Antihyperlipidemic Activity of Hydroxyl Methylglutaryl Coenzyme A Reductase Inhibitor on Lipid Profile in Secondary Hyperlipidemia

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Abstract

Objectives: To observe the variations in lipid profile in patients with secondary hyperlipidemia using HMG-CoA reductase inhibitor.

Methods: This study was done at private hospital in patients predominantly suffering from secondary hyperlipidemia. The duration of study was about 4 months. Body weight, height and blood pressure of subjects were assessed. The subjects were asked to answer the related question on cigarette smoking, health related complaints, detailed history of family, drug usage, and nutritional habits. Subjects were requested to make up a permission form before starting the research study. This case control study was performed at local private Hospital, located at Karachi from 1st April 2017 to 30th July 2017. The aim of research was to analyze the effects of HMG-CoA reductase inhibitor on lipid profile in patients of secondary hyperlipidemia. Age between 35 to 65 years and secondary hyperlipidemic patients were included in the inclusion criteria. Lactating/pregnant women, renal, liver and established coronary artery diseases were included in exclusion criteria.

Results: Sixty patients having deteriorated lipid profile were included in this research (age 30-60 years). Subjects were prescribed simvastatin orally 20 mg/day (international product) for 04 months. The total cholesterol, triacylglycerol, LDL and HDL were analysed using simvastatin (20mg/day) of international standard in the serum of secondary hyperlipidemic patients.

Conclusion: During this study it is observed that Simvastatin raises the HDL level and reduces LDL level and cholesterol level.

Keywords: Secondary hyperlipidemia, HMG-CoA reductase inhibitor, lipid profile, coronary heart disease.

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Introduction

Increase in plasma cholesterol (> 200 mg/dl) concentration is known as hypercholesterolemia and is observed in many disorders like coronary artery disease and atherosclerosis; they are most commonly caused by dyslipidemia. Primary hyper or hypolipoproteinemia are due to genetic defects in lipoprotein metabolism and transport. The casual performance of increase blood cholesterol in the atherosclerosis genesis, especially coronary vascular disease is well established. Coronary vascular disease (CVD) is the most common cause of morbidity and mortality in the region of Pakistan[1]. The number of cases of cardiovascular illness in Pakistan is as greater as in the western countries. Among people with high blood glucose level, CVD is a considerable cause of mortality, along with factors like high blood pressure which causes this high prevalence of CVD. As compared to the non-dia-

