

Case images

Olgu görüntüsü

Hiatal hernia presenting like a large left atrial mass

Büyük bir sol atriyal kitle gibi prezente olan hiatal herni

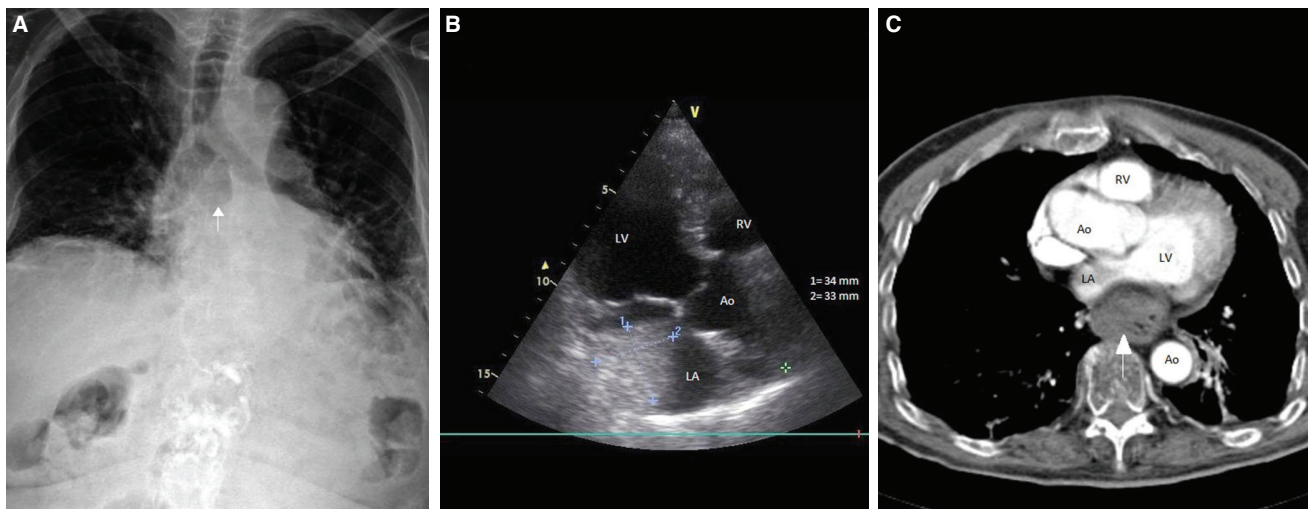
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Paraesophageal hiatal hernia is described as prolapsus of the stomach through the diaphragmatic esophageal hiatus. These hernias are usually latent and discovered incidentally. However, some catastrophic complications may occur, such as bleeding and incarceration. Presently described is an unusual presentation of a hiatal hernia not previously reported in the literature. A 67-year-old man was admitted with chest pain ongoing for a period of 15 days. The character of the chest pain was progressive, retrosternal, and accompanied by a burning sensation. The patient was a heavy smoker, but did not have any other traditional risk factors for coronary artery disease. His physical examination was unremarkable and electrocardiogram was normal. Chest film revealed a suspicious air space under the tracheal bifurcation (Figure A). A fast bedside transthoracic echocardiography (TTE) was performed to exclude acute aortic and acute coronary syndromes. The TTE revealed a fixed left atrial (LA) mass 33x34 mm in size adjacent to the LA lateral wall (Figure B and Video 1*). In order to better reveal the LA mass, transesophageal echocardiography was attempted; however, the patient could not tolerate it. Subsequently, a contrast-enhanced cardiac computed tomography revealed a paraesophageal hiatal hernia consisting air gap and compressing the LA from behind (Figure C). After the definitive diagnosis was made, anti-acid treatment was initiated and patient underwent Nissen fundoplication surgery and was discharged on the postoperative 13th day without further complication.



Figures- (A) Chest X-ray shows normal mediastinal and cardiothoracic ratios with the suspicious air space under the tracheal bifurcation (white arrow indicates the air space). (B) Transthoracic echocardiogram in modified 4-chamber view illustrates left atrial mass 33x34 mm in size adjacent to the lateral atrial wall. (C) Cardiac computed tomography scan illustrating that the left atrium is compressed by a paraesophageal hernia (white arrow shows the hernia).

