ASSOCIATION OF LIVER AND RENAL FUNCTION AND THE TREATMENT OF HYPERTRIGLYCERIDEMIA IN DIABETES PATIENTS

T. Abdu Rahman¹*, A. Anil Babu¹ and K. Anoop Kumar²

¹Department of Pharmacy Practice, National College of Pharmacy.
²Department of General Medicine, KMCT Medical College, Manassery, Calicut.

ABSTRACT

The incidence and prevalence of diabetes mellitus have grown significantly throughout the world. The prevalence rate of hypertriglyceridemia in diabetic population is high and is correlated with liver function and renal function parameters. Overall increase in the number of people with diabetes has had a major impact on the development of diabetic kidney disease, which is the leading cause of end-stage renal disease. In individuals who have diabetes type 2, there is a higher incidence of liver function abnormalities than individuals who do not have diabetes. Coronary heart disease is the leading cause of death among type 2 diabetic patients. Much of the increased disease is associated with a well characterized risk factor for coronary heart disease like lipids and lipoprotein abnormalities. The role of triglyceride levels in determining diabetic risk was proved and is considered as a sensitive biomarker for lifestyle habits related to the risk of developing diabetes, therefore diabetes and triglycerides are well associated. Pharmacological management of hypertriglyceridemia among diabetic patients varies with their triglyceride levels. The combination of elevated triglycerides, low high density lipoprotein cholesterol and relatively normal low density lipoprotein cholesterol carried in small, dense, cholesterol-poor low density lipoprotein particles, has been called diabetic dyslipidemia. This form of dyslipidemia does not respond well to statin therapy. Hence, the need for additional or alternative therapy is inevitable. This study will help in the management of hypertriglyceridemia in diabetes mellitus patients and improving health care by routine monitoring.
KEYWORDS: Type 2 Diabetes, Coronary Heart Disease, Diabetic Kidney Disease, End Stage Renal Disease, Diabetic Dyslipidemia.

INTRODUCTION

Diabetes is one of the leading health problems faced by the world today, affecting millions of people, approximately less than 10% of total world population.\(^1,2\) Prevalence rate of hypertriglyceridemia in diabetic population is high when compared to non-diabetic patients. Type 2 diabetes mellitus have a higher incidence of liver function test abnormalities, underlying insulin resistance is often reflected by the mild chronic elevations of transaminases in the blood.\(^3\) More than one-third of the diabetes mellitus patients develop Diabetic Nephropathy (DN) which progressively deteriorates renal function and hence diabetes is correlated with liver and renal function parameters.\(^4,5\) The appearance of low but abnormal levels of albumin in the urine is the earliest clinical evidence of diabetes nephropathy.

In a diabetic population the burden of Atherosclerotic cardiovascular disease is (ASCVD) extremely high and is a cause of concern. The prevalence of diabetes, obesity, and metabolic syndrome is high in Indians, all of which are characterized by high triglyceride levels, low HDL-C and high prevalence of small dense LDL particles.\(^6\)

In determining diabetes mellitus triglycerides play an important role and hence triglyceride level is considered as a sensitive biomarker in the development of diabetes. Therefore diabetes mellitus and triglycerides are well associated.

Among type 2 diabetes mellitus patients, the prevalence of hypertriglyceridemia in India is nearly 60% and more than fifty percentage serum LDL levels were also noted.\(^7\) A high prevalence of elevated TG and a low HDL-C was confirmed by a recent epidemiological study sponsored by Indian Council of Medical Research (ICMR).\(^8\)

The form of dyslipidemia in which triglyceride levels are very high and do not respond well to statin therapy. Statin exerts their effect on LDL cholesterol levels and their effect on reduction of triglyceride is not much significant. Hence, for the management of hypertriglyceridemia in diabetes patients there is a need to look into addition or alternate therapies currently available. Therefore, there should be early monitoring and aggressive hypertriglyceridemia management in diabetic patients.
COMPLICATIONS AND COMORBIDITIES OF TYPE 2 DIABETES MELLITUS

Diabetic Dyslipidemia in Indians

The characteristic features of dyslipidemia seen in Type 2 diabetic patients include elevated Triglycerides, low HDL-C and a preponderance of small dense LDL. Pandya et al found more than fifty percentage prevalence of hypertriglyceridemia and nearly 60 percentages of serum LDL levels among type 2 diabetes mellitus patients in India. [7]

International Diabetes Federation 2015 reported that 1 in 11 adults are suffering from diabetes worldwide. Its increasing prevalence has become a global concern. They estimate that more than 400 million people in between the age group 20 and 79 years are suffering from DM currently, with a prevalence rate nearly 10%. According to IDF 2015, there will be 692 million people living with DM in 2040 which actually is a scaring figure with a prevalence rate of more than 10%.