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betic people, patients with diabetes are likely to have high blood pressure twice as much. In diabetics, up to 75% cases of CVD can possibly be linked to hypertension, recommending a more aggressive treatment approach for those having hypertension with this disease. The disturbances of metabolism in patients with diabetes include insulin resistance, disturbance in lipids and chronic hyperglycemias. Lipoprotein disorders are due to some other diseases (e.g. nephrotic syndrome, diabetes mellitus, atherosclerosis, hypothyroidism etc.), and results in abnormal lipoprotein pattern which often resembles the primary inherited condition[2]. High blood sugar due to diabetes enervates dilatation of vessels before the formation of atherosclerotic plague. The most common cause of cardiovascular disease is diabetes mellitus and 50% of diabetic patients have greater evidence of macro vascular disease at the time of their diagnosis[3]. Type IIa is also known as hyper beta-lipoproteinemia and is caused by a defect in LDL receptors. This disorder is characterized by hypercholesterolemia[4]. Around 75% to 80% of adult subjects with diabetes die due to micro and macrovascular disease, coronary artery disease, or a consolidation of all these conditions[5,6]. Diabetes mellitus is an important contributing cause for macro-vascular illness in both women and men. Diabetic and hyperlipidemic patients have greater chances of coronary vascular disease when correlated with individuals who do not have diabetes and the possibility of death by macro-vascular disease in hyperglycaemic patients is high as compared to non-hyperglycaemic patients. The management of macro-vascular disease is poorer in subjects with hyperglycaemia than in non-hyperglycaemic patients. Increased level of serum low density lipoprotein cholesterol is a risk factor for macro vascular disease[7]. Specific lipoprotein disorders (hyper or hypolipoproteinaemia) are uncommon but with the increasing knowledge regarding the importance of apolipoproteins they have been attributed to a variety of clinical disorders. Individuals suffering from hyperglycemias due to diabetes, hypothyroidism or kidney disease as a result of secondary effects of their disorders often show abnormal metabolism of lipoprotein. For instance, because synthesis of LPL is regulated by insulin, LPL defeciencies leading to type I hyperlipoproteinaemia may occur as a secondary outcome of diabetes mellitus. Low density lipoprotein cholesterol is considered to be a leading cause for cardiovascular disease in hyperglycaemic subjects[8]. Cholesterol level is high in the blood play a key part in atherosclerotic lesion formation in the walls of coronary arteries. Familial hypercholesterolemia was the first inherited disorder recognized as being a cause of myocardial infarction (heart attack). The resulting hypercholesterolemia becomes a precursor to atherosclerotic plaque formation and premature coronary artery disease. There is substantial evidence that plasma high density lipoprotein (HDL) concentration are reduced in type 2 diabetes mellitus (NIDDM) patients and it appears that this change is associated with an high risk of coronary artery disease in these individuals[9]. HDL may be a more important protective factor for ischemic heart disease in women. The presence of high level of triacylglycerol and low HDL levels are the best predictor of coronary vascular disease in patients with type 2 diabetes mellitus according to American diabetic association (ADA). Cardiovascular disease manifesting itself as coronary vascular disease is the considerable cause of mortality and morbidity among type 2 diabetes patients. Of the many disorders of lipoprotein metabolism, familial hypercholesterolemia type II may be the most prevalent in the general population. It is an autosomal dominant disorder that results from mutations affecting the structure and function of the cell- surface receptor that binds plasma LDLs and removes them from the circulation. Management therapy is considered as an option only if non-drug interventions (altered diet and exercise) have failed to lower plasma lipids[10]. The product used in secondary hyperlipidemia is HMG-CoA reductase inhibitors (Simvastatin). Statins, such as atorvastatin, simvastatin and lovastatin, are fungal-derived antilipidemic drugs. However, since mevalonate is also required for the synthesis of other important isoprenoid compounds besides cholesterol, long-term treatments carry some risk of toxicity.

Antilipidemic agents are helpful for the management of atherosclerotic disease and dyslipidemia[11]. The initial agents named 'natural' statins in the class-Lovastatin, Pravastatin and Simvastatin - are all fungal compounds. They have all been shown to reduce plasma low-density-lipoprotein (LDL) cholesterol, coronary events, cardiovascular mortality and development of coronary artery stenosis[11]. Antilipidemic drugs are appropriately considered first-line therapy for lowering LDL cholesterol in patient of diabetes with hyperlipidemia. These drugs were constructed to hinder the enzyme which helps insynthesis of cholesterol, hence, they lower the low density lipoprotein (LDL) production, raise the hepatic LDL receptors' regulating expression, and decrease the circulating LDL concentrations in the liver. Simvastatin is a drug which is 3-hydroxyl-3-methylglutrayl coenzyme A, it reduces low density lipoprotein to larger level as compared to the results achieved with the previous drug management and diettrails. The lipid lowering drug has been shown to decrease death ratio in macro-vascular disease patients[12].

Patients and Methods

This case control research study was carried out at tertiary care hospital situated in Karachi from 1st April 2017 to 30th July 2017. The study period was four months. Patients with secondary hyperlipidemia were recruited as study participants.

Body weight, blood pressure, and height of every subject were evaluated. A questionnaire was given which asked details about tobacco smoking, health complaints, usage of drugs, dietary pattern and family history. Next subjects were requested to sign a consent form before starting the study. Age between 35 to 65 years of both sexes and patients with secondary hyperlipidemia were included in inclusion criteria. All patients having history of lactation or pregnancy, liver dysfunctions and renal dysfunctions were excluded from the study. Medical examination of all these patients was carried out.

A sample size of sixty patients was identified for the study. Biochemical analysis of serum lipid profile was carried out. Twenty mg per day of Simvastatin were orally administered to these patients for four months. Blood samples were re-collected after 04 months for the evaluation of lipid profile.

The collected sample of the blood was centrifuged for 10 minutes. From this sample, serum was collected in clean and dry Eppendorfs and was stored till further analysis. Blood samples were taken from subjects after informed consent. Friedwald formula was used for LDL. Serum levels of TG, HDL and total cholesterol were analyzed on microlab using Randox laboratories limited, UK kits. Statistical Data was entered and analyzed using SPSS version-20.