*Supplementary video files associated with this presentation can be found in the online version of the journal.

ORIGINAL ARTICLE

Identifying undiagnosed or undertreated patients with familial hypercholesterolemia from the laboratory records of a tertiary medical center

Tanı konmamış veya yeterli tedavi almayan ailevi hiperkolestrolemili hastaların bir üçüncü basamak sağlık merkezi laboratuvar kayıtlarından tespit edilmesi

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ABSTRACT

Objective: Familial hypercholesterolemia (FH) is a life-threatening genetic disease associated with elevated low-density lipoprotein cholesterol (LDL-C) and premature coronary heart disease that is undiagnosed and undertreated around the world. This study aimed to examine the demographic characteristics, awareness, and treatment adherence of undiagnosed or undertreated FH patients based on laboratory records.

Methods: In a 16-month retrospective survey using laboratory records, patients with elevated LDL-C (>250 mg/dL) were identified (n=395). Patients younger than 18 years of age or with secondary causes of dyslipidemia were excluded (n=98). In all, 297 patients were called and asked to participate in a phone interview regarding their demographic characteristics, awareness of dyslipidemia, and treatment adherence.

Results: A total of 147 patients (mean age: 51.7±16.6 years; 59.2% female) completed the interview. The mean LDL-C level of the patients was 292.8±49.9 mg/dL. According to the Dutch Lipid Clinic Network criteria, 18.4% of the patients had definite FH, 66.0% had probable FH, and 15.6% had possible FH. Although the majority of the patients (93.9%) were aware of their high LDL-C level, only about half of them (n=75; 51.0%) were in treatment. Of all the patients who were interviewed, 21% (n=31) had never taken medication to lower their LDL-C, and 28% (n=41) had stopped taking a lipid-lowering drug.

Conclusion: This pilot study revealed that a significant number of FH patients were not taking statins despite having a very high LDL-C level. Nationwide detection of likely FH patients using hospital records and interviewing them via a phone survey may help to better understand and manage these high-risk patients.

ÖZET

Amaç: Ailevi hiperkolestrolemi (AH), düşük yoğunluklu lipoprotein kolesterol (LDL-K) yüksekliği ve erken koroner kalp hastalığı ile birlikte seyreden ve genellikle tanı konmayan veya yeterli tedavi almayan hayatı tehdit edici genetik bir hastalıktır. Bu çalışmada, biyokimya laboratuvar kayıtlarına dayanarak, tanı konmamış veya yeterli tedavi almayan AH'li hastaların demografik özelliklerinin, farkındalıklarının ve tedaviye uyumlarının araştırılması amaçlandı.

Yöntemler: Laboratuvar kayıtları kullanılarak yapılan 16 aylık geriye dönük çalışma sonucunda LDL-K değeri >250 mg/dL olan hastalar tespit edildi (n=395). On sekiz yaşından genç veya ikincil dislipidemi olan hastalar çalışma dışında bırakıldı (n=98). Sonuçta, 297 hasta telefonla arandı ve demografik özellikleri, dislipidemi farkındalıkları ve tedaviye uyumları hakkında sorular yöneltildi.

Bulgular: Çalışmaya katılmayı kabul eden toplam 147 hasta (ort. yaş 51.7±16.6 yıl, %59.2 kadın) ile görüşme yapıldı. Ortalama LDL-K düzeyleri 292.8±49.9 mg/dL bulundu. "Dutch Lipid Clinic Network" kriterlerine göre kesin, muhtemel ve olası AH'li hastaların oranları sırasıyla %18.4, %66.0 ve %15.6 olarak tespit edildi. Hastaların büyük bir kısmı (%93.9) yüksek LDL-K düzeylerine sahip olduklarının farkında olmalarına rağmen yalnızca yarısı (n=75, %51.0) tedavi almaktaydı. Görüşme yapılan hastaların %21'i (n=31) hiç tedavi almamış ve %28'i (n=41) ise lipid düşürücü ilaç kullanmayı bırakmıştı.

