A Preliminary Report on the Sensitivity of Plasma Lipoproteins to Low-dose Simvastatin in Nine Turkish Men

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DÜŞÜK DOZ SİMVASTATİNE 9 TÜRK ERKEĞİNDE PLAZMA LİPOPROTEİNLERİNİN DUYARLIĞINA İLİŞKİN ÖNBİLDİRİ

ÖZET

Düşük dansiteli lipoprotein kolesterolün (LDL-K) yüksek (>160 mg/dl) ve yüksek dansiteli lipoprotein kolesterolün (HDL-K) alçak plazma düzeyleri (<35 mg/dl) erken yaşta koroner kalp hastalığı riskini yükseltir. Türk halkı, belki genetik köken sonucu, mutad olmayan ölçüde düşük HDL-K düzeylerine sahip görünmektedir. Üstelik, kenstsel alanlarda yaşayan refahlı Türk erkeklerinin birçoğunun kolesterol ile LDL-K düzeyleri yüksek olup 5'i aşan tahripkar total kolesterol/HDL-K oranını barındırmaktadır. Eldeki pilot çalışma düşük doz simvastatin'in bu oranı düzeltip düzeltemeyeceği amaciyle yapıldı.

HDL-K >35 mg/dl ve total kolesterol/HDL-K >5.5 olan 9 Türk erkeği 8 hafta süreyle günde 10 mg simvastatin ile tedavi edildi. LDL-K düzeyleri, tipik olarak ilacın daha yüksek dozlarında rastlanan dramatik biçimde, yani %42 oranında düşürüldü. Ayrıca, HDL-K düzeyleri, beklenenin ötesinde ve statin tedavisinin herhangi bir dozu için atipik sayılacak şekilde %23 oranında arttı. Bu çok arzu edilen etkiler total kolesterol/HDL-K oranını %43 mertebesinde, yani başlangıçtaki 7.5'ten, 8 haftalık ilaç tedavisi sonunda 4.3'e indirdi. Bu sonuçlar Türklerde alçak doz simvastatin'in özellikle etkin olduğunu düşündürmektedir.

Anahtar kelimeler: *Plazma lipoproteinleri, simvastatin, total kolesterol/HDL-K oranı*

Though the Turkish Risk Factor Study of the Turkish Society of Cardiology [1] has demonstrated that the Turkish population generally has low levels of total plasma cholesterol compared to Europeans and Americans, nevertheless, one out of every ten adults has cholesterol values ≥229 mg/dL. In addition, the Turkish Heart Study [2] revealed that many affluent Turkish men and women living in urban areas have unacceptably high total cholesterol and and low density lipoprotein cholesterol (LDL-C) levels similar to those seen in populations at high risk of developing coronary heart disease (CHD). For example, ~20% of Turkish men living in Istanbul and 20% of men residing in the United States have total cholesterol levels in excess of 240 mg/dL [2,3]. However, as shown in the Turkish Heart Study, Turks may be at even greater CHD risk than is indicated by their total cholesterol level beccause their levels of high density lipoprotein cholesterol (HDL-C) are 10-15 mg/dL lower than those in other populations [2]. Approximately 53% of Turkish men and 26% of Turkish women have HDL-C levels less than 35 mg/dL, a value below which CHD risk rises sharply in other populations [2,4]. By comparison, only about 15% of men and 5% of women in the United States and Europe have HDL-C levels below 35 mg/dL [5]. In combination, elevated cholesterol and LDL-C levels and reduced HDL-C levels are likely to be very detrimental with respect to CHD risk [6,7].

The low HDL-C appears to represent a major population difference and may, in part, be genetic in origin. Turks surveyed in six different regions of Turkey with very different diets had similarly low HDL-C levels [2]. Likewise, Turks living in Germany [8] and the United States (T.P. Bersot and R.W. Mahley, unpublished observations) also have low HDL-C. Specifically, the Turks have low levels of lipoprotein AI (LpAI), a subfraction of HDL similar to HDL_2 (T.P. Bersot and R.W. Mahley, unpublished observations). The HDL_2 subclass is considered to be most protective against the development of CHD[9], whereas low levels of HDL_2 appear to be detrimental.

