

HYPERLIPIDAEMIA IN DIABETES MELLITUS

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ABSTRACT

Objective: Diabetes Mellitus being a common disorder, having hyperlipidemia as one of major complications was studied.

Materials and Methods: Patients with systemic diseases such as CRF, hypertension, nephrotic syndrome, myxoedema and SLE were excluded. Those cases who were on drugs like beta blockers, thiazide diuretics, steroids, alcohol etc were excluded from this study. Blood samples from all these established cases were taken for analysis for triglycerides alongwith other lipid profile.

Results: The commonest finding was hypertriglyceridemia both in insulin and non insulin dependent diabetic patients. It was more so in non insulin dependent diabetes mellitus (65%) as compared to insulin dependent diabetics (45%). Only few (3%), all females were having morbid levels of hypertriglyceridemia.

Conclusions: Early diagnosis, good glycemic control and dietary modification are usually enough for prevention and treating hypertriglyceridemia in diabetes mellitus. Exercise not only reduces the serum lipid levels but also potentiates the effects of diet or drug therapy of glucose metabolism in diabetic patients. When these measures fail then lipid lowering drugs are instituted. HMG Co-A reductase inhibitors are of value in moderate to severe hypertriglyceridemia with coexisting hypercholesterolemia while severe hypertriglyceridemia alone is treated by fibrates.

Key words: Diabetes Mellitus, Diabetic dyslipidemia, Lipid profile.

INTRODUCTION

Diabetes mellitus is by far the most common of the endocrine disorders. It

affects forty million of the world population. In United States of America 7 million people¹ while in UK the prevalence rate is between 1-2%². One of the studies done in

Pakistan, have shown approximately similar frequency³.

In diabetes mellitus the composition of all the classes of plasma lipoproteins is altered both qualitatively and quantitatively leading to dyslipidaemia. The incidence of dyslipidemia varies between 40-60% in different groups of patients, of which hypertriglyceridaemia is more frequent and is known to be present when serum triglyceides level exceeds more than 2.2 m.mole/L (200 mg.dl)⁴.

The incidence also increases with poor glycaemic control and prolonged duration of diabetes mellitus. It is more common in type II diabetic patients than type I.

At times hypertriglyceridaemia is picked up as a chance laboratory finding especially in early mild cases. While in moderate cases it may present clinically as tuberous and or eruptive xanthomas, fatty liver. The sever form of hypertriglyceridaemia can end up in lipaemia retinalis and or acute pancreatitis. Hypertriglyceridaemia, probably by accelerating atherogenesis, is regarded as a major risk factor for the increased CAD in the diabetics. In sever form it is also incriminated for early mortality due to CAD.

Early diagnosis, meticulous glycaemic control, dietary modifications, regular exercise, weight reduction and avoidance of alcohol are general measures for treating hypertriglyceridemia. If these measures fail than lipid lowering drugs should be instituted. HMGCO-A reductase inhibitors are of value in moderate to sever hypertriglyceridaemia with co-existing hypercholesterolaemia, while sever hypertriglyceridaemia alone is treated by fibrates among which gemfibrozil is a drug of choice.

The aims of this study there for is 1) To know the incidence of hypertrigly ceridaemia, its age and sex distribution and prevalence in NIDDM and IDDM.

2) To know the relationship between the glycaemic control and degree of hypertriglyceridaemia and incidence of complications of hypertriglyceridaemia in diabetes mellitus.

MATERIAL AND METHODS

Sixty cases of established diabetes mellitus were selected for this study during a six months period in the department of medicine and ICU, Khyber Teaching Hospital, Peshawar. The selection criteria was 1) Every patient of these sixty cases were having established diabetes mellitus.

2) systemic diseases like CRF, nephrotic syndrome, myxoedema, SLE were excluded from the study on the basis of history, clinical examination and relevant investigations.

3) Diabetic patients taking drugs like betablockers, oral contraceptive pills, thiazide diuratics, corticosteroids, cimetidine for any reason were also excluded.

4) Smokers, and alcoholics were also excluded.

Detailed history was taken including bio-data of patients presenting complaints and any complications. Inquiry was made about the type and duration of diabetes mellitus. Past family history of IHD, stroke were asked.

