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Original Research Article

Post-prandial dylipidemia and elevated serum ferritin levels in type 2 diabetes mellitus patients: A risk marker for accelerated atherosclerotic cardiovascular events

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ABSTRACT

Aims and Objectives of the Study: The type 2 diabetes mellitus (T2DM) prevalence is increasing worldwide at alarming rates. The prevalence of T2DM is expected to be more than 350 million people worldwide in next 20 yrs. The risk of coronary and peripheral artery disease increases by 2 to 4 fold, while the risk of stroke is increased by 10 fold in type 2 diabetes mellitus patients.

In type 2 diabetes mellitus, dyslipidemia plays an important role in the pathogenesis of accelerated atherosclerosis. Hyperlipidemia in postprandial state is thought to play an important role in atherosclerosis, and concentrations of triglycerides(TG) in post prandial state are superior to those of fasting TG for predicting cardiovascular disease.

Increase in serum ferritin levels are associated with insulin resistance(IR), systemic inflammation, metabolic syndrome(MetS), type 2 diabetes mellitus and cardiovascular disease. Elevated body iron stores may contribute to insulin resistance through chronic inflammation and oxidative stress.

The present study is under taken to assess the implication of post prandial dyslipidemia in comparison to fasting dyslipidemia in the pathogenesis of cardiovascular disease and to show the importance of increased serum ferritin levels in type 2 diabetes patients which acts as a potential risk marker for coronary artery disease.

Materials and Methods: Fifty type 2 diabetes mellitus patients and fifty normal adults between age group 30-75yrs attending Medicine OPD, Rajarajeswari Medical College and Hospital, Bangalore were screened for lipid profile using enzymatic method by ERBA 360 autoanalyzer and serum ferritin levels by chemiluminiscence method. The statistical analysis was done by students unpaired t-test.

Results: Serum lipid profile including TGs, LDL-C, VLDL-C were significantly increased in the post-prandial state as compared to the fasting state in cases with $p<0.001$and they were more significantly elevated in cases, compared to controls with $p<0.001$. Serum HDL-C level was lower in the postprandial state compared to fasting state in cases with $p<0.002$. There was significant reduction in HDL-C levels in cases when compared with controls with p 0.006. Serum ferritin was significantly elevated in cases, compared controls with $p<0.001$

Conclusion: In the present study there was significant postprandial dyslipidemia in type 2 diabetes mellitus patients as compared to fasting dyslipidemia. We also noticed the significant increase in serum ferritin levels in these patients when compared to controls, which could be one of the causes for insulin resistance. Hence post prandial lipid profile and estimation of serum ferritin should be included as a routine cardiovascular risk assessment marker for evaluation in type 2 diabetes mellitus patients for early detection and prompt therapy.

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1. Introduction

Type 2 Diabetes Mellitus is a metabolic disorder, characterized by insulin resistance (IR) and associated with glucose intolerance, dysipidemia, hypertension, a procoagulant state, an increase in microvascular and macrovascular complications.[1] Dyslipidemia plays an important role in the pathogenesis of accelerated atherosclerosis in this population. Type 2 diabetes mellitus patients are frequently hyperlipedemic and are at high risk to develop coronary artery disease.[1]

The worldwide prevalence of diabetes for all age groups was estimated as 2.8% in 2000 and it is expected to reach 4.4% by 2030.[2] Based on current trends, the International Diabetes Federation projects that around 438 million individuals will have diabetes worldwide by the year 2030. The worldwide prevalence of type 2 diabetes mellitus is increasing, more in the South Asian population due to factors like genetic predisposition, susceptibility to environmental factor such as high BMI, increased upper body adiposity, a elevated body fat percentage and a high level of insulin resistance.[3]

India, a developing country in Asia with fast industrialization and a modern lifestyle is facing a serious problem in having the largest number of people with diabetes, which is expected to reach 80 million by the year 2030. India is expected to become the diabetic capital of the world in near future.[4] In India the prevalence of diabetes is 2.4% in rural and 4 -11.6% in urban dwellers. In India a population of 32 million diabetic patients were estimated in the year 2000 and this number is expected to increase to 80 million by the year 2030.