Studies in progress indicate that the Turks have significantly higher levels of hepatic lipase than United

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States age-and sex-matched controls (T.P. Bersot and R.W. Mahley, unpublished observations). Hepatic lipase is a triglyceride hydrolase and a phospholipase that converts HDL_2 to HDL_3 [10-12], and high levels would be expected to reduce both total HDL-C, as well as the HDL_2 subclass. Transgenic animals expressing high levels of hepatic lipase have markedly low HDL levels [13-15], and a deficiency of hepatic lipase in humans [16] and animal models [17,18] is associated with elevated HDL levels, especially HDL_2. The high levels of hepatic lipase in the Turkish population may be a major factor causing low HDL levels.

In other populations, the total cholesterol to HDL-C ratio (TC/HDL-C) predicts CHD risk irrespective of the etiology of the low HDL-C level. In fact, various studies suggest that a TC/HDL-C ratio >4.5 is associated with increased risk of cardiovascular disease [7]. Because of the prevalence of low HDL-C levels, many Turkish have TC/HDL-C ratios >5 and might profit from decreasing total cholesterol of increasing HDL-C. However, it is possible that Turks, with their unique genetic background, might respond differently to hypolipidemic drug therapy compared to the response seen in other populations.

The statins are inhibitors of HMG-CoA reductase, a rate-limiting enzyme in cellular cholesterol synthesis. Treatment with statin decreases hepatic cholesterol content, which increases expression of the LDL receptor gene and leads to increased receptor synthesis, enhanced clearance of LDL, and reduced plasma LDL-C and cholesterol levels [19]. Simvastatin, one of the statins widely used in Turkey, is highly effective in reducing total cholesterol, LDL-C, and very low density lipoprotein cholesterol (VLDL-C) [20]. In addition, numerous studies in Europe and the United States have shown that simvastatin reduces triglycerides moderately and slightly increases HDL-C levels by about 10%. The Scandinavian Simvastatin Survival Study (4S) has established the safety and effectiveness of simvastatin at doses of 20-40 mg/day over the 5.4 years of study of this clinical trial [21]. In various studies at doses of 5, 10, 20, and 40 mg/day, simvastatin reduced LDL-C levels by 24%, 30%, 35%, and 40%, respectively [22-25]. The purpose of the present study was to determine the effectiveness of simvastatin in lowering LDL-C and total cholesterol levels in Turkish subjects and to observe the efects on HDL-C levels in an attempt to improve the TC/HDL-C ratio in this population characterized by low HDL-C levels.

Methods

Patients

Healthy adult Turkish men living in Istanbul. Turkey, who had plasma lipid determinations after a 12-h fast as part of an annual health survey returned to the Koç American Hospital for a second phlebotomy to confirm their eligibility based on the lipid eriteria described below. Subjects who had fasting triglycerides <300 mg/dL, HDL-C ≤35 mg/dL, and TC/HDL-C>5.5 were invited to participate in the study. Patients using hypolipidemic drugs, β-blockers, or thiazide diuretics were excluded. All subjects were screened by appropriate testing to exclude secondary causes of hyerlipidemia, such as diabetes mellitus and thyroid, renal, or liver disease. All subjects were requested to maintain their usual diet and life-style.

Upon accoptance into the trial the patients were given 4-week supplies of simvastatin, 10 mg (Zocor, MSD-Turkey) and instructed to take one tablet daily at bedtime. At the end of 4 and 8 weeks, plasma lipid measurements were repeated. Compliance was assessed by pill counts at each visit. All nine patients included in this report had > 90% compliance.

Laboratory Procedures

The plasma cholesterol, triglyceride, and HDL-C concentrations were measured by enzymatic techniques in the lipid diagnostic laboratory of the Koç American Hospital. İstanbul, Turkey, a certified lipid reference laboratory [2]. The concentrations of the HDL subfractions LpAI and LpAI/II were determined by electroimmunoassay [26]. Results in the tables are mean ± SD. Student's *t* test was used to compare changes in mean values. A probability of 0.05 or below was considered significant.

