



# COMPARISON OF REAL WORLD LIPID PROFILE OF PATIENTS WITH TYPE 2 DIABETES AND GUIDELINE RECOMMENDATIONS

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**SUMMARY** – Diabetes is a major risk factor for cardiovascular disease. Despite recommendations and available therapeutic options, patients with diabetes do not always reach the recommended lipid levels. In this study, our aim was to compare the real world lipid profile of type 2 diabetes patients with guideline recommendations for dyslipidemia. Four hundred and sixty eight consecutive patients referred to Outpatient Diabetes Clinic of Istanbul Medeniyet University were recruited. Patient anthropometric measurements (height, weight, waist circumference), biochemical test results (LDL cholesterol (LDL-c), triglycerides, HDL cholesterol, HbA1c) and treatment modalities were recorded. Patients were stratified into cardiovascular risk categories according to the risk factors and their treatment dose was compared to the recommendations. Among 468 patients, 56 (12%) patients had coronary heart disease (CHD). Thirty-four percent of these patients were not on statin treatment (n=19) and their mean LDL-c level was 114±29 mg/dL (2.9±0.75 mmol/L). Nineteen percent of these patients were on high intensity statin treatment (atorvastatin 40-80 mg, rosuvastatin 20 mg). Only four patients with CHD had LDL-c levels <70 mg/dL (1.8 mmol/L). Four hundred and twelve patients had no CHD. In these patients, the mean LDL-c level was 132±38 mg/dL (3.4±0.9 mmol/L). Eighty (19%) patients had LDL-c level lower than 100 mg/dL (2.5 mmol/L). Overall 82% (n=384) of the cohort had not achieved treatment goal. In conclusion, a more pronounced approach for statin treatment is needed in diabetes patients for both primary and secondary prevention of cardiovascular diseases.

**Key words:** *Type 2 diabetes; Dyslipidemia; Coronary heart disease*

## Introduction

Cardiovascular diseases are the leading cause of death in the world<sup>1</sup>. Guidelines have been issued to decrease this rate and promote preventive cardiology<sup>2</sup>. Patients with atherosclerosis are at a higher risk compared to normal population and lowering lipid levels is essential for populations at risk.

Diabetes is a major risk factor of cardiovascular disease<sup>3</sup>. It speeds atherosclerotic process and leads to ischemic heart disease. To lessen this atherosclerotic burden, the American Diabetes Association and European Society of Cardiology recommend LDL cholesterol (LDL-c) levels to be lowered to less than 100 mg/dL (2.5 mmol/L) in patients with diabetes<sup>4,5</sup>. Statins are available as lipid lowering drugs and their efficacy in diabetes is well studied<sup>6,7</sup>.

Despite recommendations and available therapeutic options, patients with atherosclerotic heart disease do not always have low lipid levels. EUROASPIRE study has shown that almost half of the patients with

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cardiovascular disease have higher LDL-c levels than recommended<sup>8</sup>.

In this study, our aim was to compare real world lipid profile of patients with type 2 diabetes with guideline recommendations for hyperlipidemia.

## Material and Methods

The study was conducted at Outpatient Diabetes Clinic of Istanbul Medeniyet University. Ethical approval was obtained from the Istanbul Medeniyet University Ethics Committee.

### Patients

Four hundred and sixty eight consecutive patients referred to Outpatient Diabetes Clinic were recruited. Patient anthropometric measurements (height, weight, waist circumference), biochemical test results (LDL-c, triglycerides, HDL cholesterol (HDL-c), HbA1c) and treatment modalities were recorded. Patients were stratified into cardiovascular risk categories according to the risk factors and their treatment dose was compared to recommendations.

### Anthropometric measures

Height was measured with a tape, weight with a digital scale, and waist circumference according to the NHANES III protocol by the same nurse<sup>8</sup>. After overnight fast, antecubital vein blood samples were collected into blood collection tubes including plain tubes without anticoagulant and tubes that contained EDTA. To obtain serum, the tubes were left to clot for 1 hour at the most and then centrifuged at 1500 g for 15 min. Serum samples were analyzed without delay. Whole blood samples for HbA1c were collected into blood tubes containing EDTA.

