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Effect of Ezetimibe and Simvastatin Therapy in Subjects with Hyperlipidemia on Ankle Brachial Index, High Sensitive C Reactive Protein and Carotid Intima Media Thickness

ABSTRACT

Objectives: Atherosclerosis is the leading cause of mortality and morbidity. Statins alleviate the atherosclerotic process, as these drugs have been shown to decrease serum levels of C-reactive protein. Ezetimibe is another hypolipidemic drug. The ankle-brachial index (ABI) is a non-invasive method of diagnosing peripheral arterial disease, and carotid intima-media thickness (CIMT) is a measure of subclinical atherosclerosis. We sought to evaluate the effect of ezetimibe, simvastatin, and their combination on lipid parameters, ABI, and CIMT.

Methods: Sixty patients without a history of atherosclerotic vascular disease were included in this study. Patients were divided into three groups: the first group received 10 mg/day ezetimibe, the second group received 20 mg/day simvastatin, and the third group received a combination of 20 mg/day simvastatin and 10 mg/day ezetimibe. Baseline cholesterol levels, creatine kinase, alanine aminotransferase, aspartate aminotransferase, hsCRP levels, ABI, and CIMT were measured. Blood tests were repeated at the 6th week, and all baseline measurements were performed at the end of the 3rd month.

Results: All groups exhibited a significant decrease in total and LDL cholesterol levels at the end of the 6th week. There was a significant decrease in hsCRP levels in the simvastatin-only and simvastatin-ezetimibe combination groups. The ABI increased significantly in the ezetimibe-simvastatin combination group but not in the others. No change in CIMT was noted in any group.

Conclusion: The cholesterol profile improved in all groups. The hsCRP levels decreased significantly in the simvastatin and combination groups but not in the ezetimibe-only group, possibly due to ezetimibe lacking pleiotropic effects. The ABI values improved in the combination group, likely due to ezetimibe potentiating the positive effects of simvastatin on the endothelium. There was no change in CIMT in any group, probably due to the short follow-up period and small sample size.

Keywords: Ankle brachial index, C reactive protein, carotid intima media thickness, ezetimibe, simvastatin

Atherosclerosis, the leading cause of mortality in the Western world, is characterized by lipid deposition, inflammation, cell death, and thrombosis in the arterial wall. Atherosclerosis is the primary cause of myocardial infarction, stroke, aortic disease, and lower extremity vascular problems. Smoking, dyslipidemia, hypertension, age, and diabetes mellitus are the most easily recognized risk factors for atherosclerosis (1-7). Dyslipidemia is one of the most important risk factors for atherosclerosis. Since the 1950s, the relationship between serum cholesterol levels and coronary heart disease has been studied and documented (8); however, it was not until the 1990s that we uncovered that alleviating or even reversing the atherosclerotic process was possible through cholesterol lowering. The discovery and launch of hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, or statins, marked a milestone in our approach to atherosclerosis and its treatment. Large-scale randomized studies have consistently shown that these drugs decrease mortality and morbidity due to atherosclerotic events (9-13).

Studies, however, have revealed that the relationship between the favorable effects of these drugs and serum cholesterol levels is not strong (14). This led to the concept of the pleiotropic effects of statins, including anti-proliferative, anti-inflammatory, antioxidant, and plaque-stabilizing effects that are independent of cholesterol-lowering. Inflammation

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plays a key role in every step of atherosclerosis. Increased serum levels of inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) correlate with the presence and complicated clinical course of atherosclerosis (15-17). The mortality- and morbidity-reducing effect of statins can be partially explained by their anti-inflammatory properties (18).

Carotid intima-media thickness (CIMT) is a relatively simple test that reflects total atherosclerotic burden and correlates with the presence of other risk factors (19). This measurement evaluates the thickness of the intima and media layers of the common carotid artery using ultrasound, and it has been shown to correlate directly with coronary artery disease and stroke risk. Statin use has been found to decrease CIMT (20-23).

Peripheral artery disease is a clinical condition characterized by the development of atherosclerotic plaques in the arteries of the upper or lower extremities, which can block blood flow. The clinical spectrum ranges from intermittent claudication to extremity loss. The ankle-brachial index (ABI) is an inexpensive and simple method to diagnose peripheral arterial disease, relying on the simultaneous measurement of blood pressure in both upper and lower extremities. If the ratio of systolic pressure in the lower extremity to systolic pressure in the upper extremity is below 0.9, lower extremity peripheral arterial disease is suspected, and further testing is recommended. The effect of statins on ABI has been demonstrated in different patient groups, but the net effect of statins on ABI remains unclear (24,25).