Dyslipidemia is elevation of serum total cholesterol (TC), triglycerides (TGs), or both, or reduced high -density lipoprotein cholesterol (HDL-C) level which contributes to the development of atherosclerosis, and is a hallmark of diabetes. Diabetic dyslipidemia is common in type 2 diabetes mellitus and is characterized by increased levels of fasting triglycerides (TGs), low HDL cholesterol levels, and predominance of small, dense LDL cholesterol particles. Elevated and prolonged postprandial lipemia after meals is seen in majority of type 2 diabetes mellitus patients. Epidemiological data suggest that high plasma TG levels, both fasting and in postprandial state, are associated with cardiovascular diseases in patients with diabetes.[5]

The dyslipidemia in T2 DM is different than in non-diabetics, as it has been suggested that composition of lipid particles in diabetic dyslipidemia is more atherogenic than other types of dyslipidemia.[3] The high mortality seen in cardiovascular disease, which is associated with Type 2 DM is due to a prolonged, exaggerated, postprandial state. The abnormal postprandial lipid profile is more significant in causing atherosclerotic complications in Type 2 diabetics than the abnormal fasting lipid porfile.[6] A few studies have included post-prandial lipid levels in type 2 DM, hence the present study aims to compare post-prandial lipid with fasting lipid levels in individuals with type 2 diabetes mellitus.

The metabolic syndrome(MetS) is closely linked to insulin resistance and many studies have revealed the association with iron overload. Elevated serum ferritin reflecting body iron overload, is often associated with measures of insulin resistance such as increased blood glucose and insulin levels.[6]

Elevated serum ferritin levels are associated with insulin resistance, T2DM, MetS(metabolic syndrome), systemic inflammation and cardiovascular disease. Increased body iron may contribute to insulin resistance via mechanisms related to both reduced extraction of insulin and impaired insulin secretion.[7] Many studies have suggested that subclinical iron overload in non pathologic conditions leads to insulin resistance and also increased risk of type 2 diabetes mellitus.

In diabetes and metabolic syndrome, iron may contribute to risk following deposition in the liver, pancreas, and skeletal muscle, where it enhances oxidative damage and contribute to insulin deficiency and resistance. In CVD, iron with in macrophages and foam cells pre-disposes to the formation of atherosclerotic plaques. Hepcidin may promote plaque destabilization by preventing iron export from the intralesional macrophages and leads to ischemic events.

Although additional mechanisms are likely to be involved, Figures 1 and 2 illustrates some pathway through which excess iron can increase risk of CVD, metabolic syndrome and diabetes.[8]

2. Material and Methods

2.1. Study design and population

Our study included patients attending Medicine OPD in Rajarajeswari Medical College and Hospital, Bangalore. The study was approved by the institutional ethical committee. Informed consent was taken from all the individuals included in the study.

2.2. Inclusion criteria

The study group included fifty both male and female subjects between age group 30-75 yrs who were diabetic for more than 5 years. Fifty age and sex matched healthy subjects with no history of diabetes mellitus were in the control group. Control group and study cases were screened for the same parameters.

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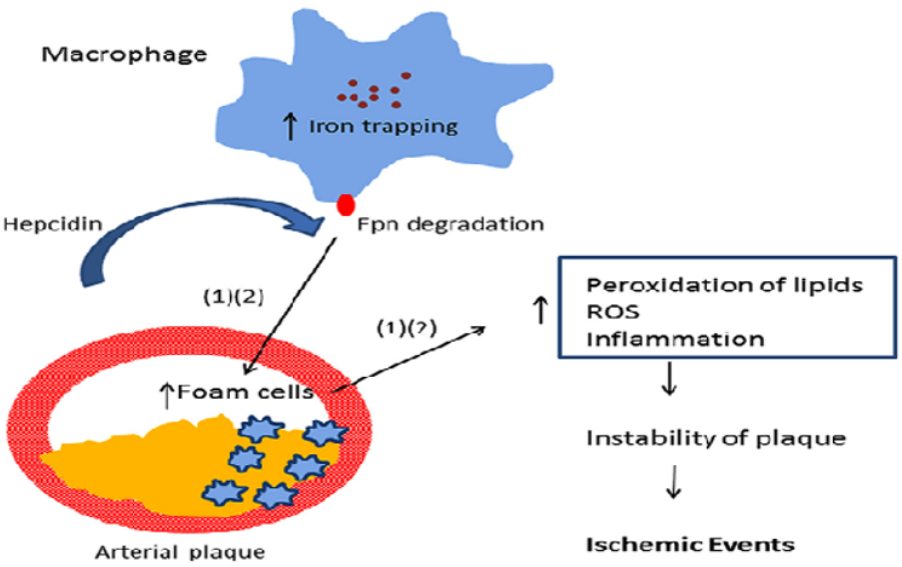

