Original Article

The Demographic and Lifestyle Characteristics of Patients with Familial Hypercholesterolemia Referred to a Dyslipidemia Clinic: A Cross-Sectional Single-Center Study

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Abstract

Background: *Familial hypercholesterolemia (FH) is one of the most prevalent dyslipidemia disorders. This study investigated the demographic and lifestyle characteristics of patients with FH referred to a dyslipidemia clinic.*

Methods: *This 5-year, single-center cross-sectional study focused on patients with low-density lipoprotein cholesterol (LDL-C) levels higher than 190 mg/dL referred to a dyslipidemia clinic in Tehran, Iran, between 2017 and 2022. The study examined their demographics, physical activity, and anxiety within the FH cohort.*

Results: *A total of 1724 patients were referred to the dyslipidemia clinic. Of these patients, 44 were diagnosed with definite FH. The mean age and LDL-C level of the FH cohort were 38.84±16.85 years and 315.95±81.73 mg/dL, respectively. A significant correlation was found between LDL-C and body mass index (BMI) (correlation coefficient = -0.31, P=0.031) and total sleep duration (correlation coefficient = -0.40, P<0.000). No correlation was observed between age and physical activity or LDL-C levels. Additionally, no significant correlation was detected between the Dutch score and patients' LDL-C, BMI, age, or physical activity. Regression analysis indicated that BMI and total sleep duration were independent predictors of LDL-C in the FH cohort.*

Conclusion: *Investigating and identifying patients' demographic and lifestyle characteristics is the first step in planning efficient and effective management strategies for chronic diseases, such as FH. Establishing a patient registry for chronic diseases enhances understanding of the target population and enables healthcare providers to design and implement appropriate preventive and control strategies.*

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Introduction

Dyslipidemia is one of the most prevalent chronic disorders, contributing to an estimated global burden of 98.6 million disability-adjusted life years.[1, 2] The significance of dyslipidemia lies not only in its high burden of disease but also in its critical role in increasing the risk of other causes of mortality, making it the eighth leading cause of death globally.[3]

Dyslipidemia is a multifactorial disorder influenced by numerous inherited and lifestyle-related risk factors.[4, 5] Among the most notable forms of dyslipidemia are the inherited types, such as familial hypercholesterolemia (FH), which exhibit significant prevalence, present from childhood and early adolescence, and pose a lifelong risk of cardiovascular diseases.[6] Notably, FH is the most common monogenic inherited metabolic disorder.[7]

Although the prevalence of FH remains undetermined in most countries, a meta-analysis revealed a prevalence rate of 1:313 in the general population, underscoring its heightened occurrence among patients with ischemic heart disease.8 In fact, FH prevalence is 20-fold higher among patients with premature ischemic heart disease and severe hypercholesterolemia and 23-fold higher than that of the general population.[8]

Despite the significance of FH, limited research has concentrated on patients living with this condition. Current evidence generally indicates that FH has been largely underestimated and underdiagnosed.[9, 10] To improve patient outcomes, it is essential to establish a comprehensive registry for this patient subset, explore their demographics and lifestyle characteristics, and enable healthcare systems to optimize disease management and follow-up strategies more effectively.[6, 11]

This study examines a 5-year single-center experience at a referral dyslipidemia clinic in Tehran. It focuses on establishing a registry of the FH cohort and investigating their characteristics among patients with high low-density lipoprotein cholesterol (LDL-C) serum levels.

Methods

This cross-sectional study explored the epidemiological and lifestyle characteristics of FH patients referred to a dyslipidemia clinic in Tehran between 2017 and 2022. The medical records of all patients with LDL-C levels exceeding 190 mg/dL were examined to identify FH patients and apply the Dutch Lipid Clinic Network (DLCN) criteria (the Dutch score) for classification.[12] The Dutch score is a scoring system that encompasses 4 domains: biochemical investigation (LDL-C levels), clinical features (the presence of tendon xanthomas and/or arcus cornealis), the patient's medical history (including premature peripheral, cerebral, or coronary artery diseases), and positive family history (involving first-degree relatives with any of the mentioned items). Upon scoring, patients can be classified into the following FH categories: unlikely (total score <3), possible (total score: 3–5), probable (total score: 6–7), and definite (total score ≥8).[12]

After obtaining written informed consent from definite FH cases, we assessed their smoking history, physical activity, and anxiety levels. The International Physical Activity Questionnaire (IPAQ) was used to evaluate physical activity.[13] The IPAQ is a self-reported questionnaire designed to measure sedentary hours, sleep time, and the amount and intensity of physical activity during work and holidays for individuals aged between 15 and 69 years.[13] Our patients completed the Persian version of IPAQ, validated by Vasheghani-Farahani et al[14] in 2011.