Sonuç: Bu pilot çalışma, çok yüksek LDL-K düzeylerine sahip olmalarına rağmen önemli oranda AH'li hastanın statin tedavisi almadığını ya da tedaviyi bıraktığını göstermektedir. Hastane kayıtlarından tespit edilen AH'li hastaların telefonla aranması ile yapılan bu çalışmanın ulusal düzeyde yaygınlaştırılması bu yüksek riskli hastalara ulaşılmasında ve bu hastaların yönetiminde yardımcı olabilir.

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Familial hypercholesterolemia (FH) is an autosomal co-dominant condition associated with elevated low-density lipoprotein cholesterol (LDL-C) and premature coronary heart disease (CHD). Although the estimated prevalence of heterozygous FH is about 1/200-500, the majority of these individuals are currently undiagnosed or undertreated.^[1] Unfortunately, the life expectancy is limited in FH patients who are not appropriately treated.^[2] However, with the current treatment modalities, we are able to reduce elevated LDL-C levels and prevent the progression of atherosclerotic cardiovascular diseases.

Several different criteria are used to diagnose FH.^[3] Organized efforts to screen and diagnose FH have helped to clarify the characteristics of these patients.^[4-6] However, despite these efforts, a considerable number of FH patients are still undiagnosed or undertreated.^[1] There are several reasons for this ignorance, such as a lack of awareness of the devastating nature of FH and fear of the side effects of statins.^[7,8] In addition, the lack of universal, nationwide screening programs and insufficient electronic health records are other important limitations to the appropriate diagnosis, treatment, and follow-up of patients with FH. Identifying patients with a high LDL-C level using the health records of community laboratories may be a practical method of determining individuals with FH.^[3,9,10]

There are emerging data about the prevalence of FH in different countries^[6,11,12] and recent reports better define the characteristics of FH patients in different regions of the world.^[4,5,13,14] However, the epidemiological data about FH patients in Turkey are insufficient.^[15,16] This pilot study was designed to examine the demographical characteristics, awareness level, and treatment adherence of FH patients. Patients with a high LDL-C level were identified from the records of the central biochemistry laboratory of a tertiary care center.

METHODS

Participants and data collection

The study group was retrospectively selected from patients who were referred to the outpatient clinics of a tertiary medical center between January 2015 and April 2016 with a central laboratory measurement of LDL-C >250 mg/dL. This LDL-C cut-off was selected in order to enroll patients with probable FH and defi-

nite FH according to the Dutch Lipid Clinic Network (DLCN) criteria.

^[17] The telephone numbers of the pa-

tients included in the study were obtained from the hospital records system. Patients who were excluded were those younger than 18 years of age and those with an International Classification of Diseases code for a potential secondary cause of hypercholesterolemia, such as hypothyroidism, nephrotic syndrome, or cholestasis. The study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki and was approved by the institutional ethics committee (December 15, 2015; number: 497).

Telephone questionnaire

Medical students called the patients and asked if they would be willing to participate in the study. During the interview, the students filled in an FH questionnaire, which included questions about demographic data, awareness of LDL-C level, history of lipid-lowering medication use, presence of cardiovascular disease, family history of hypercholesterolemia and cardiovascular disease, and daily habits, including smoking, diet, and exercise (Table 1).

Defining familial hypercholesterolemia case status

Patients who agreed to participate in the phone interview were classified according to DLCN criteria for the clinical likelihood of FH.^[17] The following modified version of the DLCN criteria and numerical score was used: Family history of a first-degree relative with known premature (55 years for men, 60 years for women) coronary artery disease (CAD) or vascular disease, and/or a first-degree relative with known hypercholesterolemia (1 point); personal history of premature CAD (ages as above; 2 points), or premature cerebral or peripheral vascular disease (ages as above; 1 point); LDL-C above 330 mg/dL (8 points), 250–329 mg/dL (5 points), 190–249 mg/dL (3 points), or 155–189 mg/dL (1 point). Two criteria of the original set, namely, the presence of tendon xanthoma or corneal arcus, either in the patient or in a first-degree relative, were excluded, as it was not possible to perform a physical examination. Participants were classified as follows: definite FH (score >8), probable FH (score 6–8 points), or possible FH (score 3–5 points).