Fig. 1: Model showing iron retention in macrophages promote sarterial plaque destabilization (Sullivan,2007;Theuri et al, 2008)

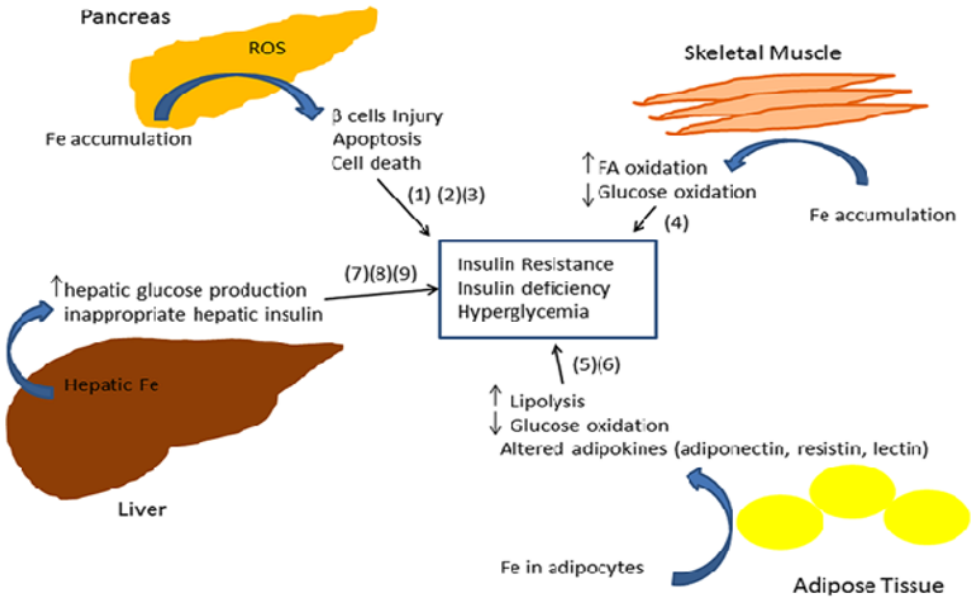

Fig. 2: Model showing multiple mechanisms through which iron can lead to insulin resistance and insufficiency (Merkel et al, 1988; Tiedge et al., 1997; Mendler et al, 1999; Ferrannini, 2000; Cooksey et al, 2004; Green et al., 2006; Huang et al., 2011)

2.3. Exclusion criteria

1. Patient with hypertension, Cardiovascular disease and family history of dyslipidemia.
2. History of endocrine disorder, renal disease and liver disease.
3. Type 1 diabetes, Pregnancy, Anemia (Hb >12gm/dl) and history of any other medical or surgical illness.
4. Patients on statin therapy and Iron supplements.

2.4. Laboratory investigations

Venous blood samples were collected at the enrollment visit with overnight fasting(12 hours).

1. Fasting blood glucose was estimated by using commercially available GOD-POD kit.
2. Serum total cholesterol andserum triglycerides (TGs) by an enzymatic method.

3. Serum HDL cholesterol by phosphotungstate precipitation, followed by enzymatic method.
4. Serum LDL Cholesterol and VLDL Cholesterol by using Friedewald's formula.[9,10]
5. All the parameters were analyzed by using a Fully automated analyzer (Transasia ERBA)
6. Serum ferritin by chemiluminiscence immunoassay. (MAGLUMI 1000)

2.5. Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. All the results were expressed as means±(SD) values. The data was recorded in Microsoft excel and analyzed using SPSS software (version 15). The significance of the difference between the groups was assessed by Student's t-test, between cases and controls and values of <0.05 were considered as statistically significant.

