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The Prevalence of Heterozygous Familial Hypercholesterolemia among Premarital Couples in Qalubya Governorate in Egypt

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ABSTRACT

Background: Premarital care is a crucial step in preventing unwanted pregnancies, which in turn protects society and allows people to live their lives to the fullest.

Objective: Our goal was to find married individuals who have heterozygous familial hypercholesterolemia (HeFH).

Subjectives and methods: Six hundred young adults (male and female) with HeFH who were going to get married participated in this cross-sectional research. The following procedures were performed for all patients: comprehensive history taking, clinical data collection, review of family history of coronary artery disease, laboratory testing, and diagnosis of HeFH.

Results: The participants that were studied had an average age of 22 ± 3 years. Of the total, 50% were men and 50% were women (50.0 %). Among those who participated in the survey, 55.7% lived in rural areas, while 44.3% lived in metropolitan areas home. At 167 ± 37 mg/dl, the mean total cholesterol was measured. There was an average of 101 ± 37 mg/dl of triglycerides. There was an average of 94.2 ± 31.1 mg/dl for low-density lipoprotein and 52 ± 11 mg/dl for high-density lipoprotein. There was a prevalence of 0.5% of HeFH observed in three cases.

Conclusions: Among 600 individuals who were contemplating matrimony, 3 (0.5 %) had potential HeFH.

Keywords: Prevalence, Heterozygous familial hypercholesterolemia, Premarital care, coronary artery disease.

INTRODUCTION

An essential stage in safeguarding society and enabling individuals to enjoy life, premarital care entails enhancing the health and wellness of both the lady and her spouse prior to conception. It is viewed as a main preventative strategy for couples preparing to have a family [1].

Midway through 2001, the first pre-marriage screening centre opened its doors to the public in Egypt. The % ages reported by Egyptians over the past four decades vary between 29 and 39 %. Premarital counselling can help identify and avoid hereditary conditions such as hearing loss, mental retardation, autosomal recessive osteoporosis, and blood problems that can occur through interracial marriage [2].

Premature coronary artery disease (CAD) is most often caused by familial hypercholesterolemia (FH), an autosomal dominant disorder in which 50% of a person's children will be born with the illness. The LDLR gene is the most common site for the causing mutations, while the apolipoprotein B and proproteinsubtilisin/kexintype 9 genes are less common (PCSK9) [3]. Also, atherosclerotic coronary disease can be sped up by 10–40 years with FH [4].

Heterozygous FH (HeFH) is a genetic disorder that affects around one in three hundred thousand people. People with this disorder have total cholesterol levels higher than 500 mg/dL and develop extremely early CAD. If left untreated, these people don't make it to adulthood [5]. Factors that contribute to the diagnosis of FH include elevated levels of bad cholesterol low-density lipoprotein-cholesterol (LDL-C), a history of hypercholesterolemia in the family, the presence of early coronary artery disease (CAD), and the development of xanthomas and/or arcus senilis, which are deposits of cholesterol [6].

It is possible to take preventative actions with an early diagnosis. When statins are administered to individuals with FH who do not have a history of CAD, the risk of CAD is lowered by 79%, to a level comparable to the general population. Despite the considerable cardiovascular risk associated with FH, most individuals with FH go undetected and untreated, according to numerous current guidelines for the therapy of FH [7].

Primary care physicians often see patients with mild to moderate FH, but those with severe cases are often referred to lipid clinics or specialists [8]. In addition, treatment is frequently initiated in the latter phases of the illness, when atherosclerosis has progressed due to persistently high levels of LDL-C. Last but not least, there are insufficient screening programs and health care systems do not recognize the problem adequately [9].

An effective family-based cascade screening programme can bridge the gap in FH diagnosis and treatment. As part of this procedure, individuals who are known to have familial hypertension (FH) are tested for the disease in their immediate family members. National initiatives for genetic detection using cascade screening have been undertaken by only a small number of nations [10]. This project's objective was to find heterozygous FH carriers who intended to enter into matrimony.

PATIENTS AND METHODS

Six hundred young adults (males and females) who are preparing to get married participated in this cross-sectional research.

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Inclusion criteria: Anyone from the city of Banha who is young enough to be a student, an independent contractor, or an employee was brought in for premarital testing.

Exclusion criteria: Those who did not meet the requirements for premarital lab testing were not eligible to participate in the study.

Cardiovascular risk factors such as diabetes mellitus (duration, oral hypoglycemic drugs and Insulin), hypertension, dyslipidemia, and current cigarette smoking were included in the comprehensive history that all patients underwent. Additionally, clinical data and family history of coronary artery disease were taken into consideration [Long history of renal illness, including a creatinine level of 2.5 mg or above, or the need for dialysis, laboratory tests (liver enzymes to rule out secondary hypercholesterolemia), fasting blood sugar (FBS), total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), and triglycerides (TGs) and total hormones (TSH, FBS, T3, T4, and FBS)].