Results

This is a preliminary report of the data from nine healthy Turkish men who completed a therapeutic 8-week trial with 10 mg/day of simvastatin taken at bedtime. All subjects enrolled in the study had an HDL-C ≤35 mg/dL, a TC/HDL-C ratio >5.5, and triglycerides <300 mg/dL. As shown in Table 1, two subjects (A.T. and A. Şeh) were obese (BMI >27 kg/m^2). The weight of the patients did not vary by more than 1 kg during the 8-week study.

The effect of 10 mg of simvastatin on various plasma lipid values at 8 weeks is summarized in Table 2. The individual data on plasma cholesterol, LDL-C,

Table 1. Characteristics of the male patients

	Age (years)	Height (m)	Weight (kg)	BMI (kg/m²)
A.A.	54	1.72	75	25.4
H.A.	40	1.67	70	25.1
Şeh.A.	48	1.69	91	31.9
Şev.A.	36	1.59	68	26.9
F.B.	49	1.75	70	22.9
I.B.	51	1.80	77	23.8
M.B.	38	1.73	67	22.4
C.E.	45	1.79	77	24.0
A.T.	53	1.75	88	28.7

BMI, body mass index.

Table 2. Effects of simvastatin (10 mg/day) on plasma lipid levels in nine Turkish men

	Baseline* (mg/dL)	8 Weeks* (mg/dL)	% change	p value
Cholesterol	225±36	160±25	↓ 29%	<0.001
LDL-C	161±34	94±25	↓ 42%	<0.001
HDL-C	30±3	37±3	↑23%	0.002
Triglycerides	166±36	146±36	↓ 12%	N.S.

**mean ± SD.* ↑

Table 3. Effects of simvastatin (10 mg/day) on HDL subfraction and apo-AI levels.

	Week 0*	Week 8*	% change	p value
LpAI	32±3	28±3	↓ 9%	N.S.
LpAI/AII	68±7	102±14	↑50%	<0.001
Apo-AI	100±8	129±14	↑30%	<0.001

**mg apo-AI/dL*

HDL-C, and triglycerides are shown in Figures 1-4, respectively. The mean total cholesterol level declined by 29% (range, 15-50%) from 225±36 to 160±25 mg/dL ($p<0.001$; Table 2 and Fig. 1). The mean LDL-C level decreased by 42% (range, 24-62%) from 161±34 to 94 ± 25 mg/dL ($p<0001$; Table 2 and Fig. 2). The mean HDL-C value increased by 23% (range, 2-40%) from 30±3 to 37±3 mg/dL ($p=0.002$, Table 2 and Fig. 3). Although the mean level of plasma triglycerides declined from 166±36 to 146 ± 45 mg/dL, this difference did not achieve statistical significance (Table 2 and Fig. 4). The mean TC/HDL-C ratio decreased by 43% from 7.5 to 4.3 compared to the baseline mean value.

The 23% increase in HDL-C levels reflects the impact of simvastatin therapy on total HDL cholesterol levels, but does not reveal the impact of this treatment on the different HDL subfractions, which differ structurally and metabolically. Accordingly, the samples of baseline HDL and those after the 8-week treatment were separated into two major subfractions, LpAI and LpAI/AII (Table 3). Total plasma apolipoprotein (apo-) AI levels were also measured (Table 3). Plasma apo-AI levels increased significantly (30%) from 100 ± 8 to 129 ± 14 mg/dL ($p<0.001$). This increase in the mean apo-AI level was due to an increase in the mean LpAI/AII concentration from 68 ± 7 to 102 ± 14 mg/dL ($p<0.001$) on treatment. Therefore, the level of apo-AI was significantly affected by simvastatin therapy, but the LpAI fraction was not.

Discussion

This study shows that low-dose simvastatin therapy markedly decreased LDL-C and increased HDL-C, resulting in a very significant decrease in the TC/HDL-C ratio. Because only nine subjects were studied, these substantial beneficial effects must be confirmed by studies with additional subjects. However, the effects on LDL-C and HDL-C are unprecedented and for this reason we are reporting them here. Why Turks respond so favorably to low doses of simvastatin compared with subjects studied in western Europe and the United States is unclear and requires further study.