Ezetimibe is a cholesterol-lowering medication that chelates cholesterol and blocks its absorption in the small intestine. When used alone, ezetimibe lowers low-density lipoprotein (LDL) cholesterol levels by 17% (26,27). When added to statin therapy, its effect is additive (27-29).

This study aims to investigate the effects of ezetimibe, simvastatin, and their combination on hsCRP levels, lipid levels, CIMT, and ABI in dyslipidemic patients without atherosclerotic vascular disease.

METHODS

Patients at the outpatient clinics of Başkent University Cardiology Department who were examined between November 2006 and May 2007 and met the criteria for lipid-lowering therapy, as specified by the Adult Treatment Panel III (ATP III), with no known history of atherosclerotic disease, were included in the study. According to ATP III criteria, an LDL cholesterol level of 160 mg/dL or above was required for the initiation of cholesterol-lowering therapy in the presence of one traditional risk factor for atherosclerotic disease, and 130 mg/dL or above in the presence of two or more risk factors. Informed consent was obtained from eligible patients willing to participate in the study. Ethics committee approval was received from the local Ethics Committee of Başkent University on August 2, 2006, with report number 06/149.

Inclusion Criteria

1. No known atherosclerotic disease (coronary artery disease, carotid atherosclerosis, history of stroke, peripheral arterial disease)
2. In the absence of or presence of only one traditional risk factor for atherosclerotic disease, an LDL cholesterol level of 160 mg/dL or above; in the presence of two or more risk factors for atherosclerotic disease, an LDL cholesterol level of 130 mg/dL or above
3. No history of statin or ezetimibe use in the last 2 months
4. Voluntary participation in the study

Exclusion Criteria

1. History of atherosclerotic disease
2. History of diabetes mellitus
3. History of chronic kidney failure
4. Chronic parenchymal liver disease of any etiology
5. Autoimmune or familial muscle disease
6. Presence or history of intermittent claudication
7. History of allergy or serious side effects related to ezetimibe or statins
8. Not consenting to participate in the study

Laboratory Tests

Following 8 hours of fasting, 5 milliliters of venous blood was drawn, and the following tests were conducted:

1. Total cholesterol
2. LDL cholesterol
3. HDL cholesterol
4. Triglycerides
5. Alanine aminotransferase (ALT)
6. Aspartate aminotransferase (AST)
7. High-sensitivity CRP (hsCRP)
8. Creatine kinase (CK)

Serum total cholesterol, HDL cholesterol, LDL, triglyceride, ALT, AST, and CK levels were measured using standard methods. LDL cholesterol levels were calculated using the Friedewald equation (LDL cholesterol = Total Cholesterol - HDL cholesterol - (triglyceride/5)). High-sensitivity C-reactive protein measurements were obtained using Sentinel kits (Sentinel CH, Via Principe Eugenio, Milan, Italy) on an Abbott Architect 8000 device (Abbott Laboratories, Abbott Park, IL, USA) via the immunonephelometric method. These measurements were repeated 6 weeks and 3 months after the baseline measurements for each patient. Target LDL cholesterol levels were below 160 mg/dL for patients with only dyslipidemia as a risk factor for atherosclerosis, while they were below 130 mg/dL for those with two or more risk factors.

Carotid Intima-Media Thickness (CIMT) Measurement

Following blood sample collection, patients underwent CIMT measurements in the ultrasound room. CIMT measurements were taken from the distal wall of the distal common carotid artery and expressed as the average of the right and left CIMT values. All measurements were performed by the same physician using the same ultrasound device (Sonoline Antares, Siemens, Erlangen, Germany) with a 7.5 MHz linear probe under standard device settings. Measurements were repeated at the third month of the study.

