Randomized Trial of Atorvastatin in Improving Endothelial Function in Diabetics without Prior Coronary Disease and Having Average Cholesterol Level

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Objective: *The aim of this study was to determine whether HMGCoA reductase inhibitor with atorvastatin can modulate endothelial function in type II diabetics having average cholesterol and no prior cardiovascular disease.*

Material and Method: *Type II diabetics, with no prior cardiovascular events and total cholesterol at admission of $\leq$ 200 mg/dl or LDL $\leq$ 140 mg/dl, were randomized to placebo (n = 20) or atorvastatin 20 mg daily (n = 22) for 30 weeks. Brachial artery endothelium-dependent dilatation or flow-mediated dilatation (FMD) and endothelium-independent dilatation or nitroglycerine-mediated dilatation (NTGMD) were measured at baseline and after thirty weeks of treatment.*

Results: *Baseline clinical characteristics were similar at admission in both groups. After thirty weeks of treatment, the FMD did not significantly change in either the atorvastatin or placebo group (4.11 $\pm$ 1.05% to 3.01 $\pm$ 1.27% vs 5.75 $\pm$ 1.93% to 6.45 $\pm$ 1.41%, respectively; p = 0.46 by analysis of covariance). Similarly, the NTGM did not change in either group.*

Conclusion: *The addition of HMGCoA reductase inhibitor with atorvastatin did not improve endothelial function in type 2 diabetes having average cholesterol with no prior cardiovascular disease, despite an improvement of the lipid profile.*

Keywords: *Type 2 diabetes, Endothelial dysfunction, Atorvastatin*

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Type II diabetics comprise 90% of diabetics stricken with premature atherosclerosis. Diabetes increases the relative risk of cardiovascular disease by two- to four-fold compared with the general population. A Multiple Risk Factor Intervention Trial (MRFIT) found that men with diabetes had three times the absolute risk of coronary artery disease mortality compared to a non-diabetic cohort, even after adjustment for established risk factors[1,2]. The initiation of the atherosclerotic process, the main mechanism of coronary disease, is injury to the vascular endothelium, and progressive endothelial dysfunction, which loses its ability to prevent abnormal vasoconstriction and to inhibit platelet aggregation and smooth muscle proliferation[3]. Because endothelial dysfunction precedes the development of clinical atherosclerosis, early identification and treatment could preclude or significantly delay the development of atherosclerosis.

The risk factors for coronary atherosclerosis includes diabetes[4-9], but angiographically normal

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coronary arteries can have endothelial dysfunction, as has been reported of coronary arteries[10,11] and the brachial artery[12] during assessment of vasodilator response.

Celermajer et al have developed a non-invasive technique for the evaluation of endothelial function with ultrasonographic imaging of the brachial artery during reactive hyperemic (flow-mediated vasodilatation), which is correlated with cardiovascular risk factors[13], the severity of coronary artery disease[14]. Takase et al. similarly demonstrated a strong correlation between flow-mediated dilatation in brachial artery and in coronary artery ($r = 0.78$, $p < 0.001$)[15]. This coronary response is also related to cardiac events[16,17].

Several clinical trials have shown that HMGCoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors reduce the incidence of cardiovascular events in diabetic patients with prior coronary disease, having high[18] to average cholesterol[19,20]. Although the inclusion of diabetics in these clinical trials has been limited, the results suggest that HMGCoA reductase inhibitors reduce the incidence of cardiovascular events in diabetics with prior coronary heart disease (comparable to those without diabetes) and improve endothelial function[21-25].

Many clinical trials of statin therapy demonstrate an improvement in cardiovascular end-points and coronary stenosis that is inadequately explained by the baseline or treated low-density lipoprotein (LDL) cholesterol level[26]. The beneficial effect of statins on clinical events may involve nonlipid mechanisms (lipid-independent)[30] that modify endothelial function (e.g. increase nitric oxide synthase - eNOS[27], reduce LDL oxidation[28] or reduce platelet aggregation[29]).

The authors aimed to determine whether atorvastatin, a strong, lipid-lowering medication, would benefit endothelial function in diabetics not having high cholesterol.

Material and Method

Study patients

This is an out-patient-based trial being performed in Queen Sirikit Heart Centre, Khon Kaen University. The authors recruited type II DM, as per WHO criteria, without history of prior cardiovascular events, ranging between 35 and 60 years of age. Patients with any of the following were excluded from the study, those having: 1) history of prior cardiovascular events (e.g. stroke, limb ischemia, angina or history of coronary re-vascularization); 2) medications that affect the measurement of endothelial function (e.g. ACE inhibitors, aspirin, b-blockers, lipid-lowering drugs) the week before doing these measurements; or liver or renal failure. The local Research Ethics Committee approved the study, and all of the subjects gave written, informed consent before enrollment.

