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Research Article

FAMILIAL HYPERLIPIDEMIA IN TYPE 2 DIABETIC PATIENTS

Yelin Koçak[1], *Atay C. Kula [2], Emre Hoca[2], Süleyman Ahbab[2] and H. Esra Ataoğlu[2]
[1]Erdek State Hospital, Internal Medicine Clinic, Balıkesir, Turkey
[2]University of Health Sciences Haseki Health Training and Research Hospital, Internal Medicine Clinic, Istanbul, Turkey
**Author for Correspondence: ataycankula@gmail.com*

ABSTRACT
*Aim***:** The present study was performed to evaluate the prevalence and antilipidemic treatment goals of familial hyperlipidemia in diabetic patients in our hospital.
*Methods***:** In the present study, 255 patients with type 2 diabetes mellitus who were followed-up at our diabetes outpatient clinic were included. The patients were evaluated according to Dutch hyperlipidemia scoring. For this purpose, the personal backgrounds, family histories, physical examination findings and laboratory values of patients were also analyzed. The patients were divided into four groups as; non-probable familial hyperlipidemia, possible familial hyperlipidemia, probable familial hyperlipidemia and definite familial hyperlipidemia.
*Results***:** As a result of the evaluation of patients according to the Dutch familial hyperlipidemia score; of the 255 patients, 166 (65.1%) had non-probable familial hyperlipidemia, 66 (25.9%) had possible familial hyperlipidemia, 17 (6.7%) had probable familial hyperlipidemia and 6 (2.4%) had definite familial hyperlipidemia. It is revealed that 139 patients (54.5%) received hyperlipidemia treatment. *Conclusion***:** Heterozygous familial hyperlipidemia has a prevalence of 1/200 to 1/250 in the context of clinical studies covering the whole population. In this study, this clinical condition was found to be 2.4% high in type 2 diabetic patients than in other patients.

Keywords: *Familial Hyperlipidemia, Type 2 Diabetes Mellitus, Dyslipidemia Treatment*

INTRODUCTION
Hyperlipidemia is a clinical condition that results from plasma lipoprotein levels exceeding the limit values determined by race, age and gender. An increase in production and release to circulation of lypoproteins, decrease in clearance and removal of lypoproteins, or both mechanisms together may lead to hyperlipidemia (Benn et al, 2012). Although hyperlipidemia with plasma LDL elevation are seen as polygenic hypercholesterolemia which is thought to be caused by environmental factors; the diagnosis and treatment of familial hyperlipidemia (FH), a cause of serious morbidity such as cardiovascular disease and cerebrovascular diseases, has a special importance. Therefore, clinical scoring systems have been developed for early diagnosis and treatment. In these scoring systems, physical examination findings, past medical history, family history and laboratory findings are used. Simone-Broome criteria and Dutch Lipid Clinic Network criteria are the most useful criteria among these. In patients with type 2 diabetes mellitus, “diabetic dyslipidemia” develops especially due to insulin resistance (da Isla et al, 2016). As a result, typically high triglyceride, low HDL and increased LDL levels are observed. The aim of this present study was to evaluate the prevalence and antilipidemic treatment goals of familial hyperlipidemia in diabetic patients in our hospital.

MATERIALS AND METHODS
In this single centered study, data in the files of overall 255 (157 female, 98 male) patients with type II Diabetes who were followed up and treated in Diabates outpatient clinic of Haseki Training and Investigation Hospital between April-July 2017 were used. Patients with type 1 diabetes mellitus, end-stage renal disease, end-stage liver failure and pregnancy were excluded.

Table 1: Dutch Lipid Clinic Network Criteria for making a diagnosis of familial hyperlipidemia in adults

Parameters	**Score**
First-degree relative with known premature coronary and/or vascular disease (men aged <55 years and women aged <60 years) or First-degree relative with known low-density lipoprotein-cholesterol (LDL-C) above the 95th percentile for age and sex	**1**
First-degree relative with tendinous xanthomata and/or arcus cornealis or Children aged <18 years with LDL-C above the 95th percentile for age and sex	**2**
Clinical history	
Patient with premature coronary artery disease (ages as above)	**2**
Patient with premature cerebral or peripheral vascular disease (as above)	**1**
Physical examination	
Tendinous xanthomata	**6**
Arcus cornealis prior to 45 years of age	**4**
LDL-C(mmol/L) levels	
LDL≥325	**8**
LDL 251-325	**5**
LDL 191-250	**3**
LDL 155-190	**1**
Stratification	
Definite familial hypercholesterolaemia (FH)	**≥8**
Probable FH	**6-8**
Possible FH	**3-5**
Unlikely FH	**<3**