Special attention was given to patient's dietary history and his / her physical activities. Clinically the patients were looked specially for any xanthomas, lipemia retinalis, diabetic retinopathy; and any signs of IHD. The history, clinical examinations and investigations were recorded on a specified proforma. Two types of investigations were done.

1. Base line investigations like blood CP with ESR, Blood urea, urine RE, ECG and x-ray chest.

Planned investigations: These included fasting and 2 hours post prandial blood glucose estimation, serum electrolytes, serum creatinine, serum amylase, uric acid, LFT's, TFT's, ETT and abdominal ultra sound to look for liver texture and for any evidence of fatty change; morphology, texture of kidney and pancreas and other abdominal viscera. Total lipid profile which include:

- a. Total fasting lipids
- b. Total fasting triglycerides
- c. Total fasting cholesterol
- d. HDL cholesterol
- e. LDL cholesterol

Blood sampling for lipoproteins analyses

The diagnosis of lipoproteins abnormality is mainly based on results of laboratory investigations. These results in turn not only depend upon the accuracy and precision of the analyses but also on the care taken during blood sampling. The major criteria for standardizing the collection of blood samples for lipid analyses which were strictly followed during this study were as follows.

1. Because of major effect of dietary pattern and caloric intake on the serum lipids and lipoproteins level, the patients were asked to continue on the same diet in order to get the actual values.
2. Serum lipids are known to fall during the first few days of hospitalization. To avoid this fallacy almost every patient blood for lipid analysis was taken on the next day.
3. All the patients were kept on fasting over night for 14 hours before the blood sample was taken for lipid analysis in order to avoid variability of triglycerides concentration⁵.
4. Clean vene puncture was done and the blood was drawn only when cuff was

released. Prolonged venous stasis was avoided in order to get accurate cholesterol concentration, because it is known that cholesterol concentration increases considerably after protracted venous occlusion probably as a result of haemoconcentration⁶.

5. At the time of investigation none of the patient was receiving any lipid lowering drug.
6. The sampling of those patients who had a recent history of major illness, surgery, trauma or any other stressful condition was postponed. They were recalled after about a month time.

After observing the above protocol 3cc blood was taken in a disposable syringe from the patient. After proper labeling the blood sample was sent to the pathology department of Khyber Teaching Hospital, Peshawar for analysis of triglyceride along with other lipid profile. Triglycerid estimation was done by enzymatic photometry.

RESULTS

The total number of cases finally included in the study were 60. All of them were known diabetics. The female to male ratio was 2:1. The majority of patients were in the age group ranging from 35-55 years. Only 10% were above the age of 55 years. Majority of patients were from Peshawar and Mardan divisions. 10 out of total 60 cases were Afghans. Regarding the occupational status of patients majority were house wives and businessman. 20% were having IDDM and 80% NIDDM. Regarding the duration of diabetes mellitus 70% of the cases were having diabetes mellitus for the last 5-15 years. The dietary intake in 50% of patients were complex carbohydrates and high fibre diet. 20% were having liking for taking fat enriched diet of which female were maximum. 15% were not following dietary restriction.

Regarding the physical activity 55% of patients had strict sedentary life pattern vast majority of female patients were restricted to their house keeping. Very few patients were doing various sports. Body mass index was evaluated by the following formula in all patients. $BMI = \text{weight in kilogram} / \text{height in meters}^2$. 56% had normal body mass index, 14% below normal, while 30% had the body mass index above the normal range. The triglyceride levels were raised only in 62% patients. 36% patients were having only raised serum triglyceride without any clinical evidence of hyperlipidemia. Eruptive xanthomas were present in 25% patients, while tuberous xanthomas were found in 10% patients.

Regarding the fasting blood glucose it was found more than 140 mg/dl in all the cases. The majority of patients had a poor to uncontrolled glycemic levels. Renal functions test i.e. blood urea, serum creatinine and electrolytes were done to rule out any renal pathology, but they were found within the normal limits. Liver function tests, thyroid functions tests were normal.