Study design

The present study was a randomized, double-blind, placebo, controlled trial with a parallel group design, in a single center between June 2003 and February 2004. The patients were randomly assigned according to a computer generated list, concealed from both the patients and their doctor(s).

An independent nurse filled and numbered the medication trays. The doctor received the trays from the study coordinator, to be used in the numbered order. Patients received either 20 mg of atorvastatin or the placebo once a day (at bed-time), for 30 weeks. The matching placebo tablets were supplied by Pfizer International (Thailand) Corporation.

Study protocol

Subjects underwent a fasting blood test in the morning for measurement of their baseline lipid profile, blood glucose, liver transaminases, creatine kinase and hemoglobin A1c. All measurements were repeated every 8 weeks. Height, weight, waist and hip circumferences were measured at baseline. The assessment of endothelial functions were measured at baseline and at 30 weeks after treatment.

Non-invasive assessment of endothelial function

The examinations were performed early in the morning when patients were in a fasting state. No tobacco consumption (smoking or chewing) was allowed. They rested in a supine position for a minimum of 10 minutes before the study.

High resolution ultrasound examination of the brachial artery was performed with a 7.5 MHz transducer connected to a VIVID3 echocardiographic machine, General Electric (Thailand) Company. Increased forearm blood-flow was induced by inflating a blood pressure tourniquet around the widest part of the forearm to 200 mmHg for 5 min. Repeat brachial artery diameter and blood flow scans were obtained immediately and 1 min after deflation of the tourniquet. Resting brachial artery diameter and blood flow were repeated 15 min later. Sublingual nitroglycerine (400 g) was given, and a final scan was performed after 3 min.

Flow-mediated vasodilation (FMD) was calculated as the ratio of brachial artery flow after reactive hyperemia to the baseline diameter, expressed as a percentage of change. Nitroglycerine-mediated vasodilation (NTGMD) was calculated by an analogous method.

Statistical analysis

The primary end-point, the effect of treatment on the change of FMD and NTGMD, was assessed by an analysis of co-variance (ANCOVA) adjusted for the baseline measurements. The sample size was determined in order to demonstrate an absolute 3% change in the FMD (assuming a standard deviation of 2.5%) in the atorvastatin vs the placebo group (a = 0.05 and b = 0.20; two-tailed test). A p value of < 0.05 was considered statistically significant.

Results

Patient characteristics and safety profile

According to the baseline characteristics of the 42 type II diabetics, the placebo had more women than the atorvastatin group. The atorvastatin group took more metformin and thiazolidinedione than placebos (Table 1). Medication compliance was over 95% in both groups. Two of the patients assigned to the placebo group withdrew before the end of the study for personal reasons. No adverse events or biochemical side-effects occurred.

Effects on FMD and NTGMD

At baseline, the end-diastolic brachial artery diameter, the FMD and the NTGMD, between the atorvastatin and placebo groups were similar (Table 2 and Fig. 1). After the treatment, the difference in FMD between the two groups was not clinically meaningful (difference = -2.12, 95%CI: -7.92 to 3.67, p = 0.463). Notwithstanding, evidence is insufficient to determine any difference between the FMD and NTGMD, as the 95% confidence intervals of the differences were wide. Compared with the placebo group, the atorvastatin treatment significantly reduced triglycerides, both the total and LDL cholesterol levels, whereas there was no significant change in the HDL cholesterol level in either group (Table 3).

Discussion

Among diabetics with no prior coronary disease with average cholesterol, the authors found no evidence of improved flow-mediation or NTG-induced vasodilatation by atorvastatin; even after adjusting for known factors (though not for dyslipidemia) that negatively affect vascular responses (i.e. smoking, hypertension, ACE inhibitor, aspirin, and other lipid lowering treatments). The present study had a few more male patients on diabetic medication in the atorvastatin group, but after the authors analyzed the data with an ANCOVA, adjusted for analogous data at baseline and gender, the trend persisted. Shechter et al[31] also reported that there was no correlation among the percent change of FMD, gender and/or use of diabetic medication.