The striking 42% reduction in the mean LDL-C in Turks treated with 10 mg of simvastatin is equivalent to the effect of 40 mg of simvaslatin reported in the Scandinavian Simvastatin Survival Study (4S) and other clinical trials conducted in western Europe and in the United States [21-23,25]. These Turkish patients also had substantially greater reductions in LDL-C levels (42% versus ~ 31%) than patients with comparably low HDL-C levels treated in the United States with 20 mg lovastatin, a dose equivalent to ~10 mg of simvastatin [27].

Even more striking was the marked effect of low-dose simvastatin on the mean HDL-C level, which increased by 23%. In virtually all of the clinical trials of statins, including simvastatin, conducted outside of Turkey, mean HDL-C levels increased only 3-12%, irrespective of baseline HDL-C levels

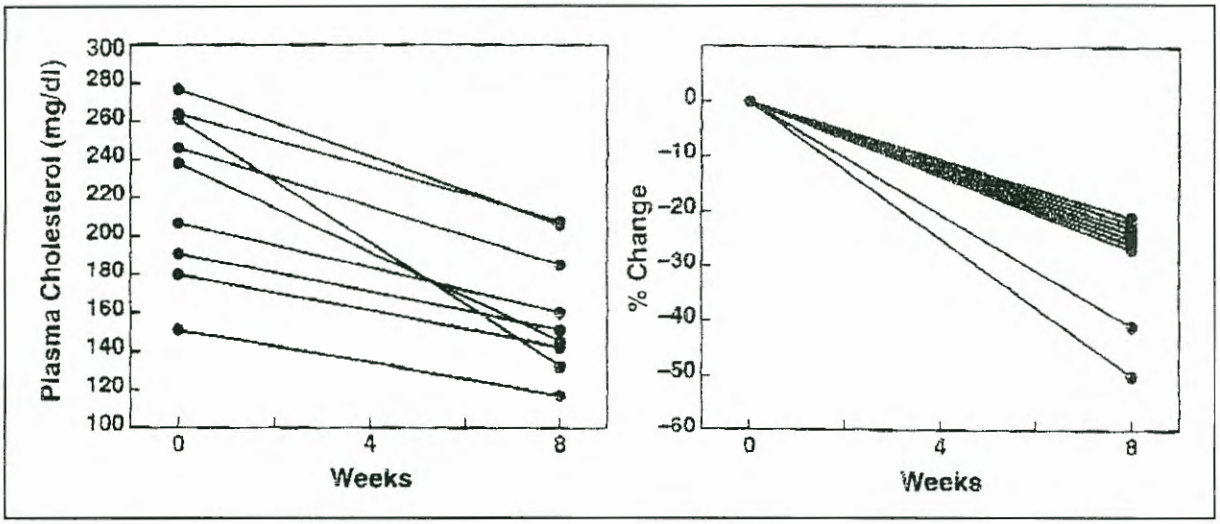

Figure 1. A. Plasma cholesterol levels at baseline and after 8 weeks of simvastatin therapy (10 mg/day). B. Percent change in total cholesterol from baseline.