India stands at the second position next to China, with more than 60 million people with diabetes. The ‘Asian Indian Phenotype’ of Indian puts them at a higher risk of developing type 2 DM and associated metabolic disorders.[9]

Dyslipidemia is a major cardiovascular risk factor especially in diabetic patients and is commonly associated with insulin resistance and free fatty acid reflux. Joshi SR et al reported in their study that 3/4th of study subjects had at least one of the lipid parameter abnormality. No significant difference was noted among urban and rural Indians in the prevalence of dyslipidemia.[8]

A study conducted to evaluate the prevalence and pattern of dyslipidemia in Indian Type2 DM patients showed that more than 80% of male and nearly 90% of female diabetic patients suffer from dyslipidemia.[10] Another study on the prevalence of dyslipidemia in young adult Indian population revealed that males in the age group of 31-40 years are at more prevalent to dyslipidemia owing to impaired glucose tolerance.[11] In a study by De Boer IH et al the prevalence of dyslipidemia in adult males was found to be 80% and 86% in females. Low HDL-C and mixed dyslipidemia (high TG, high LDL-C, and low HDL-C) were the most common pattern observed. The study also revealed that nearly 50% patients had achieved LDL-C goals and above 60% patients with HDL-C levels as per American Diabetes Association (ADA) 2010 guideline with lipid lowering during study period requiring the need for further lipid management.[12]
Diabetic Kidney Disease

According to De Boer et al diabetes mellitus is the most frequent cause of Chronic Kidney Failure in both developed and developing countries. Diabetic nephropathy is called by many clinical names like Kimmelstiel-Wilson syndrome or nodular diabetic glomerulosclerosis or intercapillary glomerulonephritis. The structural changes associated with diabetic kidney disease include meningeal expansion, glomerular basement membrane thickening, and glomerular sclerosis. Diabetic nephropathy is characterized by albuminuria, a decrease in GFR which is permanent and irreversible and arterial hypertension. Albuminuria must be confirmed on at least two occasions 6 months apart.\(^{[13]}\)

In a study (Steno type2) aimed to examine the potential efficacy of intensive combined therapy in patients with type2 DM and moderately increased albuminuria, they assigned randomly 160 patients to standard or multifactorial intensive therapy. Behavioral therapy (advice concerning diet, exercise and smoking cessation) and pharmacological intervention were contained. The primary end point was progression of overt nephropathy at 4 years and a composite CV end point at 8 years.\(^{[14,16]}\)

They found that at a mean follow-up of more than 7 years, intensive therapy reduced both microvascular and macrovascular diseases. There was a significant improvement in albumin excretion and in progression to overt nephropathy, defined as urine albumin in excretion greater than 300 mg/day with respect to diabetic nephropathy. In contrast, both groups of GFR fell to the same degree in both groups.

They concluded that an aggressive combined approach is required to prevent disease progression for patients with either type of DM.

Liver and Type2 DM

Diabetes is the major cause of liver disease like kidney disease leading to high mortality. The third leading indication for liver transplantation is cryptogenic cirrhosis, the cause of which is diabetes according to the study conducted by Porepa L et al. The incidence of nonalcoholic chronic liver disease (CLD) and hepatocellular carcinoma (HCC) was twofold greater in DM patients compared with non-diabetic patients\(^{[17]}\). The Verona study showed that cirrhosis was the fourth leading cause of death and accounted for more than 4% of diabetes-related deaths. The standardized mortality ratio (SMR), for cirrhosis, was more when compared with cardiovascular disease (CVD).\(^{[18]}\)
A higher incidence of liver function test abnormalities is seen in patients with diabetes type 2 than in individuals who do not have diabetes. Serum aminotransferases, alkaline phosphatase, bilirubin, albumin and prothrombin time are the most common liver function tests.

Aminotransferases, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), measure the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury. Increased activity of these markers is associated with insulin resistance.

Aspartate aminotransferase and alanine aminotransferase elevation are seen in about nearly half percentage of the population, whereas in diabetics, it is elevated in about more than 5% of patients. Nonalcoholic fatty liver disease (NAFLD) is the commonest cause of aminotransferase elevation in diabetics. In an Indian study among diabetic patients with NAFLD, there was only a mild elevation of aminotransferase levels. Thus, even a mild AST/ALT elevation in diabetics is a risk factor for NAFLD.

Severe liver fibrosis is more common in diabetics. The association of cirrhosis and diabetes is complicated by the fact that cirrhosis itself associated with insulin resistance. Impaired glucose tolerance is seen in nearly 90% and overt diabetes in nearly 30% of patients with diabetes. Diabetes increases complication of cirrhosis and is associated with the development of ascites, higher mortality in refractory ascites, risk and severity of hepatic encephalopathy. The incidence of acute liver failure appears to be increased in patients with diabetes compared with background population.

Patients with hepatitis C virus (HCV) are more likely to develop diabetes. Furthermore, patients who are transplanted for HCV are more likely to develop diabetes than those who are transplanted for other liver diseases. And hence liver disease and diabetics are well associated.