Ankle-Brachial Index (ABI) Measurement

After CIMT measurements, patients rested in a quiet room for 5 minutes. A properly sized cuff was placed on the right arm, and a 7.5 MHz linear probe was positioned at the right antecubital fossa. The cuff was inflated to a pressure above the systolic blood pressure and then deflated at a rate of 2 mmHg/sec. The systolic pressure was recorded at the point where the first sign of brachial artery flow was detected by the Doppler probe. Next, a proper-sized

Table 1. Basal characteristics of the study group

	Ezetimibe Group (n=21)	Simvastatin Group (n=20)	Combination Group (n=19)	p
Male sex (%)	9(42.9)	9(45)	6(31.6)	0.193
Age(years)	54.19±9.2	56.3±10.3	52.8±11.4	0.567
Hypertension (%)	12(57.1)	12(60)	11(57.9)	0.982
Smoking (%)	8(38.1)	6(30)	6(31.6)	0.346
Total Cholesterol (mg/dl)	258.3±23.4	258.3±23.6	274.7±27.8	0.068
LDL cholesterol (mg/dl)	169.3 ±17.3	169.8±20.2	170.3±22.0	0.980
HDL cholesterol (mg/dl)	52.9±16.4	55.7±16.3	62.7±14.8	0.145
Triglyceride (mg/dl)	183.9±96.0	171.3±79.6	193.5±121.1	0.785
CK (mg/dl)	113.1±49.8	109.8+56.57	99.5±37.2	0.844
hsCRP (mg/L)	3.4±1.8	3.61±3.20	3.11±2.20	0.826
AST (U/L)	23.4±9.8	19.4±5.5	23.4±12.5	0.334
ALT (U/L)	32.9±19.9	24.1±13.2	32.9±19.6	0.589
Body Mass Index (kg/m^2)	30.24±4.5	27.59±3.4	28.86±4.9	0.157
ABI	0.99±0.075	1.00±0.083	0.99±0.072 0.908	0.908
CIMT	0.68±0.21	0.66±0.23	0.61±0.17	0.422

LDL: Low density lipoprotein; HDL: High density lipoprotein; hsCRP: High sensitive C reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ABI: Ankle brachial index; CIMT: Carotid intima media thickness.

cuff (2/3 the width of the tibial length) was placed 2 centimeters above the ankle, and systolic pressure was measured in the same manner from the dorsalis pedis and posterior tibial arteries. These measurements were then taken from the left lower extremity and subsequently from the left upper extremity. All measurements were repeated in reverse order, and the average was calculated for each extremity. Measurements were performed by the same physician using the same device (Sonoline Antares, Siemens, Erlangen, Germany) with a 7.5 MHz linear probe under standard device settings. The ABI was calculated as the ratio of the lowest lower extremity systolic pressure to the highest upper extremity systolic pressure. This study was conducted for each patient at the beginning of the study and again 3 months later.

Study Groups

Following baseline blood tests, CIMT, and ABI measurements, patients were randomized into three groups in a 1:1:1 ratio. The first group received 10 mg/day ezetimibe (Ezetimibe group), the second group received 20 mg/day simvastatin (Simvastatin group), and the third group received a combination of 10 mg/day ezetimibe and 20 mg/day simvastatin (Combination group). All patients were re-evaluated for any possible drug side effects six weeks later. A CK level 10 times the upper limit of normal (ULN), an AST or ALT level 3 times the ULN, and symptomatic muscle ache were considered serious side effects, and statin therapy was withdrawn in such cases. All patients enrolled in the study were also advised to follow a diet that restricted lipid intake to 7% of total caloric intake and cholesterol intake to 200 mg/day.

Statistical Analysis

Statistical analysis was performed using SPSS 13 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequency and percentage. Group comparisons were carried out using the Chi-square test for categorical variables and the independent samples t-test for continuous variables. Analysis of changes within each group over time was conducted using a univariate general linear model, while Bonferroni analysis was used for post-hoc testing. Post-hoc analysis of simultaneous values was performed using one-way ANOVA with Bonferroni correction. The independent samples t-test was used for comparing simultaneous variables across paired groups. Regression analysis was performed to identify factors affecting changes in hsCRP levels. Statistical significance was defined as a p-value of less than 0.05 in all analyses.

RESULTS

A total of sixty patients were enrolled in the study. The mean age of the study group was 54.48±10.26 years. Thirty-six (60%) of the patients were female, while 24 (40%) were male. Twenty-one patients were randomized to the Ezetimibe group, 20 patients to the Simvastatin group, and 19 patients to the Combination group. All patients completed the follow-up period.

The baseline characteristics of the groups were similar, with no significant differences between them (Table 1). All patients completed the study period within their original group and treatment regimen.