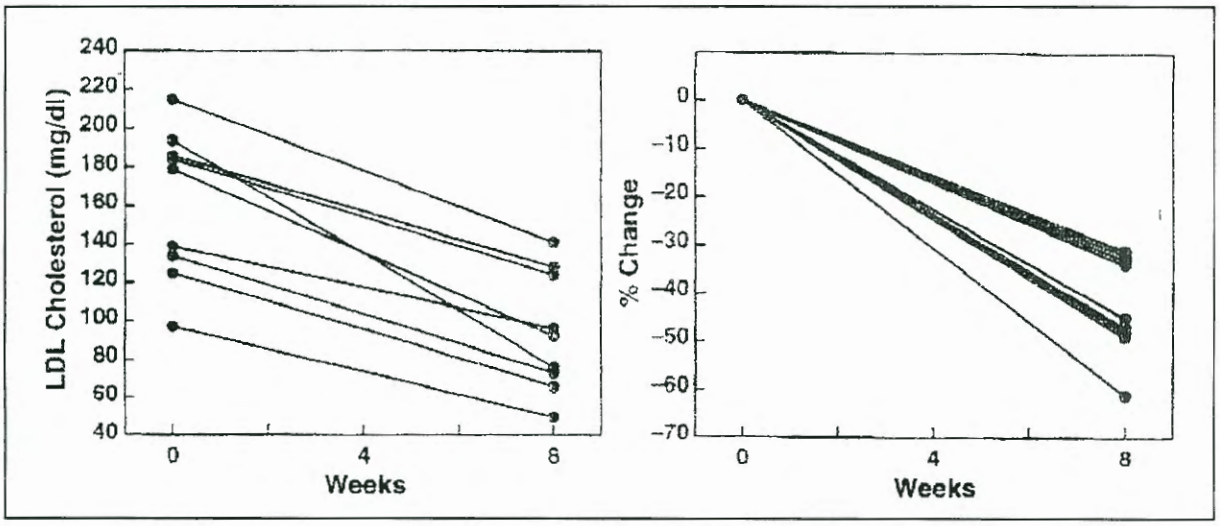

Figure 2. A. LDL cholesterol levels at baseline and after 8 weeks of simvastatin therapy (10 mg/day). B. Percent change in LDL cholesterol from baseline.

or the dose of statin employed [21,27-30]. It is possible that the effects of simvastatin in Turks who have low HDL-C may be a function of the specific genetic trait(s) that mediates low HDL-C in this population. Specifically, in the context of high levels of hepatic lipase, simvastatin may be especially effective in elevating HDL levels.

The increase in HDL-C was associated with a 30% increase in mean apo-AI levels. The HDL subfraction affected was the LpAI/AII subfraction, which increased by 50%. Although it is the concentration of the LpAI subfraction of HDL that correlates best with CHD risk, there are few data on the effects of various treatments (diet, drug, or exercise) on LpAI or LpAI/AII concentrations in patients with low HDL-C levels. In the Monitored Atherosclerosis Regression Study (MARS), hypercholesterolemic patients with normal HDL-C levels treated with lovastatin (80 mg/day) experienced no statistically significant change in HDL-C, LpAI, or LpAI/AII levels [31]. In a study of hypercholesterolemic patients with normal HDL-C levels treated with simvastatin (20 or 40 mg), LpAI levels increased slightly [5,69], but there was no effect on LpAI/AII levels [32]. However, pravastatin, in a study of subjects with normal HDL-C levels, increased LpAI/AII levels significantly (33%) and also had a significant effect on LpAI levels [33]. The variable effects of statins on

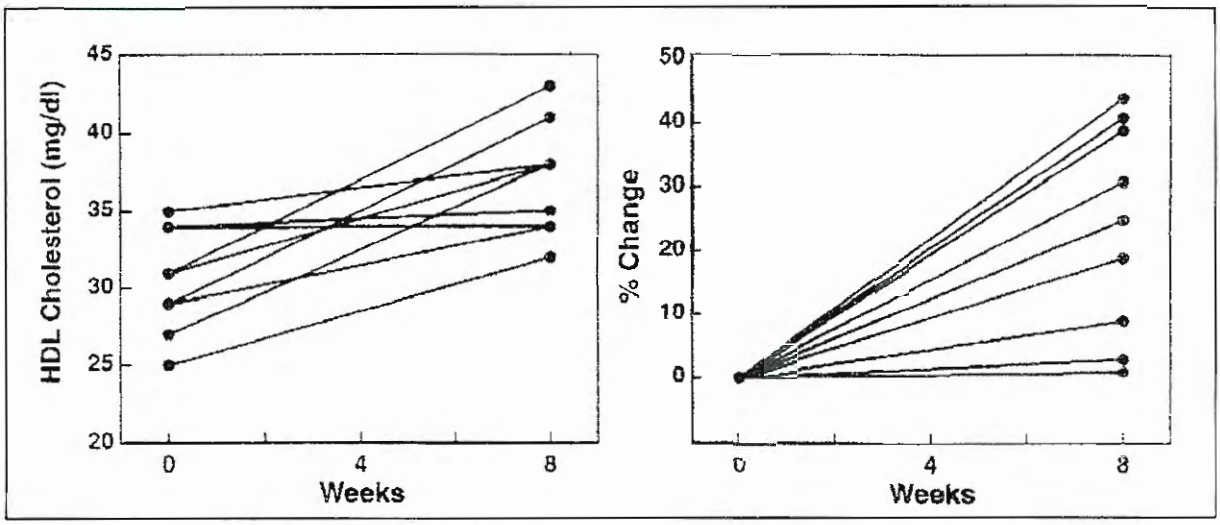

Figure 3. A. HDL cholesterol levels at baseline and after 8 weeks of simvastatin therapy (10 mg/day). B. Percent change in HDL cholesterol from baseline.