Abbreviations:

CAD	Coronary artery disease
CHD	Coronary heart disease
DLCN	Dutch Lipid Clinic Network
FH	Familial hypercholesterolemia
LDL-C	Low-density lipoprotein cholesterol

Table 1. Familial hypercholesterolemia telephone interview questionnaire

Familial Hypercholesterolemia Telephone Questionnaire Form			
Age:			
Marital status:			
Place of birth:			
Smoking:	<input type="checkbox"/> I don't smoke	<input type="checkbox"/> I quit smoking (< 5 year)	<input type="checkbox"/> I smoke (cigarettes /day)
Alcohol:	<input type="checkbox"/> Never	<input type="checkbox"/> Rare (social)	<input type="checkbox"/> 1-2 times a week
	<input type="checkbox"/> 3-4 times a week	<input type="checkbox"/> 5-7 times a week	
Exercise:	<input type="checkbox"/> Never	<input type="checkbox"/> 1-2 days a week	<input type="checkbox"/> 3-4 days a week <input type="checkbox"/> 5-7 days a week
Diet:	<input type="checkbox"/> Makes an effort to eat healthily (low in saturated fat, high fiber)		
	<input type="checkbox"/> No specific effort made toward healthy eating		
1 - Do you know that you have high cholesterol?			
Yes	No		
2 - Are you still being treated for high cholesterol level?			
Yes (Drugs)			
No			
3- Have you been treated previously because of the high cholesterol level?			
Yes (Drugs)			
No			
4- If you were treated before, why was the treatment discontinued?			
Adverse effect	Own request	Other	
5- Do you have a atherosclerotic cardiovascular disease*?			
No	Yes (Age)		
6- Any other metabolic disease?		Drugs	
Obesity		
Diabetes mellitus		
Hypertension		
Renal disease		
Liver disease		
Other		
7- Do any of your first-degree relatives (father, mother, siblings) have atherosclerotic cardiovascular disease* at an early age (men: <55 years, Women <60 years)?			
Yes	No	Unknown	
8- Is there anyone else in your family who has a high cholesterol level like you?			
Yes	No	Unknown	
*The term "atherosclerotic cardiovascular disease" will be explained as having one of the following conditions:			
• Coronary artery disease (Including myocardial infarction, chronic unstable angina, having revascularization or coronary artery bypass graft operation previously)			
• Peripheral artery disease			
• Cerebrovascular disease			
• Aortic aneurysm			

Statistical analysis

All data were recorded on a computer database and analyzed using PASW Statistics for Windows, Version 18.0. (SPSS Inc., Chicago, IL, USA). Results

were expressed as mean±SD. The variables were assessed for normality using the Kolmogorov–Smirnov test, and Levene’s test was used to evaluate the equality of variance. Intergroup differences were analyzed

with a chi-squared test. A Kruskal-Wallis test was run to determine if there were differences in the LDL-C level according to FH status (i.e., definite, probable, possible). Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. Differences were considered significant at a p value of <0.05.

RESULTS

A retrospective laboratory survey of 16 months identified a total of 395 (0.6%) adult patients with an LDL-C level over 250 mg/dL among 65,320 LDL-C records. Ninety-eight patients were excluded due to the criteria previously described. In all, 297 individuals were enrolled in the study and were called by the medical students. Three of these patients were reported to have died (traffic accident, myocardial infarction, and cause of death not identified) by relatives, 135 individuals could not be reached, and 12 patients did not want to participate in the study. Finally, 147 patients (mean age: 51.7 ± 16.6 years; 59.2% female) were interviewed, and the study questionnaire forms were completed (Fig. 1). About 75% of these patients were referred from 5 outpatient units (endocrinology, internal medicine, cardiology, cardiovascular surgery, and neurology). The clinical and demographic parameters of these patients were not significantly different from other outpatient units.