The Hospital Anxiety Scale (HAS) was utilized to evaluate patients' anxiety levels.[15] HAS is a subset of the Hospital Anxiety and Depression Scale (HADS), which assesses anxiety and depression in medical patients. Developed in 1983, HADS consists of 14 questions, 7 addressing anxiety and 7 focusing on depression symptoms; each domain can be administered independently. Each question examines a specific anxiety or depression symptom, and patients respond using a 4-point scale ranging from never, rarely, sometimes, to always.[15] A total score above 7 indicates an anxiety or depression disorder, with scores correlating to the severity; a total score of 8 to 10 suggests a mild disorder, 11 to 14 indicates a moderate disorder, and 15 to 21 represents a severe disorder.[16] To assess the extent of anxiety in our patients, we used the anxiety subset of questions, which Montazeri et al[17] validated in 2003 with a Cronbach's α coefficient of 0.78 for the HADS anxiety domain.

The relationships between LDL-C levels and Dutch scores and age, body mass index (BMI), and physical activity components were also explored.

IBM SPSS Statistics for Windows (Version 26.0, IBM Corp, Armonk, NY, USA) was employed for data analysis. Quantitative and qualitative ordinal variables were expressed as mean±standard deviation (SD) and percentage, respectively. The one-sample Kolmogorov-Smirnov test assessed the normal distribution of variables. The Pearson and Spearman correlation tests investigated correlations between patient-related factors, LDL-C, and Dutch scores. Simple linear regression quantified the relationship between LDL-C and BMI, Dutch scores, and physical activity elements. Stepwise (forward) regression removed collinearity between predictor variables. Significance was set at a P value of less than 0.05.

The study protocol was approved by the institutional research ethics committee before study initiation and was registered under the ethical code IR.BMSU.REC.1401.059. Following the research center's internal policies, written informed consent for the anonymous use of epidemiological

data from all referred patients was obtained during their initial visit. The research team explained the study's objectives to the FH cohort, who subsequently signed a separate informed consent for study participation and data publication.

Results

Between 2017 and 2022, a total of 1724 patients were referred to our dyslipidemia clinic, with 44 identified as definite FH patients. Thus, the prevalence of FH among patients referred to our clinic during this period was 2.55%. The age of the total cohort was normally distributed, with a mean of 51.21±13.28 years. In contrast, the FH cohort was significantly younger and left-skewed, with a mean age of 38.84±16.85 years. Serum LDL-C levels in both cohorts were normally distributed, measuring 215.09±29.87 mg/dL and 315.95±81.73 mg/dL in the total and FH cohorts, respectively (Table 1).

The majority of the FH cohort (54.5%) had a Dutch score of 9 or 10. Table 2 displays the frequency of each score within the FH cohort.

The mean BMI of the FH cohort was 27.95±5.51 kg/m², and 18.1% had a smoking history. As mentioned, the physical activities of the FH group were evaluated during work and on holidays. Table 2 summarizes the corresponding values.

Our correlational analysis revealed significant correlations between LDL-C levels and both total sleep duration (correlation coefficient [CC]= -0.40, P=0.00) and BMI (CC= -0.31, P=0.03). Table 2 provides further details on the correlations between LDL-C, the Dutch score, and various aspects of physical activity. Notably, no correlation was observed between age and any physical activity components or LDL-C levels in the FH cohort. Additionally, there was no significant correlation between the Dutch score and patients' LDL-C, BMI, age, or physical activity. Our simple linear regression analysis demonstrated a statistically significant relationship between LDL-C and patient characteristics, including BMI, the Dutch score, and physical activity components (t=3.86, $P<0.000$). These charac-teristics accounted for 40.8% of the explained variability in LDL-C levels among the FH cohort. Our stepwise re-gression identified that only BMI and total sleep hours independently correlated with LDL-C levels ($P<0.05$). De-tailed information on the linear model regression and stepwise regression can be found in the supplementary file. Our anxiety assessment revealed significant anxiety-related features experienced by patients most of the time, with common symptoms including sudden panic attacks, restlessness, and apprehension about the future. Table 3 pro-vides a detailed summary of these results.

Table 1. The baseline characteristics of the total cohort, the FH cohort, and the Dutch score distribution

	FH Cohort (n=44)	Total Cohort (n=1724)
Age	38.84±16.85	51.21±13.28
LDL-C level (mg/dL)	315.95±81.73	215.09±29.87
The Dutch score of the FH cohort	Absolute frequency (%)	N/A
8	6 (13.60)	N/A
9	13 (29.50)	N/A
10	11 (25.0)	N/A
11	8 (18.20)	N/A
12	6 (13.60)	N/A

FH, Familial hypercholesterolemia; LDL-C, Low-density lipoprotein

Table 2. The familial hypercholesterolemia cohort's physical activity and their correlation with LDL-C and the Dutch score of the cohort

Item (unit)	Mean±SD	Correlation with LDL-C	P	Correlation with the Dutch Score	P
Heavy activity at work (min)	42.73±17.30	-0.07	0.63	-0.13	0.38
Moderate activity at work (min)	40.23±17.72	0.23	0.12	0.08	0.58
Walking (min)	35.68±17.97	0.23	0.12	0.01	0.90
Biking (min)	23.64±22.31	0.23	0.11	0.01	0.92
Heavy activity on holidays (min)	35.00±21.62	0.00	0.97	0.00	0.97
Moderate activity on holidays (min)	33.41±21.56	0.20	0.19	-0.21	0.15
Sedentary daily life (h)	3.52±1.92	-0.09	0.55	-0.27	0.07
Total sleep (h)	8.07±0.73	-0.40*	0.00	-0.14	0.35