The current files of the patients were retrospectively observed and the information about age, gender, height, weight, body mass index, waist circumference, duration of diabetes and hyperlipidemia, drug use for hyperlipidemia (with active substance and amount) were obtained. Also, fasting blood glucose, urea, creatinine, ALT, AST, CRP, HbA1c, TSH, fT4, spot urine protein / creatinine ratio, total cholesterol, LDL, HDL, triglyceride levels were screened retrospectively. Myocardial infarction, ischemic cerebrovascular disease, and peripheral arterial disease were defined as cardiovascular diseases. The patients' past medical and family history, physical examination findings and LDL cholesterol levels were evaluated using the Dutch hyperlipidemia scoring system, (Table 1).

RESULTS

This study was consisted of 157 female, 98 male patients. Mean age of all patients was 59.5 ± 10.4 (59.97 ± 10.6 for women, 58.87 ± 10.2 for men). The mean duration of diabetes was 13.3 ± 8.3 years and the mean duration of hyperlipidemia was 9.7 ± 6.7 years. According to the Dutch familial hyperlipidemia score, 166 of the 255 patients (65.1%) had a total score of less than 3 and were classified as unlikely familial hyperlipidemia. 66 (25.9%) patients were found to have a total score of 3-5. These patients were evaluated as possible familial hyperlipidemia. It was realized that the mean age of the patients between these groups were not significantly different (p: 0,102).

Table 2: Mean values of age, diabetes duration, duration of hyperlipidemia, waist circumference and body mass index in the risk groups and a significant difference between these groups

	Unlikely FH (score:<3, n:163)	***Possible FH (score:3-5, n:64)***	***Probable FH (score:6-8, n:17)***	***Definite FH (score:>8, n:6)***	***p value***
Age	60.31±10.35	59.26±10.93	55.88±7.58	52.00±10.95	0.102
DM (years)	12.85±8.48	14.59±7.99	12.23±7.52	13.50±8.26	0.499
HL (years)	9.18±6.76	10.75±6.94	9.47±6.39	9.40±2.61	0.529
WC	102.43±13.8	98.96±10.7	103.12±16.3	100.33±14.9	0.333
BMI	31.05±6.38	30.56±6.21	32.06±5.37	29.87±6.75	0.800

(FH: Familial Hyperlipidemia, DM: Diabetes Mellitus, HL: Hyperlipidemia, WC: Waist Circumference, BMI: Body Mass Index)

Table 3: Evaluation of biochemical parameters of our patients among groups separated according to Dutch criteria

	Unlikely FH	***Possible FH***	***Probable FH***	***Definite FH***	***p value***
FBG (mg/dL)	164.31±67.81	158.33±71.16	178.94±64.06	186.67±67.35	0.590
Urea (mg/dL)	41.30±23.71	37.57±14.23	32.41±30.77	39.00±20.28	0.347
Crea. (mg/dL)	0.93±0.44	0.82±0.26	0.83±0.72	0.98±0.52	0.307
ALT (U/L)	22.42±14.10	21.33±17.89	24.06±9.71	23.67±10.01	0.902
AST (U/L)	23.29±11.50	22.15±8.56	23.18±8.68	20.17±5.53	0.808
HbA1c (%)	7.96±1.74	8.27±2.12	8.11±1.74	9.20±2.32	0.327
CRP (mg/dl)	6.53±9.95	6.96±8.50	7.05±8.19	12.44±6.91	0.589
PCR	360.92±864.77	577.72±1489.27	635.29±1300.70	710.00±1193.65	0.442
TSH (mg/dl)	2.15±1,52	2.36±2.07	2.67±2.14	2.34±1.77	0.615
fT4 (mg/dl)	0.92±0.24	0.87±0.19	0.94±0.32	0.88±0.08	0.439