Results

Arteriosclerosis is a general term describing any loss of elasticity of medium or hardening or large arteries, and refers to the atheromatous plaque formation. It is a syndrome that affects arteries. It is believed to be initiated when LDLs become oxidized. Developmental process of atheromatous plaques is called atherogenesis. Involving the concomitant accumulation of fatty substances called plaques and it is characterized by a remodelling of arteries. Normally cholesterol is transported in the form of peculiar particles in the blood which include both proteins and lipid. The most common lipoproteins are HDL, LDL and VLDL in the serum of a lipid profile. Most of the studies have shown a confirmative communication between increased lipoproteins and mortality due to coronary vascular disease. In the recent research sixty patients were evaluated for the antilipidemic activity of HMG-CoA reductase inhibitor (simvastatin) in patients with secondary hyperlipidemia. Figure 1 shows the variation of serum lipids in secondary hyperlipidemia before and after four months with Simvastatin (20 mg/day) treatment. The serum cholesterol was decreased to 189.24 ± 2.68 mg/dl, while triglyceride and low density lipoprotein were also reduced after the Simvastatin (20 mg/day) treatment to the range of 160.04 ± 1.77 mg/dl and

144.12 ± 1.91 mg/dl respectively. This decrease when compared from before and after treatment was found to be statistically significant ($p < 0.05$). There were no significant changes observed in high density lipoproteins. Figure 2, 3 and 4 show the variation & correlation of cholesterol, triglyceride and low density lipoprotein in secondary dyslipidemia before and after four months simvastatin (20 mg/day) treatment. Figure 2 represents positive correlation ($r = 0.895$) of total cholesterol when compared from before and after treatment. Figure 3 and 4 also represent the positive correlation ($r = 0.935$, $r = 0.952$) of triglyceride and low density lipoprotein (LDL) when compared from before and after treatment.

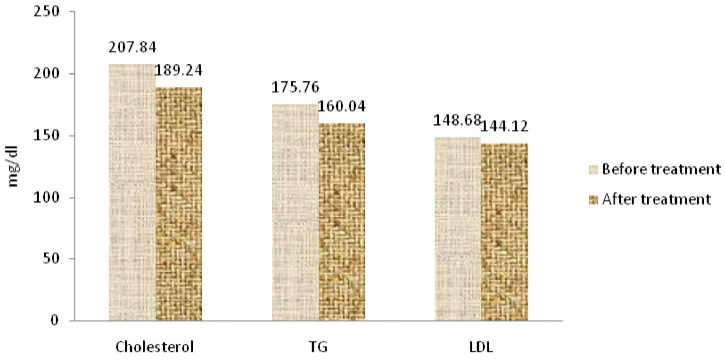

Fig 1. Changes in mean serum cholesterol, triglyceride, low density lipoprotein before & after 04 months of treatment with HMG-CoA reductase inhibitor (simvastatin 20mg/day) in secondary hyperlipidemic patients.

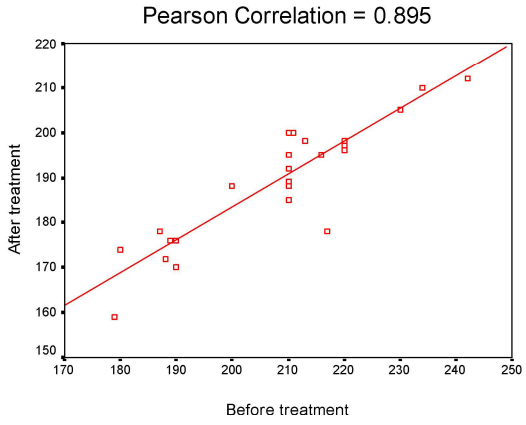

Fig 2. Correlation of cholesterol between before and after 04 months of treatment with HMG-CoA reductase inhibitor (simvastatin 20mg/day) in secondary hyperlipidemic patients.