Table 2. Change of total cholesterol. LDL cholesterol. HDL cholesterol. triglyceride. hsCRP levels during study according to groups

	Ezetimibe Group			p		
	Basal	**6 weeks**	**3 months**	**Basal- 6 weeks**	**Basal- 3 months**	**6 weeks- 3 months**
T. Chol	258.3±23.4	222.8±33.2	223.7±26.4	<0.001	<0.001	0.878
LDL	169.3±17.3	135.7 ±23.0	140.8±20.6	<0.001	<0.001	0.254
HDL	52.9±16.4	52.5 ±17.0	52.24±19.5	0.780	0.749	0.807
Triglyceride	183.9±96.0	180.9±95.2	166.6+93.4	0.862	0.466	0.445
hsCRP	3.40±1.89	3.10±1.81	3.07±1.62	0.324	0.056	0.195
	Simvastatin Group			**p**		
	Basal	**6 weeks**	**3 months**	**Basal- 6 weeks**	**Basal- 3 months**	**6 weeks- 3 months**
T. Chol	258.3±23.6	171.3+31.7	184.6 42.7	<0.001	<0.001	0.059
LDL	169.8±20.2	91.4±22.4	100.1±35.3	<0.001	<0.001	0.163
HDL	55.7±16.3	56.8±15.5	54.3213.8	0.406	0.488	0.201
Triglyceride	171.3±79.6	144.4±67.5.	143.2±58.4	0.047	0.008	0.899
hsCRP	3.61±3.20	2.48±2.12.	2.25±1.58	0.01	0.004	0.393
	Combination Group			**p**		
	Basal	**6 weeks**	**3 months**	**Basal- 6 weeks**	**Basal- 3 months**	**6 weeks- 3 months**
T. Chol	274.7±27.8	175.2±38.3	172.7±26.9	<0.001	<0.001	0.690
LDL	170.3±22.0	90.3±32.7	86.8±24.6	<0.001	<0.001	0.522
HDL	62.7±14.8	61.2±11.2	60.2±10.8	0.412	0.277	0.373
Triglyceride	193.5±121.1	123.8±64.4	144.3±72.7	<0.001	0.014	0.068
hsCRP	3.11±2.20	1.93±1.45	1.78±1.43	<0.001	<0.001	0.346

T. Chol: Total Cholesterol; LDL: Low density lipoprotein cholesterol; HDL: High density lipoprotein cholesterol; hsCRP: High sensitive C Reaktive Protein.

Table 3. Change in ABI and CIMT during treatment according to groups

	Ezetimibe Group			Simvastatin Group			Combination Group		
	Basal	**3 Months**	**p**	**Basal**	**3 months**	**p**	**Basal**	**3 months**	**p**
ABI	0.99±0.07	0.99±0.06	0.849	1.00±0.08	1.01+0.06	0.596	0.99±0.07	1.02±0.07	0.026
CIMT	0.68±0.21	0.65+0.14	0.295	0.66±0.23	0.61±0.13	0.155	0.61±0.17	0.63±0.19	0.409

ABI: Ankle brachial index; CIMT: Carotid intima media thichness.

Changes in lipid parameters and hsCRP levels are summarized in Table 2. Statistically significant reductions in LDL cholesterol levels were recorded in each group at the end of 6 weeks. At the end of 3 months, no additional statistically significant decline in LDL cholesterol levels was observed in any group. No significant change in HDL cholesterol levels was noted in any group at the end of both 6 weeks and 3 months. Significant reductions in triglyceride levels were observed in the Simvastatin and Combination groups but not in the Ezetimibe group at the end of 6 weeks. Triglyceride levels at the end of 6 weeks and 3 months were statistically similar across all groups. High-sensitivity CRP (hsCRP) levels did not change in the Ezetimibe group at the end of 6 weeks or 3 months. Conversely, significant reductions in hsCRP levels were observed in the Simvastatin and Combination groups at the end of 6 weeks. No further decline in hsCRP levels was noted at 3 months, with the 6th week and 3rd-month average hsCRP levels remaining statistically similar. The reductions in hsCRP levels in the Simvastatin and Combination groups were 27.6% and 33.2%, respectively, with no statistically significant difference (p=0.673). In the single-variable analysis that included all groups, the only variable determining the reduction in hsCRP levels was the reduction in total cholesterol levels (p=0.022, R2: 8.9%).

At the end of the study period, only 5% of patients in the Ezetimibe group reached their target LDL levels, while 85% in the Simvastatin group and 94% in the Combination group reached their target LDL levels according to ATP III criteria. Differences between the Ezetimibe group and the other two groups were statistically significant, while the difference between the Simvastatin and Combination groups did not reach statistical significance.