Diagnosis of Familial Hypercholesterolemia (FH): In individuals who have not received treatment, the suspicion of FH should be raised if the LDL-C level is above 190 mg/dL, there is a personal or family history of early coronary artery disease, there are physical symptoms such as xanthoma and Xanthelasma, or if there is a known relative with FH [7]. The DLCN score is utilised to ascertain the likelihood of FH, which may be classified as certain, probable and plausible, or improbable.

Ethical approval: The patients signed informed consents for participation. The research proceeded after the Ethical Committee at Banha University and Al-Qadisiya University in Iraq gave their clearance (Approval code: Rc. 7.5.2022) through the period from June 2022 to June 2023. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

To handle and analyse the data, SPSS version 28 was used (IBM, Armonk, New York, United States). Means and standard deviations were used to summarise the quantitative data. Numbers and % of ages were used to summarise the categorical data. The Student t test was utilized to compare parametric quantitative variables between the two groups. A significance level of $P \leq 0.05$ was considered significant.

RESULTS

The participants that were studied had an average age of 22 ± 3 years. Of the total, 50% were men and 50% were women. Among those who participated in the survey, 55.7% lived in rural areas, while 44.3% lived in metropolitan areas home (Table 1).

Table (1): Demographic characteristics of the studied individuals

Age (years)		22 ±3
Gender	Males	300 (50.0%)
	Females	300 (50.0%)
Residence	Rural	334 (55.7%)
	Urban	266 (44.3%)

Data are presented as mean ± SD and number (%)

The mean total cholesterol level was 167 ± 37 mg/dl. The mean triglyceride was 101 ± 37 mg/dl. The means of LDL and HDL were 94.2 ± 31.1 and 52 ± 11 mg/dl respectively (Table 2).

Table (2): Lipid profile of the studied individuals

	Mean ±SD
Total cholesterol (mg/dl)	167 ±37
Triglycerides (mg/dl)	101 ±7
LDL (mg/dl)	94.2 ±3.1
HDL (mg/dl)	52 ±1

Data are presented as mean ± SD. LDL: Low density lipoprotein; HDL: High density lipoprotein.

The frequency of heterozygous FH was 0.5 %, and three individuals were found to have it (Table 3).

Table (3): Prevalence of HeFH in the studied patients

	n (%)
HeFH	3 (0.5%)

Data are presented as mean SD and number (%). HeFH: Heterozygous Familial Hypercholesterolemia

DISCUSSION

Originally, 1 in 500 people were found to be heterozygous FH (0.2 %). This estimation is predicated on research that computed the frequency in heterozygotes using Hardy-Weinberg principles and established the prevalence in homozygous individuals. Subsequent investigations of samples drawn from the general population have showed similar frequency distributions. Nevertheless, there have been new criticisms of the estimate about its lack of accuracy [11].

A total of 600 participants were included in the current study, with an average age of 22 ± 3 years. Of the total, 50% were men and 50% were women. Among those who participated in the survey, 55.7% lived in rural areas, while 44.3% lived in metropolitan areas home.

The average total cholesterol level in this research was 167 ± 37 mg/dl. There was an average of 101 ± 37 mg/dl of triglycerides. An average of 94.2 ± 31.1 mg/dl was found for LDL and 52 ± 11 mg/dl for HDL. In their study, **Reda *et al.*** [12] found that the average initial values of total cholesterol, triglycerides, LDL-C, and HDL-C were 339 ± 100, 217 ± 137, 249 ± 98, and 46 ± 15 mg/dl respectively. **Bogsrud *et al.*** [13] found that out of 41 patients, 11 had a positive FH genetic test (FH1) and 41 had a negative one (FH2). In contrast to triglyceride levels, which were much lower

in FH1 individuals, TC and LDL-C levels were substantially greater. Approximately 28.5 million individuals, or 11.7% of the adult U.S. population, have total cholesterol levels that are too high (240 mg/dL, or 6.2 mmol/L) [14].

Monogenic FH is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), as demonstrated by **Humphries *et al.*** [15]. Interestingly, impacted persons were more likely to have CAD if they possessed a mutation in either the LDL - R gene (odds ratio of 1.8), the ApoB gene (odds ratio of 3.4), or the PCSK9 gene (19.9).

In this study, heterozygous FH was reported in three patients, with a prevalence of 0.5%. A meta-analysis by **Akioyamen *et al.*** [11] of 19 cohort studies including 2,458,456 persons revealed a 0.40 % prevalence of FH in the whole population. This indicates that around 1 in 250 persons (95 % CI: 1 in 345 to 1 in 192) may be susceptible to FH, which equates to approximately 30 million people globally [16]. This finding adds credence to the widespread belief that FH is underdiagnosed and, consequently, undertreated, as it is more common than in previous publications [17]. Results from 62 studies involving over 7.3 million people showed that the overall prevalence of FH among the general population (GP) was 1:311 (0.32 %), according to **Hu *et al.*** [18] who aimed to provide a more comprehensive assessment and more reliable estimation of the prevalence of FH than hitherto possible in both the GP and patients with ASCVD. As per the findings of **Meshkov *et al.*** [19] they set out to examine the frequency of HeFH in eleven distinct Russian areas. The researchers found that 1/477 individuals had genetically verified HeFH.