**Lipid Management in Diabetes: Looking Beyond Statins**

Indians have a high prevalence of diabetes, obesity, and metabolic syndrome, all of which are characterized by high triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C), and higher prevalence of small dense low-density lipoprotein (LDL) particles which are also known as atherogenic dyslipidemia.
A recent epidemiological study sponsored by Indian Council of Medical Research\textsuperscript{[8]} has confirmed a high prevalence of elevated TG and low HDL-C. This form of dyslipidemia does not respond well to statin therapy. Hence, it need for additional/alternative therapy.

American Diabetes Association guidelines, including the latest (2016), indicate the need for statin therapy in virtually all patients over 40 years.\textsuperscript{[22]} This alone may not be sufficient in Indian diabetics. Statins mainly reduce LDL-C levels, statin does not reduce TG significantly and have limited effect on HDL-C leaving the benefit and desired effect incomplete. Statins have the pleiotropic effect that leads to plaque stabilizations. This is independent of their lipid lowering effect and is a major contributor to the success of statin trials.

Statins also have a legacy effect this was best illustrated in the West of Scotland Coronary Prevention Study (WOSCOPS)\textsuperscript{[23]} study where beneficial effects of prevastatin were seen even many years after completion of the study. This further increases the utility of statins when needed.

Epidemiological studies have suggested that TG is a relevant measure in evaluating coronary heart disease (CHD) risk. However, the extent to which TG serves as an independent CHD risk factor remains uncertain because of its strong association with other covariates. In the largest population-based prospective study, the strong linear association between TG levels and CHD risk persisted until adjustment for non-HDL-C and HDL-C. This weakens the importance of TG as an independent risk factor and the need for isolated TG reduction.

Statins do not reduce TG significantly; their main effect is on LDL cholesterol. Furthermore, in a subgroup analysis of the ACCORD\textsuperscript{[24]} (Action to Control Cardiovascular Risk in Diabetes) lipid study on diabetics, there was a suggestion that men with higher baseline TG and lower HDL-C levels benefited from fenofibrate therapy in addition to preexisting simuvasatin therapy, which was similar to the findings in the post hoc analyses in other fibrate trials on bezafibrate and gemfibrozil.

A meta-analysis of 18 trials\textsuperscript{[25]} providing data for more than 40000 participants, including major cardiovascular (CV) events, and deaths confirmed these findings. It was found that fibrates could reduce the risk of major CV events predominantly by prevention of coronary events, and might have a role in individuals at high risk of CV events and in those with combined dyslipidemia. This is always in addition toastatin.
Alternatives or Additions to statins include Fibrates, Niacin, Ezetimibe, Omega-3 fatty acids, Diet, and Lifestyle. Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)\textsuperscript{26} study using fenofibrate showed nearly 30\% reduction in cardiac events with fenofibrate in patients with high TG and low HDL-C and lesser benefit on mortality. Ezetimibe selectively inhibits the absorption of cholesterol from the small intestine. It thus reduces LDL-C and TG levels and increases HDL-C levels in patients with combined dyslipidemia. It can be used along with statin for LDL-C reduction, and with statin and fenofibrate in mixed dyslipidemia.

Omega-3 fatty acids reduce TG and it acts by interfering with many transcription factors. They have been recommended for use in severe hypertriglyceridemia and as an add-on to a statin in combined dyslipidemia to achieve non-HDL-C targets.

**CONCLUSION**

Diabetes is rising rapidly, globally as well as in India. Dyslipidemia is the most frequent comorbid risk factor associated with diabetes. Diabetes is the major cause of liver disease and kidney disease leading to high mortality, From the above studies we conclude that liver and kidney disease are well associated with diabetics. A relevant focus on the characteristic dyslipidemia of type 2 diabetes which includes high triglyceride (TG) levels, low high-density lipoprotein cholesterol (HDL-C), and higher prevalence of small dense low-density lipoprotein (LDL) particles which are also known as atherogenic dyslipidemia. The prevalence of hypertriglyceridemia in diabetic group in India is more than 50 and high serum LDL levels nearly 60\% were noted among type 2 diabetic patients. This form of dyslipidemia does not respond well to statin therapy. Hence, there is a need for additional/alternative therapy. Alternatives or Additions to statins include Fibrates, Niacin, Ezetimibe, Omega-3 fatty acids, Diet, and Lifestyle. The prevalence of hypertriglyceridemia in type 2 diabetes mellitus population is more. Plasma triglycerides and insulin may contribute to cardiac hyper trophy and arterial stiffening independently of hemodynamic and hormonal factors. Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than individuals who do not have diabetes. Diabetes has had a major impact on development of diabetic kidney disease. Diabetes is the leading cause of end-stage renal disease (50\%) in the world. Therefore the prevalence rate of hypertriglyceridemia in diabetic population and its correlation with liver function and renal function parameters helps to identify such problems and provide appropriate measures.
REFERENCES


7. Hetal Pandya, Lakhani JD, Dadhania J, Trivedi A. The Prevalence and Pattern of Dyslipidemia among Type 2 Diabetic Patients at Rural Based Hospital Gujarat, India. Indian Journal of Clinical Practice, 2012 May; 22(12): 36-44.