*Significant correlation
LDL-C, Low-density lipoprotein

Table 3. The patients' anxiety assessment according to the Hospital Anxiety Scale (HAS)

Statements	Frequency			
	Never	Rarely	Sometimes	Always
I feel tense or wound up.	2	2	28	12
I get a sort of frightened feeling as if something awful is about to happen.	8	16	10	10
Worrying thoughts go through my mind.	3	6	13	22
I can sit at ease and feel relaxed.	4	8	14	18
I get a sort of frightened feeling like "butterflies" in my stomach.	4	15	14	11
I feel restless as I have to be on the move.	6	6	22	10
I get sudden feelings of panic.	2	18	10	14

Discussion

This study aimed to explore the demographic and lifestyle characteristics of FH patients referred to a dyslipidemia clinic in Tehran. We identified significant findings regarding the prevalence and association of various lifestyle characteristics, which we discuss below. One significant finding of our study is the higher reported prevalence of FH among our patient population. Although current literature suggests a worldwide FH prevalence of less than 0.4% in the general population,[18] it increases to 7.2% among those with severe hyperlipidemia and 3.2% in patients with cardiovascular diseases.[19, 20]

Importantly, Vaseghi et al[21] reported a high prevalence of FH in a 4-year FH patient registry project in Isfahan, Iran. Among 522 patients with hyperlipidemia, they identified 350 possible, 98 probable, and 75 definite FH cases. The higher reported FH prevalence in our study and the one conducted by Vaseghi and colleagues can be attributed to the focus on dyslipidemia clinics, where FH cases are more likely to be identified and treated.

Another significant finding of our study was the negative correlation between BMI and LDL-C levels in the FH cohort. Moreover, BMI was identified as an independent predictor of LDL-C levels in our final regression model. This finding is in contrast to the results reported by Baila-Rueda et al.[22] In their investigation of cholesterol synthesis among different subtypes of primary hypercholesterolemia, Baila-Rueda and colleagues observed that increased BMI was associated with increased cholesterol synthesis and decreased cholesterol absorption among both FH and non-FH patients, based on attributable markers. However, they found that BMI was an independent factor for cholesterol synthesis and absorption only in non-FH patients. The discrepancy between our findings and those of Baila-Rueda et al may be due to the difference in mean BMI between the 2 studies. In the study by Baila-Rueda and co-workers, the mean BMI of the FH cohort was 24.3±3.5 kg/m², which falls within the normal range, whereas, in our study, the mean BMI of FH patients was 27.95±5.51 kg/m², indicating that our patients were generally overweight. This difference in BMI could potentially explain the contradictory results observed in the 2 studies.

Another noteworthy aspect of our study is the examination of patients' physical activity levels and their association with LDL-C levels, Dutch scores, and overall activity levels. Similar to other studies, our patients generally displayed suboptimal physical activity levels.[23] Additionally, Kuman et al[24] found a direct link between an individual's physical activity and mental health, highlighting the importance of considering both factors for overall well-being.

Remarkably, our study revealed a general correlation between physical activity at work and leisure-time physical activity. Based on these findings, we recommend increasing physical activity in the workplace and incorporating simple exercises into patients' daily routines. This approach may significantly enhance health and disease management, ultimately reducing the risk of cardiovascular events.[25]

A crucial finding in our study is the absence of an association between age and physical activity components or LDL-C levels in the FH cohort. Given the established benefits of physical activity in disease management, this finding underscores the significance of promoting increased physical activity across all age groups, taking individual needs and abilities into account. Previous studies and recommendations have supported this notion as well.[26, 27]

Examining the psychological impact of FH on patients' mental health is another critical aspect of our study, with findings consistent with those of other similar research. Our results demonstrated that patients with FH experienced anxiety disorders and a diminished quality of life due to the chronic nature of the disease, as reported elsewhere.[24, 28] Addressing the adverse psychological effects of FH is essential, as these can pose significant barriers to effective disease management.[29] Therefore, implementing a comprehensive screening process and a stepwise action plan to identify and address psychological issues promptly is crucial.[30]

Although our study provides useful insights into the lifestyle characteristics of FH patients, it has certain limitations. Firstly, the single-center design restricts the generalizability of our findings. Additionally, we could not assess patients' cardiovascular status or follow them to examine short- and long-term cardiovascular event rates. To address these limitations, we strongly recommend that

future studies adopt a multicenter design with short- and long-term follow-up. Such studies should assess the impact of patient-level dietary, mental health, and physical activity modifications on LDL-C levels and cardiovascular event rates to further enhance our understanding of effective FH management strategies.

Conclusion

Examining and characterizing patients' demographic and lifestyle features is a crucial initial step in developing efficient and effective management strategies for chronic conditions like FH. Establishing patient registries for chronic diseases can facilitate a deeper understanding of the target population and empower healthcare providers to develop and implement suitable preventive measures and control strategies.

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