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Research Article

ATORVASTATIN IMPROVES ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH CONTROLLED TYPE 2 DIABETES MELLITUS

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ABSTRACT
Endothelial dysfunction occurs in diabetes which may improve with its control. Statins have been claimed to improve the endothelial dysfunction, independent of control of hyperglycemia in diabetics. Objective behind the study was to evaluate the effect of atorvastatin on endothelial function in patients with type 2 diabetes mellitus after achieving control (HbA1c<7.0%) with antidiabetic therapy. 50 patients with controlled type 2 diabetes mellitus (i.e. HbA1c<7.0%) received fixed dose atorvastatin 40mg/day and diabetic diet. Patients continued their antidiabetic therapy as usual. Target parameters i.e. serum lipids and brachial artery flow mediated vasodilatation (FMD) were measured at the beginning of study and repeated at 12 weeks. Serum lipid levels and flow mediated vasodilatation (FMD) improved significantly after 12 weeks of therapy with atorvastatin ($p<0.001$). The controlled status of the patients (i.e. HbA1c<7.0%) of the patients was maintained throughout the course of the study (i.e. 6.81 $\pm$ 0.13% and 6.64 $\pm$ 0.19% at 0 and 12weeks respectively). The study documents the beneficial effect of atorvastatin on endothelial dysfunction over and above the control of diabetes. This effect is attributed to its lipid lowering property in addition to its antioxidant property.

Keywords: *Endothelial Function, Brachial Artery Flow Mediated Vasodilatation (FMD), Atorvastatin*

INTRODUCTION
Macrovascular complications, particularly cardiovascular disease are most important cause of mortality and morbidity in patients of type 2 diabetes mellitus (Feng *et al.,* 2011). Atherosclerosis, the precursor of macrovascular disease, occurs two and half times more frequently among type 2 diabetics. Endothelial function is the earliest to be affected in this cascade of events leading to atherosclerotic plaque formation (Mandosi *et al.,* 2010). The metabolic abnormalities characteristic of type 2 diabetes (e.g. hyperglycemia, hyperlipidemia, insulin resistance) provokes various molecular mechanisms which contribute to endothelial dysfunction (Feng *et al.,* 2011). These include decreased bioavailability of nitric oxide, increased oxidative stress (Sodha *et al.,* 2008), disturbances of intracellular signal transduction and activation of receptors for advanced glycation end products (RAGEs) (Feng *et al.,* 2011). Statins improve endothelial dysfunction by their ability to increase nitric oxide (NO) availability; by increasing endothelial nitric oxide synthase expression (eNOS), and inhibit expression of endothelin-1, a potent vasoconstrictor (Usharani *et al.,* 2008; Amin and El-Twab, 2009; Economides *et al.,* 2004). So far studies conducted, have concentrated on the use of statins in diabetics, irrespective of its control and have documented its beneficial effect (Koksal *et al.,* 2011). From these studies, it is not clear whether the improvement in endothelial dysfunction is due to control of hyperglycemia or due to atorvastatin or both. Therefore this study was designed to evaluate the endothelial dysfunction in controlled diabetics (i.e.HbA1c<7.0%) at 12 weeks of atorvastatin therapy.

MATERIALS AND METHODS
The present study included 50 patients of controlled type 2 diabetes mellitus of >1 year (HbA1c<7.0%). Patients with hypertension, coronary artery disease or impaired cardiac function, chronic infections,

peripheral artery disease, hepatic, renal, neurological or haematological diseases were excluded from the study. Blood sugar (fasting and postprandial), glycosylated haemoglobin (HbA1c), renal function tests (blood urea), serum transaminases, electrocardiography (ECG), chest X-ray and blood pressure were measured at the start of study. Along with above mentioned baseline investigations, two target parameters i.e. serum lipids and brachial artery flow mediated vasodilatation (FMD) were performed to establish the basal values in these patients. Then all patients received atorvastatin 40mg per day and diabetic diet. Patients were continued on usual antidiabetic drugs and were asked to come for follow up at 2, 4, 6, 8, and 12weeks. On each visit, patients were evaluated for compliance of atorvastatin, antidiabetic drugs and diabetic diet. Patients were also asked about the side effects of atorvastatin therapy. If any patient developed the side effects of atorvastatin (increased transaminases, myopathy, acute renal failure, sleep disturbances, headache, nausea, bowel upset and rashes) during the study period, he/she was dropped. HbA1c was measured again at 12weeks (visit 6) to know whether the diabetic status of patient remained under control or not. On serial follow up, blood sugar (fasting and postprandial) remained controlled. At 12weeks, in addition to other investigations, target parameters i.e. serum lipids and FMD were repeated and recorded for comparison. The study was then terminated. The data thus collected was compiled and analysed using paired t-test.