Serum glucose, transaminases, cholesterol (total cholesterol and HDL-c) and triglyceride levels were measured by an Architect c4000 analyzer (Abbott Laboratories, IL, USA). HbA1c levels were analyzed using high performance liquid chromatography (Primus Ultra2; Trinity Biotech USA Inc., NY, USA). LDL-c was estimated indirectly using Friedewald equation.

### Statistical analysis

Statistical analyses were conducted with SPSS 21.0 (IBM Corp., Armonk, NY, USA). The normality of

distribution of variables was assessed with Shapiro-Wilk and Kolmogorov-Smirnov tests. Subjects were compared for differences in two measurements using the paired samples t-test or Wilcoxon test. Correlations between variables were determined by Pearson correlation test or Spearman's rho. Data were expressed as mean  $\pm$  standard deviation. The level of statistical significance was set at  $p < 0.05$  (two-tailed).

## Results

Four hundred and sixty-eight patients (271 female and 197 male) were enrolled in the study. Their mean age was  $58.1 \pm 10$  years. Demographic characteristics of the patients are reported in Table 1.

The mean LDL-c level of the patients was  $129 \pm 38$  mg/dL ( $3.3 \pm 0.9$  mmol/L). The mean LDL-c level in patients without statin treatment was  $134.7 \pm 37$  mg/dL ( $3.4 \pm 0.9$  mmol/L). There were 20 (4%) patients with LDL-c  $< 70$  mg/dL (1.8 mmol/L) and 105 (22%) patients with LDL-c  $< 100$  mg/dL (2.5 mmol/L).

There were 56 (12%) patients with coronary heart disease (CHD). Thirty four percent of these patients were not on statin treatment ( $n=19$ ) (Table 2) and their mean LDL-c level was  $114 \pm 29$  mg/dL ( $2.9 \pm 0.75$  mmol/L). Nineteen percent of these patients were on high intensity statin treatment (atorvastatin 40-80 mg, rosuvastatin 20 mg). Only four patients with CHD had LDL-c levels  $< 70$  mg/dL (1.8 mmol/L), which is the treatment goal for this patient population.

Four hundred and twelve patients had no CHD. Their mean LDL-c level was  $132 \pm 38$  mg/dL ( $3.4 \pm 0.9$  mmol/L) (Fig. 1). Sixty-seven patients were on statin treatment and 44% ( $n=30$ ) had reached treatment goal. With or without treatment, 80 (19%) patients had LDL-c level lower than 100 mg/dL (2.5 mmol/L). Overall 82% ( $n=384$ ) of the cohort had not achieved treatment goal.

There were 104 (22%) patients on statin treatment. Eight (7%) and 48 (44.4%) patients had LDL-c levels  $< 70$  mg/dL (1.8 mmol/L) and  $< 100$  mg/dL (2.5 mmol/L), with the mean LDL levels of  $65 \pm 2$  mg/dL ( $1.6 \pm 0.005$  mmol/L) and  $80 \pm 10$  mg/dL ( $2 \pm 0.2$  mmol/L), respectively. Overall, 65% of the patients on statin treatment had not reached treatment goal.

Among patients on statin treatment, 8% ( $n=9$ ) used high intensity treatment, whereas 92% ( $n=99$ ) were on moderate intensity treatment. Forty nine percent ( $n=53$ )

Table 1. Demographic characteristics of the cohort

Demographic characteristic	Mean	Standard deviation
Age (yrs)	58.1752	10.2
Height (cm)	163.1049	8.9
Weight (kg)	83.1413	13.8
Duration of diabetes (yrs)	8.4209	6.6
Glucose (g/dL)	188.1028	83.5
Creatinine (g/dL)	1.0205	3.4
Triglycerides (g/dL)	179.4528	87.2
High-density lipoprotein cholesterol (g/dL)	43.0325	10.8
Low-density lipoprotein cholesterol (g/dL)	129.6966	38.8
Alanine aminotransferase (g/dL)	26.6681	27.0
HbA1c (%)	8.7465	2.2
Body mass index (kg/m <sup>2</sup> )	31.4815	5.1
Total cholesterol (g/dL)	209.7539	48.3