According to the Current National Cholesterol Education Program (NCEP), the Adult Treatment Panel III Guidelines for desirable low-density lipoprotein cholesterol in patients with diabetes is $\leq$ 100 mg/dl. Many studies have demonstrated the amelioration of endothelial dysfunction by aggressive lipid lowering medications in non-diabetics.

Shechter et al[31], for example, demonstrated that various lipid-lowering regimens for patients with coronary disease, significantly caused a greater FMD after treatment (LDL cholesterol $\leq$ 100 mg/dl vs LDL $>$ 100 mg/dl).

Table 1. Clinical characteristics of the patients

Characteristic	Atorvastatin (n = 22)	Placebo (n = 20)
Age (year)	54±8.2	57±8.9
Males, n (%)	11 (50)	7 (35)
Current smoker, n (%)	4 (18)	4 (20)
Hypertension, n (%)	2 (9)	3 (15)
Postmenopausal/Female, n (%)	9/11 (0.82)	10/13(0.77)
BMI (kg/m^2)	26.4±4.2	27.2±6.6
Waist-to-hip ratio	0.91±0.07	0.89±0.05
Blood pressure (mmHg)	126±15/72±8	129±20/75±9
Fasting glucose (mg/dl)	124±34	126±36
HbA1c (%)	8.5±1.3	7.9±1.5
Treatment of diabetes		
Diet control only, n	1	0
Medication in use, n		
Glibenclamide	21	17
Metformin	16	8
Thiazolidinedione	8	3
Insulin	1	2
Other medications, n		
ACE inhibitors	2	3
Aspirin	0	0
Lipid lowering therapy	0	0
β-blockers	1	1
Diuretics	1	1

Data are presented as the mean ± SD or number (%) of patients
ACE = angiotensin-converting enzyme; HbA1c = hemoglobin A1c; BMI = body mass index

Table 2. Endothelium-dependent, flow-mediated dilatation and endothelial-independent dilatation to sublingual nitroglycerine of brachial artery after 30 weeks of atorvastatin therapy in type II diabetes

Characteristic	Placebo (n = 20)	Atorvastatin (n = 22)	Difference between treatment groups (atorvastatin - placebo)		p-value
			Unadjusted	Adjusted for baseline (95%CI)*	
Diameter (mm), Mean ± SE					
Baseline	4.56±0.13	4.26±0.17			
30 weeks	3.97±0.15	4.05±0.13	0.08	0.16 (-0.19 to 0.52)	0.353
FMD (%), Mean ± SE					
Baseline	5.75±1.93	4.11±1.05			
30 weeks	6.45±1.41	3.01±1.27	-3.44	-2.12 (-7.92 to 3.67)	0.463
NTGMD (%), Mean ± SE					
Baseline	9.60±2.00	9.04±1.88			
30weeks	10.15±1.78	10.43±1.54	0.28	0.37 (-4.34 to 5.07)	0.875

* Results from analysis of covariance (ANCOVA) adjusted for analogous data at baseline
Mean ± SE = Mean ± standard deviation of mean or standard error
CI = confidence interval

Table 3. Serum lipids at baseline and after 30 weeks of treatment with placebo or atorvastatin

Variable	Placebo (n = 20)	Atorvastatin (n = 22)	Difference between treatment group* (atorvastatin-placebo)	p value
Total cholesterol (mg/dl)				
At baseline	187±21	187±25		
At 30 weeks	190±25	143±27	-47 (-62.44 to –32.58)	<0.001
LDL cholesterol (mg/dl)				
At baseline	122±42	116±29		
At 30 weeks	128±54	71±20	-53 (-73.01 to –32.75)	<0.001
HDL cholesterol (mg/dl)				
At baseline	49±11	49±8		
At 30 weeks	51±13	49±11	-2 (-8.40 to 4.36)	0.526
Triglycerides (mg/dl)				
At baseline	149±65	154±78		
At 30 weeks	167±76	113±62	-56 (-91.59 to –20.91)	0.003

* Result from analysis of covariance (ANCOVA) adjusted for analogous data at baseline
Data are presented as mean ± SD

Wassmann et al[32] reported improved hyperemic forearm blood flow and decreased serum markers of oxidative stress and inflammation with 80 mg of atorvastatin in 18 non-diabetics (having a pre-treatment LDL level of 112 ± 4 mg/dl) in contrast to many trials on diabetics.

Even though the authors had a lower level of pre-treatment LDL, our findings agree with results from Sheu et al[33], who demonstrated that endothelial dysfunction was not reversed after 24 weeks of 10 mg simvastatin in 21 diabetics with hypercholesterolemia.