RESULTS

The baseline characteristics of patients are depicted in table 1.

Table 1

AGE	31-71yrs
SEX (M:F)	1:1
BODY MASS INDEX	25.84±2.69kg/m^2
BLOOD SUGAR FASTING	119±24.4mg/dl
BLOOD SUGAR POSTPRANDIAL	177±32.8mg/dl
HbA1c	6.81±0.13%
TRIGLYCERIDES	285.00±27
TOTAL CHOLESTROL	250.00±25
HDL-C	32.00±3.0
LDL-C	168.00±11.5
BLOOD UREA	28.34±6.8
SGOT	33.3±5.25
SGPT	29.5±6.6

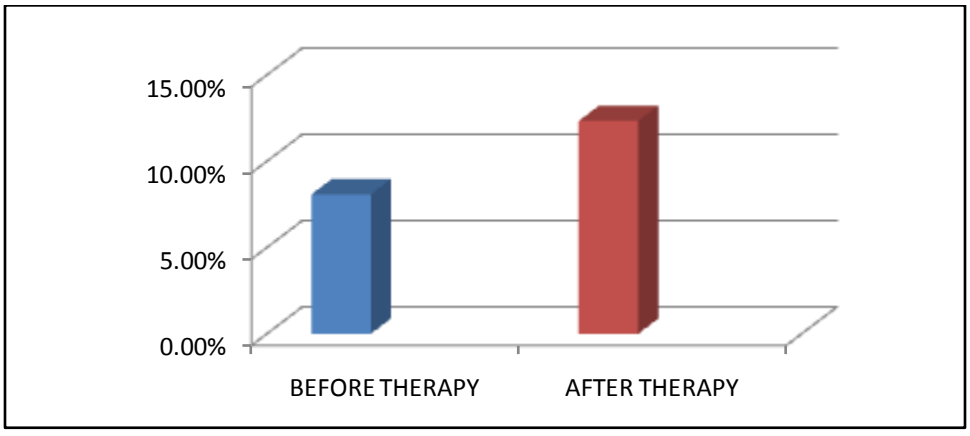

Figure 1

Effect of Atorvastatin on Endothelial Dysfunction

FMD increased significantly from 8.08±1.92% in the beginning of the study (visit 1) to 12.34±3.28% at 12 weeks (visit 6) of therapy with atorvastatin 40mg/day (Figure 1).

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Effect of Atorvastatin on Serum Lipids

The serum lipid levels in patients with type 2 diabetes are depicted in table 2 and figure 2. There was 20.98mg/dl fall in serum triglyceride, 31.72mg/dl fall in total cholesterol and 31.32mg/dl fall in LDL-cholesterol at 12weeks of atorvastatin therapy. HDL-cholesterol increased by 4.38mg/dl at 12weeks, indicating beneficial effect of the drug.

Table 2

Parameters (mg%)	Before Therapy	After Therapy
Triglycerides	285.00±27	264.02±26.0
Total Cholesterol	250.00±25	218.28±21.0
HDL-C	32.00±3.0	36.38±3.5
LDL-C	168.00±11.5	136.68±12.0