Table 2. Rate of statin use according to coronary heart disease (CHD)

Statin use	With CHD n=56	Without CHD n=412
Using statin	37 (66%)	67 (16%)
Not using statin	19 (34%)	345 (87%)

of them were on atorvastatin 10 mg, 27% (n=29) on atorvastatin 20 mg, 5.5% (n=6) on atorvastatin 40 mg, 14.8% (n=16) on rosuvastatin 10 mg, 0.9% (n=1) on rosuvastatin 20 mg, 0.9% (n=1) on rosuvastatin 40 mg, and 1.9% (n=2) on both fibrate and statin treatment (atorvastatin 40 mg, rosuvastatin 10 mg).

The mean triglyceride level in study patients was 179±87 mg/dL (2.02±0.9 mmol/L). Fourteen patients were only on fibrate treatment. In these patients, the mean triglyceride level was 206±90 mg/dL (2.3±1 mmol/L).

According to ADA guidelines, 80% (n=375) of the patients aged 40-75 should have received moderate-intensive statin treatment; however, 82.4% (n=309) of this population had received no treatment. ADA also recommends moderate-intensive statin therapy in patients aged >75 (n=20). In our cohort, 95% (n=19) had

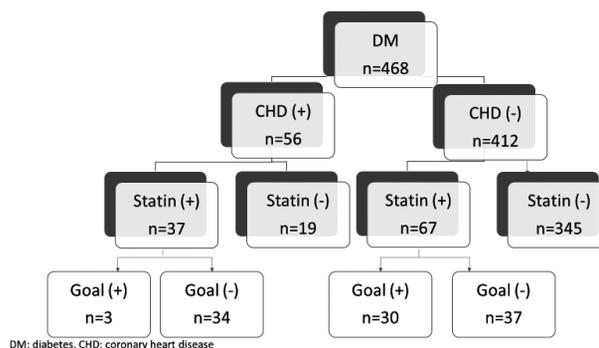


Fig. 1. Number of patients on statin therapy.

received no treatment and 5% (n=1) were on moderate statin treatment.

The mean HbA1c percent in patients using statin therapy was 8.2%±2, whereas in those without statin therapy it was 8.8%±2, yielding a statistically significant difference (p=0.01). There was no difference between the groups using statin and not using statin according to waist circumference, LDL-c levels, BMI, total cholesterol, fasting serum glucose, and age.

## Discussion

The results of our study showed that they were far from achieving treatment goals for hyperlipidemia in patients with diabetes. Study results revealed that patients with diabetes did not use statin treatment as indicated, and patients with established CHD did not use statin for secondary prevention. The reasons for underachievement of treatment goals should be thoroughly examined.

Aside from the fact that patients with diabetes were not on recommended therapy for primary prevention, a more disturbing finding was that patients with both CHD and diabetes were not on recommended therapy. Ninety percent of CHD patients had not reached recommended LDL levels and 34% of them did not use statin at all. A worldwide analysis showed that statins were used in only 16.7% of patients for secondary prevention of CHD<sup>9</sup>. A large gap exists even between high-income countries and upper middle-income countries (70.9% *vs.* 20.1%). Also, Mansur *et al.* report on the financial burden of statins as one of the main causes of the lack of adherence<sup>10</sup>; however, in Turkey, drug costs are covered by the government, therefore, it is an unlikely cause for nonadherence in this cohort.

Patients sometimes abandon statin therapy due to side effects. Patients may have myalgia and rarely more serious effects can be observed, such as myopathy or rhabdomyolysis. In a meta-analysis with 46,262 subjects by Finegold *et al.*, side effects attributed to statin treatment were minor and most of them were also seen with placebo<sup>11</sup>. Guidelines advocate that there is no need for creatinine kinase follow up in patients started on statin therapy<sup>5</sup>. It is only indicated in patients with symptoms.

Polypharmacy is a major concern in patients with diabetes. Patients without glycemic control often use both oral and injectable drugs. A study by Grant *et al.* reports that the mean number of drugs used by diabetes patients is 4<sup>12</sup>. Addition of another drug for prevention is not welcome by most of the patients. However, our analysis showed better glycemic control in patients on statin treatment. This finding may reflect the patient overall behavioral pattern related to his/her health care.