Reductions in LDL cholesterol and total cholesterol levels were significantly greater in the Simvastatin and Combination groups than in the Ezetimibe group. Reductions in LDL cholesterol and total cholesterol levels were more prominent in the Combination group at the end of 3 months, with only the difference in total cholesterol levels reaching statistical significance (for LDL cholesterol, p=0.133; for total cholesterol, p=0.028).

Carotid intima-media thickness did not change significantly after treatment in any group. Ankle-brachial index (ABI) measurements did not change significantly in the Ezetimibe or Simvastatin groups but increased significantly in the Combination group at the end of 3 months (Table 3).

Table 4. Change in AST. ALT and CK during treatment according to groups

	Ezetimibe Group			Simvastatin Group			Combination Group		
	Basal	3 Months	p	Basal	3 months	p	Basal	3 months	p
AST (U/L)	23.4±9.8	**25.9±8.9**	23.9±7.2	19.4±5.5	**24.5±9.8**	**24.7±6.3**	23.4±12.5	26.3±12.0	**26.3±10.1**
ALT (U/L)	32.9±19.9	35.3±21.3	29.7±15.2	24.1±13.2	30.8±19.9	26.9±11.0	32.9±19.6	36.1±16.3	28.6±15.2
CK (mg/dl)	113.1±49.8	136.7±63.1	108.9±30.5	109.8±56.5	102.7±67.4	102.3±57.5	99.5±37.2	104.6±40.9	96.1±26.5

AST: Aspartat aminotransferase; ALT: Alanin aminotransferase; CK: Creatin kinase.

No significant side effects were observed in any group that required discontinuation of the study drug. Aspartate aminotransferase (AST) levels rose in the Ezetimibe group at 6 weeks, in the Simvastatin group at both the 6th week and 3rd month, and in the Combination group at the third month. These changes were statistically significant but did not lead to discontinuation of the drug in any patient (Table 4).

CONCLUSIONS

This study sought to investigate the effect of two different cholesterol-lowering medications and their combination on lipid parameters, CIMT, and ABI in the short term. As expected, total cholesterol and LDL cholesterol levels decreased in all treatment groups. The reductions in total cholesterol and LDL cholesterol were 13.9% and 20%, respectively, in the Ezetimibe group, consistent with previous studies reporting reductions of 15-19% in total cholesterol and 15-20% in LDL cholesterol (30,31). A slight increase in LDL levels was observed at 3 months compared to levels at 6 weeks, which did not reach statistical significance and may be due to dietary inconsistencies or a compensatory increase in lipid production by the liver. High-density lipoprotein (HDL) levels did not change significantly throughout the study. Conflicting results exist regarding the effect of ezetimibe on HDL cholesterol (30,32). Some studies report a slight increase in HDL levels with ezetimibe therapy, thought to be due to a reduction in triglyceride-rich lipoproteins and cholesteryl ester transfer protein (29,32). Although previous studies observed a reduction in triglyceride levels similar to that in this study, the reduction here did not reach statistical significance. Regarding side effects, there was a slight increase in AST levels with ezetimibe at the end of 6 weeks, which reached statistical significance, though 3-month AST levels were similar to baseline. Previous studies did not report increases in liver enzymes or CK with ezetimibe (29,30,32), suggesting that the AST fluctuation may not be related to ezetimibe. A slight, insignificant decline in hsCRP levels was observed with ezetimibe, consistent with previous studies that report no reduction in hsCRP levels with ezetimibe (27,33,34).

As in the Ezetimibe group, total cholesterol and LDL levels declined in the Simvastatin group, with reductions of 28% and 40%, consistent with previous studies (35). HDL levels did not change significantly in this group, although previous studies report a 10-15% increase in HDL under statin therapy (35). This may be due to increased hepatic Apo A-1 production and prevention of HDL consumption following enhanced LDL receptor expression which depletes cholesteryl esters. This effect with statins is dose dependent and under high dose atorvastatin a reduction in HDL levels was reported (36). The reduction in triglyceride levels was 16%, consistent with previous studies (29,32). No patient in this group experienced significant side effects that necessitated drug withdrawal. Increases in liver enzymes that reached statistical significance were consistent with prior data. The reduction in hsCRP levels with simvastatin (40 mg/day) in this group was 37%. Statins are known to reduce hsCRP through anti-inflammatory effects independent of cholesterol lowering. Statistically significant decreases in hsCRP of 22-30% have been reported with simvastatin (37), with reductions up to 47% with high-dose statin therapy (38). The major factors influencing hsCRP reduction are high-dose statin use, combination with ezetimibe, and a reduction in LDL levels greater than 45%. While our Simvastatin group lacked these factors, baseline hsCRP levels were higher than in other studies (39,40).