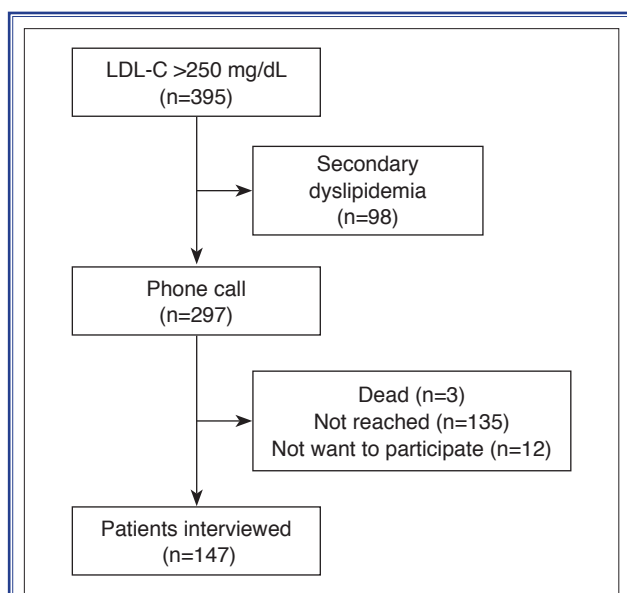


Figure 1. The study flow chart and an illustration of the approach used to identify patients with familial hypercholesterolemia from the data of central laboratory.

According to the DLCN criteria, the percentage of patients with definite FH (DLCN score >8), probable FH (DLCN score 6–8), and possible FH (DLCN score 3–5), was 18.4%, 66.0%, and 15.6%, respectively. Although the majority of the patients (93.9%) were aware that they had a high LDL-C level, only about half of these patients (n=75; 51.0%) were under treatment (Table 2).

The mean LDL-C level was 292.8 ± 49.9 mg/dL. The median LDL-C level was significantly different between groups ($H=41.721$; $p<0.005$). Pairwise comparisons revealed that the differences between definite and possible FH ($p<0.005$), and definite and probable FH ($p<0.005$), were statistically significant, whereas the difference between probable and possible FH was not significant ($p=0.964$). There were no significant

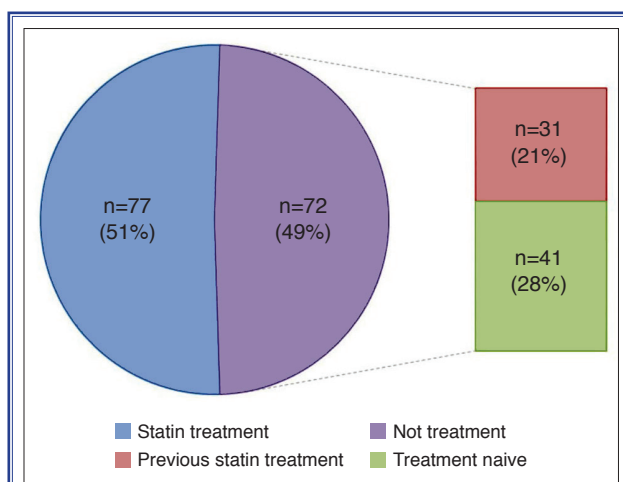


Figure 2. A graphic illustrating statin usage among patients with dyslipidemia.

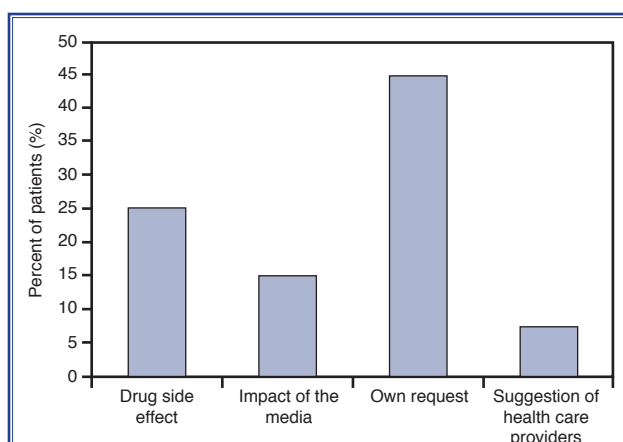


Figure 3. The reasons for discontinuing use of lipid-lowering drugs in familial hypercholesterolemia patients.