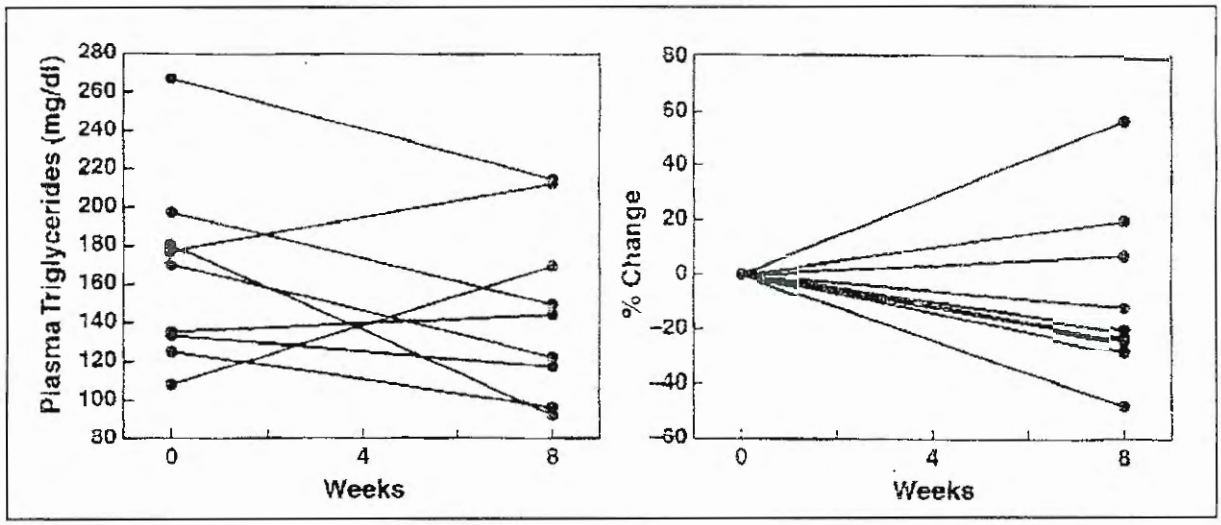

Figure 4. A. Triglyceride levels at baseline and after 8 weeks of simvastatin therapy (10 mg/day). B. Percent change in triglycerides from baseline.

LpAI and LpAI/AII levels reported in these studies suggests that further work is needed to determine the specific effects of these drugs on HDL subfractions and their metabolism. Similarly, further study of Turkish patients with low HDL-C levels is necessary to confirm the effects of simvastatin on specific HDL subfractions.

In our study, the beneficial effects of simvastatin increasing HDL-C and decreasing LDL-C, decreased the TC/HDL-C ratio by 43% from 7.5 to 4.3. Epidemiologic data suggest that TC/HDL-C values greater than 4.5 to 6.0 are associated with substantial increases in risk of developing CHD [6,34,35]. From all that we know, a ratio of 7.5 (the mean for our Turkish patients at baseline) is certainly a high risk ratio, and low-dose simvastatin therapy dramatically reduced this ratio and apparently the associated risk. In both observational and intervention trials, CHD risk has decreased by 2-3% for each 1 mg/dL increase in HDL-C [34,36]. In our Turkish subjects, the mean HDL-C level increased by 7 mg/dL, which might be expected to produce a 14-21% decrease in CHD risk in these subjects due to the improved HDL-C levels alone. An even greater reduction in CHD risk might be expected from the additional benefit associated with the 42% reduction in the mean LDL-C level in our subjects.

In summary, we have made a preliminary observation that a low dose of simvastatin (10 mg) reduced LDL-C by 42% and increased HDL-C by 23% in a small group of Turkish men who had low HDL-C levels and high-risk TC/HDL-C ratios. If confirmed, these results suggest that low-dose statin therapy may have a unique therapeutic effect in Turks that could substantially reduce CHD risk in this population.

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