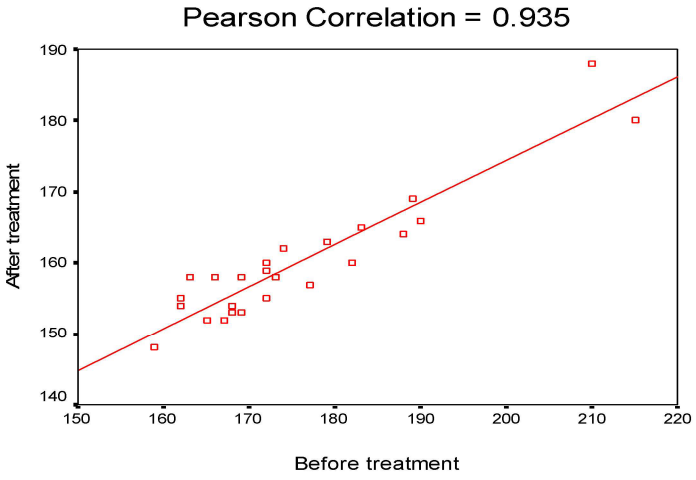

Fig 3. Correlation of triglyceride between before and after 04 months of treatment with HMG-CoA reductase inhibitor (simvastatin 20mg/day) in secondary hyperlipidemic patients.

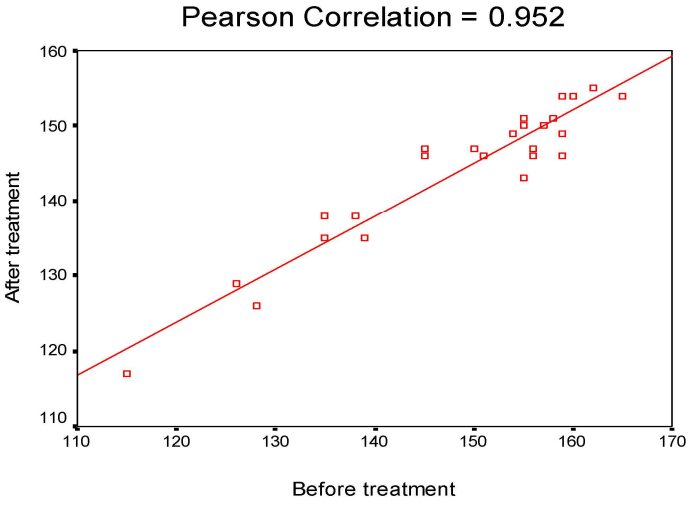

Fig 4. Correlation of low-density lipoprotein between before and after 04 months of treatment with HMG-CoA reductase inhibitor (simvastatin 20mg/day) in secondary hyperlipidemic patients.