Table 2. Demographic and laboratory characteristics of patients with definite, probable, and possible familial hypercholesterolemia

	All patients	Definite FH	Probable FH	Possible FH	p
Number (%)	147 (100%)	27 (18.4%)	97 (66%)	23 (15.6%)	
Gender (% women)	59.2	48.1	61.9	60.9	0.43*
Age (years)	51.7 (\pm 16.6)	43.2 (\pm 18.1)	53.4 (\pm 16.2)	54.6 (\pm 13.7)	0.012**
LDL-C (mg/dL)	292.8 (\pm 49.9)	359.5 (\pm 65.6)	279.4 (\pm 29.8)	271.1 (\pm 28.6)	<0.001***
Smoking (%)	32.7	40.7	32.0	26.1	0.92****
Diet (%)	44.9	51.9	43.3	43.5	0.72*
Physical activity (%)	68.0	77.8	67.0	60.9	0.58*
Awareness of high LDL-C (%)	93.9	92.6	95.9	87.0	0.36****
Statin treatment (%)	51.0	48.1	53.6	43.5	0.64*
Treatment naive (%)	21.1	14.8	18.6	39.1	0.06*
Family history of premature CAD (%)	48.3	74.1	51.5	4.3	<0.001****
Family history of dyslipidemia (%)	68.7	92.6	77.3	4.3	<0.001****
Personal history of premature CAD (%)	26.5	29.6	32.0	0	0.007*

FH: Familial hypercholesterolemia; CAD: Coronary artery disease; LDL-C: Low-density lipoprotein cholesterol.

*Chi-square test; **Analysis of variance test; ***Kruskal-Wallis test; ****Fisher's exact test.

differences in the clinical and demographic characteristics of the patients in these groups.

About half of the patients were not in treatment ($n=72$; 49%). Of these untreated patients, 43.1% ($n=31$) had never used any lipid-lowering drug, and 56.9% ($n=41$) had stopped using a lipid-lowering drug (Fig. 2). The primary reasons for discontinuing the drug were patient request ($n=19$; 46.3%), drug side effect ($n=11$; 26.8%), impact of the media ($n=7$; 17.1%), and suggestion of healthcare providers ($n=4$; 9.8%) (Fig. 3).

The smoking rate was highest among the definite FH cases, but it was not statistically significant. Thirty-two percent of the patients were not performing regular exercise, and 55% were not following a dietary program. Family history of premature CAD and dyslipidemia was significantly higher in patients with definite FH ($p<0.001$ for both); however, the prevalence of premature CAD was significantly higher in patients with probable FH ($p=0.007$) (Table 1).

DISCUSSION

The results of this pilot study conducted at a tertiary center demonstrate that the majority of FH patients were aware that they had a very high LDL-C level. Yet, about half of them were not taking lipid-lower-

ing medication. About one-fifth of all these patients had never used a lipid-lowering drug. This study also showed that identification of patients with a high LDL-C level based on the records of the central laboratories may be a practical approach to identify individuals with undiagnosed or undertreated FH.

FH is one of the most common genetic disorders of lipid metabolism with an increased risk for atherosclerosis, premature CHD, and heart failure.^[18,19] Life expectancy is significantly shortened due to cardiovascular disease in patients with undertreated FH. However, the majority of patients with FH are undiagnosed and patients who are diagnosed often are undertreated.^[1,4,5,20] Unfortunately, neither the prevalence of FH, nor the clinical condition of these patients is clearly known in Turkey. There are few data, other than a genetic study^[15] and a long-term follow-up study, about homozygous FH patients.^[16] As a result of the high frequency of consanguineous marriage, the prevalence of FH is expected to be higher than in most other regions of the world.^[21] A nationwide study, AHIT-2, designed to investigate the clinical and demographic characteristics of FH patients, is expected to be completed before the end of 2017.^[22] Early recognition of FH is important, as statin treatment reduces the risk of cardiovascular disease and mortality in patients with FH.^[23,24] However, there is

no systematic screening program in most countries. In this regard, central laboratories may play a pivotal role in the identification of patients with FH, as they measure the lipid profile of a large number of patients.^[3,9,10] In the current study, we used the data of the central laboratory of our tertiary hospital and identified patients who have an LDL-C level above 250 mg/dL and made a telephone call to determine demographic characteristics and other information. About 85% of the participants were either definite or probable FH patients, according to the DLCN criteria.^[17] None of the patients in the study had achieved target LDL-C level. Therefore, the results of this study are very important, as they helped us to identify undiagnosed and undertreated FH patients and understand the reasons behind the inadequate health support.