Similarly, van Venrooij et al[34] observed that aggressive lipid lowering by atorvastatin in 133 type II diabetics with dyslipidemia, without any history of cardiovascular disease, did not reverse endothelial dysfunction, despite a marked improvement in the lipid profile. By contrast, Tan et al[35] demonstrated the beneficial effect of 20 mg of atorvastatin on endothelial function in type II diabetes with hypercholesterolemia but this benefit has borderline clinical significance as it showed the improvement of FMD had increased from 5.3 ± 2.6 at baseline to 6.5 ± 2.8 after 6 months of the atorvastatin treatment. The authors also demonstrated the lack of any improvement in the NTGMD (endothelial-independent vasodilatation) in diabetics, which was associated with both the availability of and responses to nitric oxide (NO), which represents permanent structural and morphologic changes of blood vessels in diabetics.

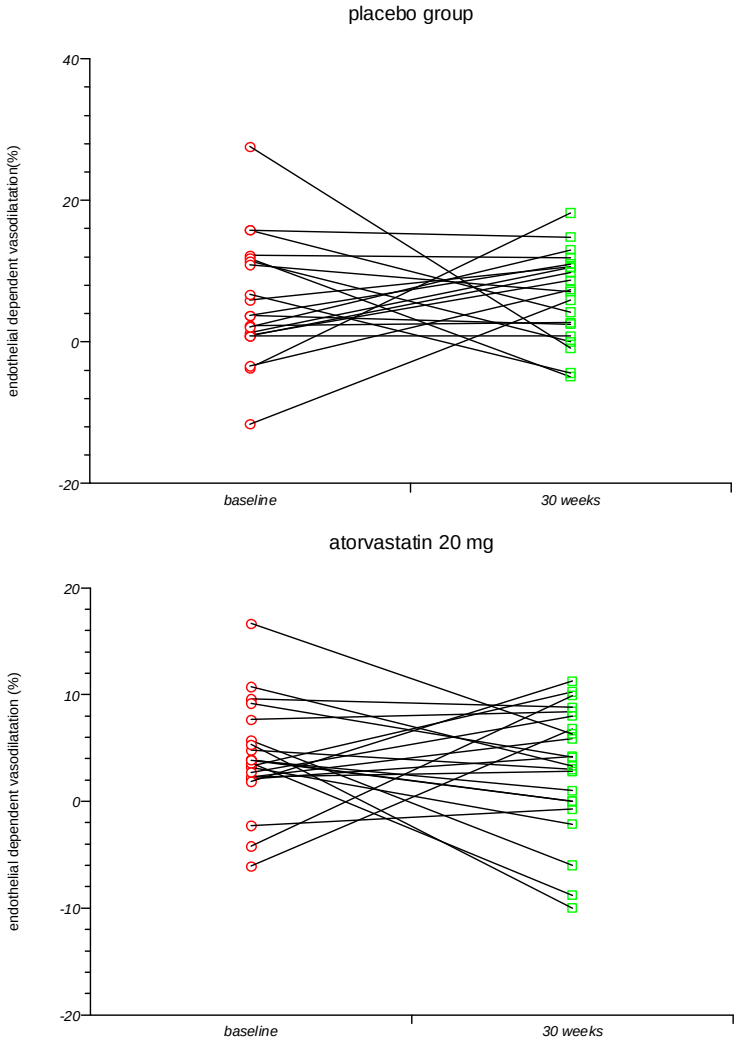

Fig. 1 Endothelial-dependent vasodilatation at baseline and after 30 weeks of atorvastatin treatment

According to these parameters, the present results support the findings of these studies vis- -vis the irreversibility of endothelial dysfunction in well-established diabetes; in persons having average cholesterol as opposed to non-diabetics or insulin resistant patients.

Study limitations

The limitations to the present study included:

1) In addition to dyslipidemia, hyperglycemia might cause increased formation of endothelial oxygen radicals[36] and eNOS dysfunction[37]. In the present study, during follow-up about one-third of the subjects in both groups had a fasting blood sugar over 126 mg/dl. Therefore, it is likely that hyperglycemia contributes to impaired vaso-reactivity and blunts any potential beneficial effects of lipid lowering on vascular responses.

2) The present study did not aim to determine the effects of the drug on vascular inflammation at the cellular level by serum inflammatory marker measurement; therefore, the authors cannot comment on the anti-inflammatory effects of atorvastatin.