Discussion

Hyperlipoproteinaemia is the state of highly increased levels of lipoproteins or lipids in the blood. It is stated by WHO (World Health Organization) that most of the lipids in plasma are present as lipoproteins i.e. VLDL, LDL, chylomicrons, and HDL. A National health survey in Pakistan between 1990 and 1994 revealed that 13% of Pakistani people have increased random blood cholesterol > 200 mg/dl. Patient with hyperglycaemia due to diabetes (Non-insulin dependent) have a two to four times excess chances of macro-vascular disease as compared to patients with non-diabetic[13]. Secondary hyperlipidaemia are caused by generalized metabolic dysfunctions such as hypothyroidism or biliary cirrhosis, diabetes mellitus and intake of alcohol. Atherosclerosis is the deposition of lipids in the connective tissues of intima of arteries. It leads to blood flow obstruction, leading coronary vascular disease, myocardial infarction and stroke etc. The process is originated when there is damage to endothelial cells of blood vessels. The condition is compounded by hyperlipidemia. Atherosclerotic plaques formation is the process of atherogenesis, a critical step in the disease, atherosclerosis. Low-density lipoprotein complexes (LDLs), which are the primary means of transporting cholesterol in the blood, are readily oxidized. Normally white blood cells recognize the oxidation and absorb the LDL through its scavenger receptor. They over indulge and are called foam cell. Foam cells fascinate other white blood cells, which leads to deposition of more cholesterol. Conclusively, this deposition of cholesterol becomes one of the chief chemical elements of the atherosclerotic plaque that forms at the site. Circulating monocytes deposit at the site of injury and ingest most of the lipids. If the damage to the intima continues, there is infiltration of platelets at the site. Platelets and aggregate foam cells, and release substances resulting in atheromatic plaque formation[14]. At the end of year 2020, cardiovascular disease or macrovascular disease is major problem in Asia. The major factors that contribute to the arteriovascular disease, like hyperlipidemia, obesity, hyperglycaemia and smoking tobacco lead to increasing death ratio across the globe. Many research trials have shown that increased risk of arteriovascular disease in South Asian countries is higher than other countries. Pakistan is at higher risk of death due to macrovascular disease among all asian populations. Harmful factors like hypertension and hyperglycaemia are greatly linked with atherogenic formation of macrovascular disease among asians. In Pakistan increased lipidaemia develops major vascular disease has a public health issue[1]. Diabetic dyslipidaemia leads to disturbances of metabolism like hypothyroidism and diabetes mellitus, or intake of alcohol, therapy with estrogens, glucocorticoids, beta adrenergic antagonists, isotretinoin, nephrotic syndrome, HIV, protease inhibitors, thiazide diuretics and cyclosporine[15]. Ischemic heart disease is most commonly caused by dyslipidemia in type 2 diabetic patients[16]. Secondary hyperlipidemia due to diabetes is of the major causes of myocardial infarction. CVD is culpable for 80% of total diabetic mortality. Increased blood sugar due to diabetes is associated with an increase in high TG, small LDL particles and low HDL levels. Hormone sensitive lipase is activated due to lack of insulin; more free fatty acids are formed, which are catabolised to produce acetyl CoA. So, acetyl CoA pool is increased, and it is channelled to synthesis of cholesterol. Diabetic dyslipidemia plays a major role in the development of heart disease[17]. In diabetes, there is an increase in the atherogenicity of LDL while a the protective effect of HDL is decreased. In diabetes mellitus, the TAG pool in the cell is increase and the LDL particles formed from VLDL are of the small dense variety that is highly atherogenic[18]. The most common hypolipidaemic drugs used in disturbance of lipid contain simvastatin. They are effective in reducing the cholesterol level and lowering the incidence of CAD. C25H38O5 is the formula of simvastatin and 418.57 its molecular weight[19]. Most of the drugs, especially Simvastatin and atrovastatin are first choice of drugs in this subset of the population for hypercholesterolemia[20]. According to the research firm IMS Health, HMGCoA reductase inhibitors represent the

highest class of drugs in the United States with regard to their sale; Atorvastatin and Simvastatin were the first and second most prescribed statins in 2006, respectively[21]. "Statins are among our best drugs for treating individuals who have elevated cholesterol," said Robert Eckel, M.D president of the American Heart Association. "Overwhelmingly, in most cases the majority of individuals use statins very well, and the absolute risk of side effects is low". Simvastatin is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase, a key enzyme in the synthesis of cholesterol pathway[22]. The effects of international product of Simvastatin were assessed on secondary (diabetic) hyperlipidaemic patients in the present study. In this study when patients were given with product of Simvastatin in secondary hyperlipidemic patients, their serum triglyceride, LDLand cholesterol were considerably low ($p < 0.05$) in comparison to the patients before treatment (Figure 1). Raised blood cholesterol level plays a leading role in atherosclerotic plague formation in the walls of coronary vessels[23,24]. The present study matches with the study of Kostakou (2009) who observed decreased concentrations of total cholesterol (262 to 189 mg/dl, $p<0.001$), low-density lipoprotein cholesterol (177 to 114 mg/dl, $p<0.001$). Simvastatin (HMG-CoA reductase inhibitors) also reduced the concentration of triglycerides in the present study as was found by Kostakou[4]. Another study by Guyton also observed that decrease in LDL-cholesterol and triglycerides are dose dependent. They observed significantly greater reductions in LDL-C, triglycerides ($p < 0.001$) at the dose of simvastatin 20 mg per day for 24 weeks. In this study similar differences in lipid profile are analysed in patients treated with simvastatin 20 mg for 04 months[25].

Conclusion

This study showed that international product of Simvastatin (HMG-CoA reductase inhibitors) is most effective drug to decrease serum triglycerides, serum cholesterol, serum LDL-cholesterol and to increase HDL cholesterol in secondary hyperlipidemic patients. To help mitigate the increasing cost of imported drugs, one strategy of the National Drug Policy is to promote the usage of locally made products. Simvastatin is the drug of which the local production and utilization are strongly encouraged.

Conflict of Interest

Authors have no conflict of interest and no grant/funding from any organization.

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