Statins are the basic treatment modality to reduce cardiovascular disease and the mortality risk in patients with FH. Numerous studies have demonstrated that the atherosclerotic burden in patients with FH is significantly reduced after the initiation of statin treatment.^[25,26] The rate of use of lipid-lowering medications in FH patients differs in various reports. Knickelbine et al.^[4] reported that two-thirds of patients with FH were on statin treatment in a large ambulatory study population. Similarly, in the study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH), it was reported that 70% of the patients with FH were on statins, with 80% achieving an LDL-C <100 mg/dL.^[5] However, in a Danish study, about half of the patients with FH had taken statins.^[6] From the present, small, single-center data, it is not possible to estimate the percentage of statin usage among FH patients in Turkey. Also, patients under statin treatment with lower LDL levels were probably ignored due to the enrollment criteria. However, our results clearly show that about one-fifth of the patients interviewed had never used any lipid-lowering medication at all.

Patients with dyslipidemia have various states of awareness about their condition. In the US population, almost half of the patients with dyslipidemia were aware of their disease.^[27] However, only 10% to 20% of patients with dyslipidemia were aware of their disease in the Chinese population.^[28,29] In the current study, about 90% of our patients were aware of having a very high LDL-C level. The awareness rate was similar in patients from different outpatient

units. Furthermore, there was no difference in awareness rate between the patients with possible, probable, or definite FH status. Using the registry of a tertiary center and including patients with a very high LDL-C level (LDL-C >250 mg/dL) may be the reason for this higher rate of awareness. However, although they knew that they had dyslipidemia, half of these patients were not under a lipid-lowering regimen. Moreover, the rate of lipid-lowering treatment did not differ between the 3 groups, despite the fact that the patients with definite FH had a higher LDL-C level, and greater family history of CAD and dyslipidemia. Patients within these 3 categories were also similar in terms of demographic and clinical characteristics.

Several reasons may explain the lack of adequate treatment in these patients. Patient concerns about the necessity of taking statins may be one of the most common. Worry about joint and muscle side effects of statins is also a very common reason. Finally, there is also a lack of knowledge about the efficacy and importance of statin treatment among healthcare providers.^[7,8] Likewise, in the present study, there were patients who had stopped using lipid-lowering drugs at their own request, as a result of minor drug side effects, the negative impact of media reports, and even due to the suggestion of healthcare providers. In this regard, identifying patients with a very high LDL-C level using central laboratory records could be a useful and practical method to inform patients and healthcare providers about the treatment of FH.

Study limitations

This study has a number of limitations. First, a large part of the study data was based on self-reported information and could be subject to recall bias. Second, a physical examination of the patients was not performed (e.g., tendon xanthoma, arcus cornea). Therefore, we did not include this information in the scoring, which may have led to an incomplete definition of FH case status. For this reason, some cases may have scored lower than they would have otherwise. Also, as the data were collected from patients of a tertiary hospital, the findings may not directly be extrapolated to the wider population of FH patients in Turkey. Finally, subjects under statin treatment who had an acceptable LDL-C level were not included as a result of the enrollment criteria of this study.

Conclusion

The results of the present study indicate that detecting patients with a high LDL-C level using the records of the central laboratories may be a practical method to identify undiagnosed or undertreated FH patients. Since only half of the FH patients in this study were use lipid-lowering medication and none of them had their cholesterol level under control, this method should be generalized to centers in different regions of the country to have more comprehensive data about the reasons for underdiagnosis and undertreatment of FH in Turkey.

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