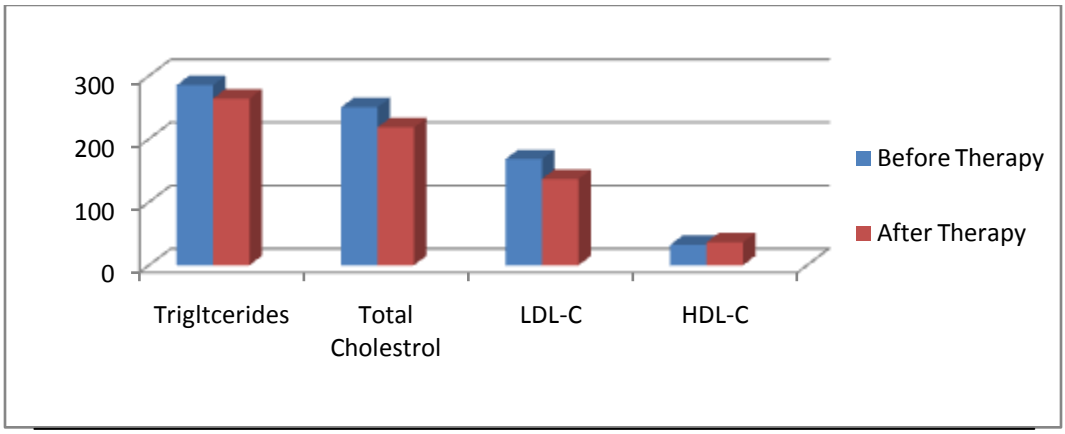

Figure 2

Effect of Atorvastatin on Blood Pressure

The blood pressure decreased insignificantly with atorvastatin therapy

Safety Profile of Atorvastatin

On each follow up visit, the patients were asked about its toxic effects. Any patient developing any side effect, during the course of the study was dropped from the study. During the period of study, two patients developed raised serum transaminases, hence, were dropped.

DISCUSSION

Endothelial dysfunction in diabetes mellitus is multifactorial and is attributed to lipid abnormalities, oxidative stress induced by decreased nitric oxide production, increased LDL oxidation, production of advanced glycation products and some other unidentified factors (Feng *et al.,* 2011). Atorvastatin has been claimed to improve endothelial dysfunction both by lipid lowering effect and antioxidant property (Sodha *et al.,* 2008; Usharani *et al.,* 2008; Nakamura *et al.,* 2010; Rubba, 2007). Out of various methods to judge endothelial dysfunction, flow mediated vasodilatation is the simplest and best method (Amudha *et al.,* 2008; Economides *et al.,* 2004). In our study, the brachial artery flow mediated vasodilatation (FMD) increased significantly from 8.08±1.92% to 12.34±3.28% at 12weeks of therapy with atorvastatin 40mg/day against the FMD of 13% in normal healthy subjects (as per value standardised by our institute). Our observations demonstrated that atorvastatin resulted in more or less complete reversal of endothelial dysfunction. The effect was over and above the control of diabetes. Hence we agree that statins improve the endothelial dysfunction independent of control of hyperglycemia in diabetics.

The beneficial effects of atorvastatin are attributed to its lipid lowering and non lipid lowering antioxidant effects. Though variable doses of atorvastatin have variable effects on serum lipids (Economides *et al.,* 2004; Koksal *et al.,* 2011; Abbas *et al.,* 2012; Rosen *et al.,* 2013; Barakat *et al.,* 2013; Sindhu *et al.,*

2011) but to optimise this effect, we used optimal fixed dose of atorvastatin (40mg/day) so as to avoid the side effects (Barakat *et al.*, 2013). Our results indicated that fixed dose atorvastatin therapy reduced the total serum cholesterol and LDL-cholesterol; increased the HDL-cholesterol to target level. Hence, we agree with the fact that atorvastatin therapy reduces serum lipids especially cholesterol in diabetic patients.

Since there was a linear correlation between the decrease in serum cholesterol level and improvement in endothelial dysfunction, hence we can say that the effect of the atorvastatin on endothelial dysfunction was mainly because of its lipid lowering property as other identifiable factors before and after atorvastatin therapy, therefore we are not able to comment on its effect on oxidative stress and on other mechanisms.

In our study, there was beneficial effect of atorvastatin on blood pressure. As patients with hypertension were excluded from the study, there we do not comment whether blood pressure has any influence on the endothelial function.

To conclude, the study documents the beneficial effect of atorvastatin on endothelial dysfunction over and above the control of diabetes. This effect is partly attributed to its lipid lowering properties.

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