(FBG: Fasting Blood Glucose, Crea.: Creatinine, PCR: protein / creatinine ratio in spot urine, TSH: Thyroid Stimulating Hormone, fT4: Free T4)

The duration of diabetes and hyperlipidemia did not significantly differ between the groups (p: 0.49 for diabetes duration, p: 0.52 for duration of hyperlipidemia). Also it was shown that waist circumference and body mass index did not create a significant difference between the groups in the family hyperlipidemia risk scoring (for waist circumference p: 0.33, for body mass index p: 0.80), (Table 2). Fasting blood glucose, urea, creatinine, ALT, AST, HbA1c, CRP, spot urine protein / creatinine ratio, TSH and TT4 values were evaluated among groups which were separated according to Dutch hyperlipidemia score. There was no significant difference between the groups according to this evaluation. (p: 0.59 for fasting blood sugar) (p: 0.34 for urea) (p: 0.30 for creatinine) (p: 0.90 for ALT) (p: 0.58 for CRP), (p: 0.44 for spot urine protein / creatinine ratio) (p: 0.61 for TSH) (p: 0.43 for TS4) as shown in Table 3. There was no significant difference in HbA1c values between the two groups, (p: 0.43).

DISCUSSION

The prevalence of heterozygous familial hyperlipidemia is known to be 1/500 in the society, and it has been observed that it has a higher prevalence in studies covering the whole society, and in some societies, this frequency can reach up to 1/137 (Benn *et al.,* 2012). Based on the available data, the prevalence of heterozygous familial hyperlipidemia is between 1/200 and 1/250 and it can be predicted that the total number of cases in the world is 14-34 million (Nordestgaard *et al.*, 2013). The frequency of homozygous familial hyperlipidemia is estimated to be 1/160000 - 1/300000. In the present study, a total of 255 patients were included, 17 (6.7%) patients were diagnosed as probable familial hypercholesterolemia and 6 (2.4%) were diagnosed as definite familial hypercholesterolemia (De Ferranti *et al.,* 2013). The prevalence of familial hypercholesterolemia in patients with diabetes mellitus has not been studied extensively throughout the world. The frequency of development of type 2 diabetes mellitus in cases of familial hypercholesterolemia was evaluated to be more. In the group with heterozygous familial hypercholesterolemia, it was observed that type 2 diabetes development was less (Vohl *et al.*, 1997). In a study conducted on Spain, the prevalence of type 2 diabetes mellitus was found to be 5.9% in individuals with heterozygous familial hypercholesterolemia and was found to be lower than the prevalence of type 2 diabetes, known as 9.4% in the general population (Soriguer *et al.,* 2012). Familial hyperlipidemia is a disease that is under-diagnosed and untreated, especially in childhood. Only approximately 20% of cases are diagnosed (Goldberg *et al.,* 2011).

Heterozygous FH is one of the most common hereditary diseases but the data related to this subject is limited in our country. In contrast, the prevalence of type 2 diabetes was higher in the statin-using population (Sattar *et al.,* 2010). Statins increase the expression of LDL receptors in many tissues by inhibiting HMG CoA reductase. This increases the transport of transmembrane cholesterol (Swerdlow *et al.,* 2015). This is a reversal of genetically impaired cellular cholesterol uptake in familial hypercholesterolemia, which is associated with the potential for type 2 diabetes pathogenesis. Considering the need for high-dose statin therapy in low-risk FH, the risk of developing Type 2 DM is in contrast with the increased frequency of DM in treated areas. Clinical studies have shown that statin therapy destroys glycemic control in type 2 diabetic patients who take intensive statin in order to reach the target LDL cholesterol level (Adedinsewo *et al.*, 2016). Diabetic patients have a significant risk for cardiovascular disease. Statins also provide significant reduction in cardiovascular mortality, stroke and myocardial infarction in diabetic patients (Stein *et al.,* 2004). According to guidelines, a tremendous majority of diabetic patients will benefit from statin use, but despite these recommendations since 2002, less than 60% of diabetic patients receive statin therapy (Alonso *et al.,* 2013). In this present study, it is noticed that 139 (54.5%) patients were receiving hyperlipidemia treatment.

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