3. Discussion

In the present study there was significant post prandial dyslipidemia in type 2 diabetes patients as compared to fasting dyslipidemia. In the present study, the postprandial lipid parameters i.e. TGs, ($p<0.001$)VLDL($p<0.001$) and LDL-C ($p<0.006$) were significantly increased in the Type 2 DM patients as compared to the fasting lipid parameters and the postprandial HDL-C level was significantly decreased as compared to the fasting HDL-C level ($p<0.002$) [Table 4]. Also, the postprandial lipid parameters i.e. TC, TGs, VLDL and LDL-C($p<0.001$) were significantly increased in the Type 2 DM subjects as compared to those in the controls and reduced HDL-C levels ($p<0.006$)[Table 3], which was in accordance with the results of previous studies. Serum ferritin was significantly elevated in cases than controls with $p<0.001$.

V Kumar et al showed in their study that, significant postprandial hypertriglyceridemia and major delay in postprandial triglyceride clearance following a standardized fat meal challenge in type 2 diabetes mellitus patients, particularly those with macrovascular disease. Persistent postprandial hypertriglyceridemia in type 2 diabetes patients may result in a pro-atherogenic environment leading to atherosclerosis and macrovascular disease.[11]

Similar to our study Lokhande Suryabhan L et al in their study showed that, the postprandial lipid parameters i.e. TC, TGs and LDL-C were increased significantly in the type 2 diabetes mellitus patients as compared to the fasting lipid parameters and the postprandial HDL-C level was decreased significantly as compared to the fasting HDL -C level. Also, the postprandial lipid parameters i.e. TC, TGs and LDL-C were significantly increased in the type 2 diabetes mellitus subjects as compared to those in the control subjects.[7]

Thus the postprandial dysmetabolism and associated oxidative stress may link insulin resistance and type 2 diabetes to the disproportionate occurence of cardiovascular events.[1,12]

Many studies have revealed that postprandial dyslipidemia is more important in the pathogenesis of the vascular changes and atherosclerosis that increases the cardiovascular events.[11]

Exaggerated postprandial dyslipidemia is related to proatherogenic conditions and various clinical studies have proven that exposure to postprandial lipoproteins is associated with cardiovascular events. In postprandial state, as similar to hypertriglyceridemic subjects there is excess formation of atherogenic small, dense LDL particles and decreased formation of anti-atherogenic HDL-2 particles.[5,13]

Gambhir et al found low HDL -C as an independent risk factor for the premature coronary artery disease. Many studies have strongly suggested inverse correlation of HDL cholesterol level with development of Ischemic heart disease.[2,4,14]

Chronic hyperglycemia causes glycation of apolipoproteins and it interferes with the normal pathways of lipoprotein metabolism.[4,15] Hyperinsulinemia, hyperglycemia and (FFA) free fatty acids especially from abdominal deposits with direct delivery to the liver are all stimulators of VLDL- C production in the liver. Turnover of VLDL-C particles increases in the plasma as a consequence, elevation of VLDL-C concentration and reduction of HDL-C concentration in the plasma is seen.[4,16]

There is significant increase in the serum ferritin levels in the cases as compared to the controls in our study. Epidemiological studies provide evidence that elevated iron stores are a risk factor for developing cardiovascular and metabolic abnormalities.

Meghana K. Padwal et al, in their study showed that elevated serum ferritin levels, in addition to increased body iron stores might reflect systemic inflammation. Disproportionate or elevated iron deposits produce hydroxyl radicals which leads to lipid peroxidation. This in turn leads to DNA fragmentation and tissue damage. Therefore, one of the mechanisms involved in progression of MetS to Type 2 DM and cardiovascular disease is inflammation and oxidative stress mediated through ferritin.[17]

Fulden Sarac et al, stated in his studies that high body iron may contribute to insulin resistance through chronic inflammation and oxidative stress. In various studies, it has been suggested that hydroxyl radicals formation catalyzed by iron may be associated with incident diabetes. Since, highly active radicals could attack cell membrane proteins, lipids, DNA and cause tissue damage. In addition, oxidative stress may impair insulin extraction and insulin secretion.