The AUDIT study has revealed that many physicians do not acknowledge diabetes as a cardiovascular risk factor<sup>13</sup>. Another physician related issue is that the recommended dose of statin often is not prescribed. Heintjes *et al.* showed the goal achievement rates to decrease without optimal therapy, and it was also affected by the statin therapy prescribed<sup>14</sup>. With pravastatin and simvastatin, lesser decrease is seen in hyperlipidemia compared to atorvastatin and rosuvastatin. ADA recommendation for patients of all ages with diabetes and atherosclerotic cardiovascular disease is that high-intensity statin therapy should be added to lifestyle therapy. In our study, only 19% of the patients were on recommended therapy.

There are doctors who advocate against statin use in patients with clear indications for treatment and media organizations prefer to interview these doctors for more attraction. Although scientific societies clearly explain the need for drug therapy in selected populations, these statements often are not heard enough. As a result, more and more people become reluctant to the initiation of statins and patient compliance decreases daily. Although nonadherence is a major problem for statin use, the use of other drugs such as hypertension medication is not optimal either<sup>15</sup>. There are single pills to increase adherence to hypertension and hyperlipidemia drugs and they are well tolerated<sup>16</sup>.

Limitations of the study include observational nature of the study. Also, patient history of statin use was

not inquired, therefore we could not provide information regarding the causes of not using statins.

In conclusion, our study showed that a more pronounced approach for statin treatment is needed in patients with diabetes for both primary and secondary prevention of cardiovascular diseases. Along with patient education, physician centered educational courses are needed.

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#### Sažetak

### USPOREDBA STVARNOG PROFILA LIPIDA U BOLESNIKA S DIJABETESOM TIP 2 I PREPORUKA IZ SMJERNICA

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Dijabetes je glavni čimbenik rizika za srčanožilne bolesti. Usprkos preporuka i dostupnih terapijskih mogućnosti bolesnici s dijabetesom ne postižu uvijek preporučene razine lipida. Cilj ovoga istraživanja bio je usporediti stvarni profil lipida u bolesnika s dijabetesom tip 2 s preporukama za dislipidemiju iz dotičnih smjernica. U istraživanje je bilo uključeno 468 uzastopnih bolesnika upućenih u Ambulantu za dijabetes Sveučilišta Medeniyet u Istanbulu. Bilježena su antropometrijska mjerenja (visina, težina, opseg struka), rezultati biokemijskih pretraga (LDL kolesterol, trigliceridi, HDL kolesterol, HbA1c) i načini liječenja. Bolesnici su podijeljeni u skupine kardiovaskularnog rizika prema rizičnim čimbenicima, a doze lijeka kojom su liječeni uspoređene su s preporukama. Među 468 bolesnika 56 (12%) ih je imalo koronarnu srčanu bolest (KSB); 34% (n=19) tih bolesnika nije primalo terapiju statinima, a njihova srednja razina LDL bila je 114±29 mg/dL (2,9±0,75 mmol/L); 19% tih bolesnika primalo je visoko intenzivnu terapiju statinima (atorvastatin 40-80 mg, rosuvastatin 20 mg). Razine LDL <70 mg/dL (1,8 mmol/L) zabilježene su u samo četvero bolesnika s KSB. Četiristodvanaest bolesnika nije imalo KSB. U ovih bolesnika srednja razina LDL bila je 132±38 mg/dL (3,4±0,9 mmol/L). Razine LDL niže od 100 mg/dL (2,5 mmol/L) zabilježene su u 80 (19%) bolesnika s LDL. Dakle, cilj liječenja sveukupno nije postignut u 82% (n=384) ispitivanih bolesnika. Zaključuje se kako je potreban snažniji pristup terapiji statinima u bolesnika s dijabetesom kako za primarnu tako i za sekundarnu prevenciju srčanožilnih bolesti.

Ključne riječi: *Dijabetes tip 2; Dislipidemija; Koronarna srčana bolest*