being a consequence of it, as elevated basal levels of insulin are expected to desensitize insulin target cells to insulin stimulation.[15]

Objectives

1. To estimate average Free Fatty Acid levels in Type II Diabetes Mellitus Patients.
2. To estimate average fasting Insulin levels in Type II Diabetes Mellitus Patients.
3. To correlate Insulin resistance in Type II Diabetes Mellitus Patients with the Free Fatty Acid level.

MATERIALS AND METHODS

Source of Data

Type II Diabetes Mellitus Patients above the age group of 30 years attending Medicine OPD of Dr. B.R. Ambedkar Medical College and Hospital, Bangalore.

Exclusion Criteria

Patients with pre-existing medical disease affecting blood sugar levels like thyroid disorders, addisons etc

Inclusion Criteria

This study is Type II Diabetes Mellitus Patients above the age group of 30 years attending Medicine OPD of Dr. B.R. Ambedkar Medical College and Hospital, Bangalore.

Method of data collection

The sample size will consist of 290 Type II Diabetes Mellitus Patients above the age group of 30 years attending Medicine OPD of Dr. B.R. Ambedkar Medical College and Hospital, Bangalore, Bangalore

- FBS is estimated by GOD-POD method. Reference range of FBS is 70-110 mg/dL
- HbA1c is estimated by HPLC method. Reference range of HBA1c is 4- 6%
- Free Fatty Acid is estimated by enzymatic method. Reference range in fasting is 0.1-0.9 mmol/l.
- This Insulin assay is a “sandwich” chemiluminescent magnetic microparticle Immunoassay. Reference range is 2.00 mIU/L ~ 20.00 mIU/L

Insulin resistance is calculated by HOMR formula

HOMA-IR = Insulin in mIU/L x Fasting Blood Sugar mg/dL / 405

Reference range of HOMA-IR: generally considered to be normal in the range of 1.0- 2.0. Values above 2.5 often indicate Insulin Resistance[22].

Statistical Methods to be Employed: The data analysed using descriptive statistical tools and the correlation between the pair of parameters measured using product moment correlation coefficient. The statistical significance are analysed with the help of T-Test, Normal tests for proportions.

RESULTS

In our study Insulin resistance is positively correlated with FBS and serum Insulin levels, whereas serum Free Fatty Acid levels are negatively correlated with Insulin resistance.

Insulin resistance score changes as FBS changed positively and it is statistically significant with P value (< 0.001).

Serum Insulin and Insulin resistance scores show positive correlation with P value (<0.001).

Serum Free Fatty Acid and Insulin resistance score shows negative correlation and significant statistically with P value (<0.001).

Table 1: Descriptive Comparison of means of parameters between genders

Parameters	Total Mean ± SD	Gender	Number of Patients (N=290)	Min	Max	Mean ± SD	P value
Age in years	53.4 ± 12.7	Female	162	30	80	51.8 ± 12.8	0.018*
		Male	128	30	86	55.3 ± 12.4	
HbA1C (4-6%)	8.7 ± 2.5	Female	162	4.9	15.2	8.2 ± 2.5	0.050*
		Male	128	4.6	15.9	8.8 ± 2.5	
Estimated Average Blood Glucose (70-130 mg/ dL)	196.0 ± 71.8	Female	162	93	389.6	188.7 ± 70.4	0.050*
		Male	128	85.3	409.6	205.3 ± 72.9	
Fasting Blood Sugar (70-110mg/dL)	148.9 ± 71.3	Female	162	76	433	150.3 ± 71.2	0.706
		Male	128	76	433	147.1 ± 71.6	
Serum Insulin level (2.0 mlU/L - 20.00 mIU/L)	10.9 ± 5.8	Female	162	1.8	24	11.2 ± 6.2	0.372
		Male	128	1.8	24	10.6 ± 5.2	
Serum Free Fatty Acid Level (0.1 - 0.9 mmol/L)	1.5 ± 0.9	Female	162	0.1	3	1.5 ± 0.9	0.142
		Male	128	0.1	3	1.6 ± 0.9	
Insulin Resistance Score	3.9 ± 2.7	Female	162	0.34	13.8	3.9 ± 2.6	0.755
		Male	128	0.34	14.4	3.9 ± 2.9	

Statistically significant

Table 2: Correlations

Correlated Parameters	Correlation	P Value
FBS and Insulin resistance Score	0.58	0.0001
Serum Insulin and Insulin resistance Score	0.68	0.0001
Serum Free Fatty acid and Insulin resistance Score	-0.15	0.0001