Reduction in lipid parameters were far above other groups in the combination group reaching %37 and %49 in total cholesterol and LDL levels respectively at the end of 3 months which is consistent with previous data (29,41-43). High density lipoprotein cholesterol levels did not change significantly under combination therapy. Previous studies report %8-9 increase in HDL levels under statin ezetimibe combination. Increase in HDL levels achieved under statin ezetimibe combination is reported to be significantly higher than that achieved with a statin alone (29,31). In this study, no increase was observed under statin alone or statin ezetimibe combination. Achieved trigliyceride reductions with ezetimibe simvastatin combination is similar to previous data (29,43). Side effects of the combination was favourable and no patient had to discontinue the drugs due to side effects. High sensitive C reactive protein levels declined by %42 in the combination group at the end of 3 months. This reduction is slightly less than that was achieved by simvastatin alone but the difference between two groups is insignificant. Previous data about hsCRP is unclear. Some studies report a higher decline in hsCRP levels under combination therapy (44) while some report no difference in the reduction achieved under statin alone and combination therapy (43). The hsCRP reduction in the combination group is similar to the previous studies but the reduction achieved in simvastatin group is extremely high. Previous data and our current study does not explain the cause of this discrepancy.

The ABI values did not differ significantly with ezetimibe or simvastatin but there was a significant increase in the combination group at the end of 3 months. Ankle brachial index is a non-invasive, simple method of diagnosing lower extremity vascular disease and a reliable indicator of subclinical atherosclerosis. There are contradictory result about the effect of statins on ABI. Some studies report no improvement with statins while some report increase in ABI (45,46). Most studies performed on coronary arteries postulate a mechanism where statins increase nitric oxide in the short term and improve endothelial dependent vasodilatation (47-49). Short term statin therapy has been demonstrated to increase

myocardial perfusion (50). This kind of improvement may be true for the peripheral circulation too. In patients with peripheral arterial disease, improvements in walking performance exceeds the improvements in resting ABI values which makes one think that the clinical improvement is due to improvement in microcirculation rather than regression of atherosclerotic plaques. The patients included to this study have no known atherosclerotic disease. If we accept they don't have flow limiting plaques which is supported by normal basal ABI values, the main benefit expected from statin is an improvement in endothelial functions. Simvastatin alone did not improve ABI values but ABI values improved under combination therapy. Benefit of simvastatin may not be evident due to small sample size in this study. Ezetimibe may have augmented the positive effect of simvastation. Combining ezetimibe with a statin leads to a more prominent reduction in CRP levels (33,44) but the effect of combination on arterial stiffness has not been demonstrated (43,51). Patients with a normal basal ABI value have been included to this study. It is not clear whether an increase in an already "normal" ABI has any value. If so, this study may demonstrate an augmentation of pleiotropic effects of statins when combined with ezetimibe.

No improvement in CIMT values has been observed with treatment in any group. Many studies report reductions or attenuation of progression of CIMT with statin therapy (23,52). Follow up periods of these studies range from 6 months to 3 years. Atorvastatin has been demonstrated to attenuate CIMT in comparison to placebo (53). In another study, high dose atorvastatin (80mg/day) was compared with 40 mg/day simvastatin where reduction in CIMT was significantly more atorvastatin group (52). Finally another study reported better reduction in CIMT with atorvastatin in comparison with pravastatin at the end of 1 year (54). Considering all these study data we can conclude that aggressive statin therapy can result in improvements in CIMT. In this study, reductions in LDL cholesterol levels have been achieved in simvastatin and combination groups but no improvement in CIMT values has been observed. This may be due to small sample size and short follow up period when compared with other studies.

Study Limitations:

1. Small sample size of the study is a major limitation that may have restricted the analysis of adding ezetimibe to simvastatin.
2. Follow up period is short (3 months). This may have limited the ability of the study to detect some changes that may show up later in time.
3. Increase in ABI values has been interpreted to be due to improvement in circulation and endothelial functions. The study group is composed of persons with no known atherosclerotic disease and normal basal ABI values. The significance of increase in an already normal ABI is not known.
4. Dietary counselling has been made to all patients at the beginning of the study but their compliance with diet solely rests on their statement. This may be a factor that could not be controlled.

Ethics Committee Approval: This study was conducted with the permission of the Başkent University Local Ethics Committee (decision no: 06/149, date: 02.08.2006).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author has no conflict of interest to declare.

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