In general 48% of the patients were having normal total serum lipids, while 52% showed raised levels. Out of 52%, thirty patients (40%) had the serum lipid levels in the range of 1000-1500 mg/dl, while remaining 12% patients had the level in the range of 1500-2500 mg/dl. Total fasting serum cholesterol was found normal in 78% patients. 22% were having raised serum cholesterol in the range of 251-300 mg/dl. All these 22% cases were also having triglyceride levels more than 200 mg/dl, so fulfilling the hyperlipidaemic criteria of National cholesterol education programme of USA. LDL - cholesterol was found normal in 78% cases while 22% showed a raised level. HDL - cholesterol in 14% cases was less than 40 mg/dl, who were at a higher risk of IHD, while it was found above 40 mg/dl in the remaining 86% cases.

Hypertriglyceridaemia was found both in IDDM and NIDDM patients. It was more so in NIDDM (65%) than IDDM (45%) patients. In IDDM majority of the patients were having mild to moderate hypertriglyceridaemia. The same was the case in NIDDM patients. The only few (3%) having morbid level of hyper triglyceridaemia were females. 22% had ischaemic heart disease as evidenced by serial ECGs, while 30% patients were having diabetic retinopathy. Lipemia vetinalis was not detected even in a single patient.

DISCUSSION

Dislipidemia is frequently seen in diabetes mellitus. Amongst this hypertriglyceridaemia is the most predominant abnormality⁷. Hypertriglyceridaemia has been found more common in diabetics than non diabetics due to fourfold increase in VLDL triglyceride⁸. It predisposes the patients to life threatening complications like acute pancreatitis, IHD, DKA and lipaemia retinalis. In order to avoid this situation, it is therefore mandatory to observe strict preventive measures.

In a study done in Russia dyslipidaemia was detected in 84% diabetic patients⁹. In one of the European study 40% were hyperlipidaemic according to the criteria of National cholesterol education programme, (cholesterol and triglyceride greater than 200 mg/dl). An additional 23% showed hypertriglyceridaemia¹⁰. In another study hiperlipidaemia was found in 28% of diabetic patients¹¹. In a native study hyperlipidaemia has been found in 42.5% of diabetic patients¹².

In our study total fasting lipids of greater than 1000 mg/dl were found in 52%. Fasting hypercholesterolaemia and increased LDL cholesterol in 22% of the patients. This was in conformity with the results given by Haider and coworkers¹³. The values of

cholesterol and LDL cholesterol declined from younger to older ages; so these results are in conformity with the previous study¹⁴.

Hypertriglyceridemia was found to be the commonest of the dyslipidemia in this study i.e. 62%; greater than the previous studies. Majority of patients in my study were type II diabetics (65%) as compared to type I (35%). Winocour et al, has shown 40% hyperlipidaemia in IDDM patient. Hypertriglyceridaemia was found predominantly in all the cases while a few had combined hyperlipidaemia, pure hypercholesterolaemia however was not observed in a single case¹⁵.

Hypertriglyceridaemia, which is comparatively more common in NIDDM than IDDM¹⁶ is probably due to increased production and reduced clearance of rich lipoproteins-VLDL¹⁷. Amongst the NIDDM patients hypertriglyceridaemia is depending upon the variation in the apo E gene, because significantly higher level of VLDL - triglycerides have been found in patients with epsilon 2 heterozygote than in those without the epsilon 2 allele¹⁸. It is further interesting to note that even the 1st degree relatives of NIDDM cases have dyslipidaemia in general and hypertriglyceridaemia in particular¹⁹. In the number of European studies dislipidaemia is more common in male, beyond 35 years of age²⁰. But in our study it is more common in female. One factor which is responsible for this is that they are confined to their housekeeping without any active physical activity.

Exercise has potential benefits for these patients. It not only has lipid lowering effect but it also potentiates the effect of diet or drug therapy on glucose metabolism in NIDDM patients²¹. In our study only 24% were in the habit of regular exercise.