Diagrammatic representation of relationship between pairs of parameters

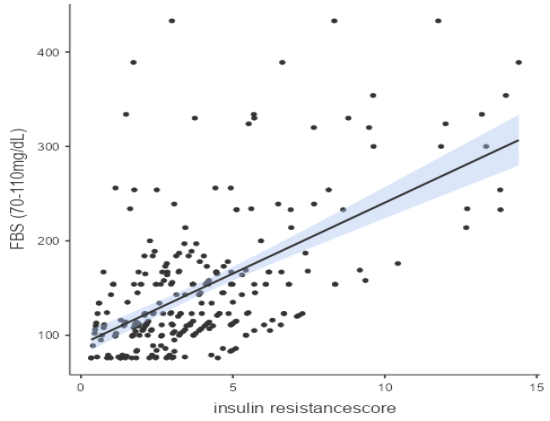

Figure 1: FBS vs Insulin resistance Graph

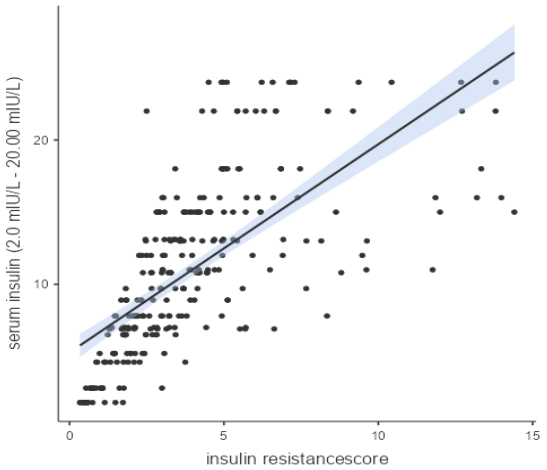

Figure 2: Insulin vs Insulin Resistance

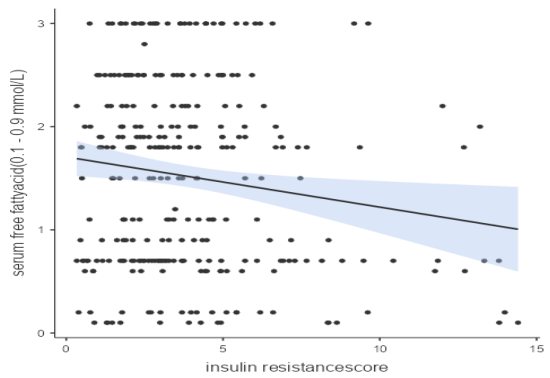

Figure 3: Serum Free Fatty Acid vs Insulin Resistance

DISCUSSION

In our present study we have estimated Serum Insulin, FBS and Insulin Resistance and we have seen the correlation between FBS and Insulin Resistance, Insulin and Insulin Resistance and negative correlation with FFA and Insulin Resistance and this was statistically significant.

FFA plays a causative/ central role in development of Insulin Resistance and Type 2 Diabetes Mellitus by promoting lipotoxicity in skeletal muscle and liver tissue. This triggers chronic adipose tissue inflammation which impairs insulin signaling and related to metabolic dysfunction.

The link between elevated free fatty acid concentrations and insulin resistance has remained firmly entrenched in the literature. For instance, in an authoritative review on metabolic syndrome in 2005, Eckel et al. Wrote that "a major contributor to the development of insulin resistance is an overabundance of circulating fatty acids.[11]"

Type 2 diabetes is characterized mainly by defects in insulin action, β-cell dysfunction and chronic inflammation. The β-cell dysfunction is the major defect in most cases, but β-cell mass reduction alone is less likely to be the primary cause. A host of inherited genes, their environmental interaction and epigenetic mechanisms make tissues resistant to insulin and/or impairs insulin secretion. Clearly, insulin resistance is an important factor and has been reported in the liver, muscle and adipose tissue. It is found even in T2DM first-degree relatives before the onset of obesity and hyperglycemia. Suggesting a causal role.[13] Type 2 diabetes manifests itself when β-cell becomes unable to adapt to chronic metabolic stress.

Recently it has been recognized that impaired FFA disposal may be as important in the accumulation of fat in non-adipose tissue increased FFA uptake. By contrast, other studies suggest that increased plasma FFA are associated with compensatory insulin secretion responsible for maintaining almost unchanged glucose tolerance in the face of increasing insulin resistance. Finally, it has been proposed that type 2 diabetes perhaps results from aberrant lipid metabolism. In animal models, it has been shown that obesity,[9,11] which is often associated with chronically elevated levels of insulin, leads to decreased FFA oxidation in the resting state. Thus, delineating the role of FFA in glucose metabolism and glucose control over FFA homeostasis will indeed require a better understanding of insulin's influence on FFA metabolism.

In a state of chronic positive energy balance, the body may reduce lipolysis (the breakdown of fats) to prevent an excessive rise in circulating FFA. This promotes adipocyte hypertrophy.

The study notes that certain genes involved in lipid accumulation are down regulated in obese patients. This along with reduced de novo lipogenesis, may be part of an integrated response to manage adipose tissue expansion and avoid excessive adipocyte hypertrophy.[10,18]

Further support to the idea that reduced b-adrenergic sensitivity and reduced de-novo lipogenesis may be part of an integrated homeostatic response to adipose tissue expansion can be derived from the fact that at least five genes implicated in lipid accumulation, which were down regulated in the obese groups, are known to be induced by b-adrenergic- cAMP signaling.

In our study there is the correlation between the FFA and Serum Insulin as well as FBS but Insulin Resistance and FFA are negatively correlated. The probable reason could be, the patients selected for study were type 2 DM who were on treatment with better glycemic (sugar) control.

Hence, further study is required with increase sample size and new onset Type 2 DM to further know the relationship between FFA and Insulin Resistance.

CONCLUSION

Our study establishes a link between Insulin resistance and increased insulin, as well as FBS levels and negatively correlated with FFA. Further study is required to establish the correlation between FFA and Insulin and the role of FFA in Insulin resistance.

Conflict of Interest: The study has no conflict of interest to declare.

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