3) Thirty weeks of follow-up may not sufficiently demonstrate endothelial function effects. Tan et al[35], however, demonstrated this improvement in diabetics having dyslipidemia after 6 months of atorvastatin treatment.

The questions requiring further study include: 1) Does the inclusion of early-stage diabetics (i.e. patients having an impaired glucose tolerance test), as in the present trial, truly indicate the reversi-

bility of endothelial dysfunction? and, 2) Should a higher dosage of atorvastatin be evaluated?

Conclusion

Treatment with atorvastatin did not appear to improve endothelial function in type II diabetics having an average cholesterol level without any history of cardiovascular disease despite a marked improvement of the lipid profile after treatment.

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ผลของยาลดไขมันอโตวาสะแตตินในการฟื้นฟูการทำงานของเซลล์เยื่อบุผนังด้านในหลอดเลือดในผู้ป่วยเบาหวานชนิดไม่พึ่งอินซูลินและมีระดับไขมันในเลือดอยู่ในเกณฑ์เฉลี่ยทั่วไปของประชากร

วิโรจน์ ตันติโกสุม, บัณฑิต ถิ่นคำรพ, จิราภรณ์ ศรีนัครินทร์, สิวนิต โอจงเพียร, นฤมล เจริญศิริพรกุล, ทรงศักดิ์ เกียรติชูสกุล

ยากลุ่มสะแตตินมีประโยชน์โดยตรงต่อเซลล์เยื่อบุผนังด้านในหลอดเลือดคือการฟื้นฟูการทำงานของเซลล์เยื่อบุผนังด้านในหลอดเลือด โดยผ่านกลไกที่นอกเหนือจากการช่วยลดระดับไขมันในเลือด

เป้าหมายหลักของงานวิจัยนี้เป็นการศึกษาผลของยา อโตวาสะแตติน 20 มก. ในผู้ป่วยเบาหวาน ชนิดไม่พึ่งอินซูลินที่มีระดับไขมันอยู่ในเกณฑ์เฉลี่ยทั่วไปของประชากร ต่อการทำงานของเซลล์เยื่อบุผนังด้านในหลอดเลือด การศึกษานี้ได้คัดผู้ป่วยเบาหวานชนิดไม่พึ่งอินซูลิน ที่ไม่มีประวัติของโรคหัวใจ และหลอดเลือดมาก่อน และมีระดับไขมันโฆเลสเตอรอลชนิดรวม ≤ 200 มก./ดล. และชนิด แอล ดี แอล ≤ 140 มก./ดล. มีผู้ป่วยได้รับ ยาหลอก จำนวน 20 คน และได้ยาอโตวาสะแตติน ขนาด 20 มก. จำนวน 22คน เป็นเวลา 30 สัปดาห์ โดยทุกคนจะได้รับการตรวจ การตอบสนองของหลอดเลือดแขน ก่อนได้รับยา และหลังจากครบระยะเวลาที่กำหนด พบว่าการตอบสนองหลอดเลือดแขนชนิดที่พึ่งการทำงานของเซลล์เยื่อบุผนังด้านในหลอดเลือด (FMD) ไม่ได้เปลี่ยนแปลงจากครั้งก่อนได้ยา ทั้งในกลุ่มที่ได้รับยาอโตวาสะแตติน และยาหลอก (4.11 ± 1.05%เปลี่ยนเป็น 3.01 ± 1.27% และ 5.75 ± 1.93% เปลี่ยนเป็น 6.45 ± 1.41%, ค่า p = 0.463 จากการวิเคราะห์ความแปรปรวนร่วม ANCOVA, ตามลำดับ) เช่นเดียวกับการตอบสนองชนิดที่ไม่พึ่งการทำงานของเซลล์เยื่อบุผนังด้านในหลอดเลือด (NTGMD) ในขณะที่ไขมัน โฆเลสเตอรอลชนิดรวม และชนิด แอล ดี แอล ลดลงอย่างมีนัยสำคัญ

สรุปว่าข้อมูลจากการศึกษานี้ยังไม่สนับสนุนผลดีของยาอโตวาสะแตตินต่อการทำงานของเซลล์เยื่อบุผนังด้านในหลอดเลือด ในผู้ป่วยเบาหวานชนิดไม่พึ่งอินซูลินที่ไม่มีประวัติของโรคหัวใจ และหลอดเลือดมาก่อน และมีระดับไขมันอยู่ในเกณฑ์เฉลี่ยทั่วไปของประชากร