The poor the glycaemic control, the higher the degree of hypertriglyceridaemia. This relationship can be explained by the

glucoregulatory and lipolytic actions of insulin, and defect in this can lead to dyslipidaemia more so in NIDDM patients²². If good glycemic control is achieved than not only the size of VLDL particle is reduced but also increase in the concentration of apo - B protein fraction of VLDL takes place. These changes in turn leads to increased clearance of VLDL particles and ultimately dislipidaemia reverts²³. In one study 28% of diabetic patients had hyperlipidaemia with a poor glycemic control as defined by a glycated hemoglobin value of more than 10%¹¹. In our study 62% of the total patients had a poor glycemic control as assessed by serial 2 hours post prandial glucose estimation according to WHO criteria²⁴. All of these showed mild to severe dislipidemia.

In WHO criteria, level less than 150 mg/dl were taken as good, between 150-200 mg/dl as permissible and above 200 mg/dl as poor glycemic control.

Apart from the blood glucose estimation glycemic control can be monitored by estimation of glycated HbA1C, glycated fructosamine and glycated serum albumin. Glycated HbA1C comprises 4-6% of the total haemoglobin. Level less than 10% reflects a good glycemic control over the preceding 8-12 weeks²⁵. However, glycated serum albumin can be a more reliable marker of short term glycemic control in IDDM than fructosamine²⁶.

The American diabetic association suggested that if diabetes was poorly controlled and dislipidaemia a problem, monosaturated fatty acids might be the useful substitute for carbohydrate to maintain caloric balance. However in the light of high incidence of obesity in persons with NIDDM and recent studies on the case of dietary fat storage in the adipose tissue, substitution of any kind of fat including monosaturated fatty acids for carbohydrate has been questioned²⁷. Fish oils, containing Omega 3 fatty acids, favourably influence plasma lipoproteins

especially triglycerides.²⁸ Recent studies, however indicates that fish oil decreases hypertriglyceridaemia on one hand but worsens hyperglycemia on the other hand in diabetic patients.²⁹ In one study 14% increase in fasting blood glucose has been found in NIDDM patients during the dietary fish oil supplementation³⁰ without any significant beneficial effects on plasma lipids. In my study 60% of the patients were found in the habit of taking carbohydrates in their diet both in simple and complex form.

Diabetic patients with hyperlipidaemia frequently develop atherosclerosis. Superoxide, which is present in diabetic patients with hypertriglyceridaemia, is suspected to play an important role in the initiation of this atherosclerosis.³¹ Other atherogenic factors specific to diabetes mellitus, however are concomitantly present which potentiate the process of atherosclerosis. Both low HDL and high triglyceride levels are frequently associated with other coronary risk factors. Correction of both of them, may reduce coronary artery disease risk without fear of adverse side effects.³²

In various studies the plasma triglyceride level exceeding 3 mmole/L (270 mg/dl) is universally accepted as hypertriglyceridaemia in diabetes mellitus¹¹ and the greater levels are positively correlated with the increased risk of coronary artery disease^{33,34}. It is noteworthy that triglyceride level greater than 2 mmole/l is the angiographically proven marker of coronary artery disease³⁵.

On long term followup, for more than 10 years, of the patients with impaired glucose tolerance test and or frank diabetes mellitus it was observed that the mortality rate with respect to IHD was remarkably high in those having moderately severe hyperlipidaemia than those with border line³⁶. Silent myocardial infarction which is seen in 15-24% of patients with diabetes mellitus¹ becomes even more common in the presence of long

standing moderate to severe hyperlipidaemia. In my study 22% had ischaemic heart disease. The lipid profile of them showed mild to moderate hypertriglyceridaemia (200-400 mg/dl, while total cholesterol, LDL cholesterol and HDL cholesterol were all normal.

CONCLUSION

The following conclusions have been drawn from this study.

1. Hypertiglyceridaemia is the most common lipid abnormality in diabetes mellitus.
2. Patients of NIDDM have more chances to develop hypertriglyceridaemia than IDDM.
3. The incidence of dislipidaemia is more in female diabetics than males, and dislipidaemia increases as the age advances.
4. The glycemic control of the patient has got a strong impact on the serum lipid level, and dislipidaemia is frequently encountered in those diabetics who have got poor glycemic control. It can be reverted if good glycemic control is achieved. Dislipidaemia is more common in those diabetics who have got sedentary life pattern.

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