Ki-Chul sung et al, have shown in their study that ferritin concentrations are associated with the presence of Coronary

Table 1: Comparison of blood glucose parameters in two groups studied

Blood glucose	Cases	Controls	P Value
FBS (Ms/dl)	169.50 ±72.29	88.10 ±10.28	<0.001
PPBS (mg/dl)	258.24 ±81.67	110.01 ±9.07	<0.001**

Table 2: Fasting lipid profile in two groups studied

Fasting Lipid profile	Cases	Controls	P value
Total Cholesterol (mg/dl)	188.66 ± 38.24	120.24 ± 12.34	<0.001**
LDL (mg/dl)	98.01 ± 23.22	90.00 ± 3.54	<0.017
HDL (mg/dl)	39.09 ± 12.44	45.16 ± 9.18	<0.006
TGL (mg/dl)	215.02 ± 126.6	159.64 ± 35.24	0.004**
VLDL (mg/dl)	86.16 ± 27.14	43.00 ± 25.32	<0.001**

Table 3: Post prandial sample for lipid profile in two groups studied

Post Prandial lipid profile	Cases	Controls	P value
Total Cholesterol (mg/dl)	194.00 ± 43.64	160.50 ± 59.40	<0.001**
LDL (mg/dl)	110.01 ± 19.73	88.01 ± 31.11	<0.001**
HDL (mg/dl)	33.58 ± 12.09	39.32 ± 8.28	0.006
TGL (mg/dl)	265.20 ± 110.08	96.20 ± 9.57	<0.001**
VLDL (mg/dl)	119.76 ± 12.12	53.04 ± 22.02	<0.001**

Table 4: A comparative evaluation fasting and post prandial sample for lipid profile in cases

Lipid profile	Fasting Lipid profile	Post Prandial lipid profile	P value
Total Cholesterol (mg/dl)	188.66 ± 38.24	189.26 ± 43.62	0.866
LDL (mg/dl)	98.01 ± 23.22	110.01 ± 19.73	0.006*
HDL (mg/dl)	39.09 ± 12.44	33.58 ± 12.09	<0.002
TGL (mg/dl)	215.02 ± 126.6	265.20 ± 110.08	<0.001**
VLDL (mg/dl)	86.16 ± 27.14	119.76 ± 12.12	<0.001**

Table 5: Ferritin levels in two groups studied

Ferritin	Cases		Controls	
	No	%	No	%
<150	10	20	39	78
150-300	26	52	11	22
>300	14	28	0	0
Total	50	100	50	100
Mean ± SD	254.90±113.32		123.06±53.53	

P<0.005 *, Significant
P<0.001**, Very significant, student t test

Artery Calcium (as a marker of pre clinical atherosclerosis), independent of MetS features, diabetes mellitus, other conventional cardiovascular risk factors, and preexisting CVD.[18]

Sharifi et al have shown a higher level of ferritin in people who are at high risk for atherosclerosis. Since insulin resistance has been considered as the basic factor in the pathogenesis of atherosclerosis, the higher serum ferritin in atherosclerotic patients can be attributed to insulin resistance.[9]

Postprandial hypertriglyceridemia has been linked to macrovascular diseases in both normal subjects and also in type 2 Diabetes Mellitus patients. The increased risk of atherosclerosis amongst them may be associated with higher postprandial lipaemia in them. The postprandial dysmetabolism and the associated oxidative stress may be related with insulinresistance and type 2 diabetes mellitus thus increasing the incidence of cardiovascular events disproportionally.[3]

4. Conclusion

In the present study there was significant post- prandial dyslipidemia in type 2 diabetes mellitus patients with increase in the TC, LDL-C, TG VLDL-C and considerable decrease in HDL-C as compared to fasting dyslipidemia, which could

be a risk factor for atherosclerosis increasing the incidence of cardiovascular disease among them.Atherosclerosis is a postprandial phenomenon with respect to lipids, since we are in the postprandial phase for most of the day, with an added ad verse effect of the post prandial hyperglycaemia.

We also noticed the significant increase in serum ferritin levels in these patients when compared to controls, which could be one of the causes for insulin resistance involved in the pathogenesis of atherosclerosis resulting in the cardiac events.

Hence post prandial lipid profile and serum ferritin estimation should be included as routine cardiovascular risk assessment evaluation in type 2 diabetes patients for early detection and prompt therapy.

5. Limitations of the study

The study included a small sample size in a single centre. A multicentric future study with large sample size correlating with duration of Diabetes is needed to explain the role of postprandial dyslipidemia and increased serum ferritin levels in the pathogenesis of accelerated atherosclerotic cardiovascular disease.

6. Conflicts of interest

None

7. Acknowledgement

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