The study by **Al-Laho *et al.*** [20] found that out of all the patients categorized as having probable FH (scoring 6-7), potential FH (score 3-5), or improbable FH (score < 3), 2.5 % had definite FH, 10 % probable, 30 % possible, and 57.5 % unlikely. One in two hundred fifty cases of FH, whether considered likely, probable, or certain, is predicted to be 0.4 %. Nine examples of phenotypic FH (DLCNC score >5) were found in a single medical practice with 12,100 recorded patients **by Grey *et al.*** [21]. **Troeung *et al.*** [22] found 32 patients out of 3,708 active patients who were at risk of FH (DLCNC score >5) using a SQL-based electronic screening program (TARB-Ex). Following a follow-up clinical evaluation by a qualified FH nurse, **Kirke *et al.*** [23] found 32 patients with phenotypic FH (DLCNC score >5) using data extraction software (Canning Tool) to search 41,100 electronic health records (EHRs) in 2 regional practices.

The total frequency of FH in the general population was estimated to be 1:303 by **Toft-Nielsen *et al.*** [24]. This is very consistent with more recent estimates given in more extensive research of 1:313 [25] and 1:311 [18]. The observed prevalence rates varied among ethnicities, with some ethnic groups having a greater risk of FH (pooled prevalence: 0.25 %; 1 in 400; 1.52 %; 1 in 192). The prevalence increased from Asian to white to brown to black, indicating that prevalence vary among ethnicities [24]. The DLCN algorithm identified a prevalence of definite/probable HeFH at 4.8% and potential HeFH at 47.1% among 1451 patients who presented with premature ACS (males younger than 55 years and females younger than 60 years) [26]. A frequency of 1.3 % for DNA-confirmed FH was reported by **Wald *et al.*** [27] in 231 individuals with AMI younger than 50 years.

Bogsrud *et al.* [13] documented that, among the 130 patients, one-fifth were 45 years old and had acute MI and LDL-C values. At a concentration of 4.0 mmol/L (155 mg/dL), genetic testing was performed on 52 subjects. FH was genetically confirmed in eleven individuals, representing a frequency of 21.2% among those tested, 8.4% among those with a reason for testing, and 3.4% among young patients with MI. It is possible that a few of the untested patients also have FH. Consequently, the actual frequency of FH is probably more than 8.4% and 3.4%. In any case, it is evident that the incidence of FH in young patients who have suffered a MI is significantly greater than the predicted 0.3 to 0.5 % in the overall population.

The frequency of genetically confirmed FH among 103 patients with ACS who were 65 years old and had LDL-C values of 1, 1 mmol/L (160 mg/dL) as examined by **Amor-Salamanca *et al.*** [28]. The prevalence of FH was determined to be 8.7 % (9 of 103 patients). The incidence of clinical FH in patients with MI has been the subject of several investigations, with prevalence estimates for probable and/or definite FH ranging from 2.0 to 20.3% [29, 30]. The youngest patients were also included in one of these investigations with the greatest frequency as conducted by **Rallidis *et al.*** [31].

All three patients in our research had normal fasting blood sugar, thyroid function, renal function, and liver enzymes; each patient had a DLCN score of 3. (Possible FH). The criteria that were most employed were DLCN and genetic test [18]. The CGP Study found that the frequency of certain or probable FH was 1/218 [32]. According to the findings of the MONICA and MONALISA investigations, the prevalence of certain or likely HeFH was 1/117 (0.95% CI: 0.63–1.06) [33]. The HAPIEE Study found that out of 183 participants, 0.55% (95 % CI: 0.39-0.69) had FH [18]. **Reda *et al.*** [12] found that between August 2017 and September 2018, a total of 49 cases with FH were recorded, with 33 % being men and the mean age being 45 ±15 years. There was a median of 8 years (range 1–20) between diagnosis and enrollment. With 31% in the sure, 12% in the almost sure, and 57% in the may be category, all patients were evaluated using Dutch Lipid Network criteria. Considering that our sample was relatively young (45 years old), all patients were given 2 points on the DLCN score upon inclusion, and **Bogsrud *et al.*** [13] found that 14.6% of patients had "definite FH" or "possible FH" based on the score (2 points for premature CAD in men,

55 years and in women, 60 years). Primary care intervention produced negligible and non-significant decreases in total cholesterol (-2%) and LDL-cholesterol (-3%) in a cohort of 32 individuals who had been diagnosed with probable FH, according to a research by **Weng *et al.* [34].** Among the three patients, one was a 26-year-old woman with a 120/80 BP, 62 kg Bw, 178 cm Ht, 19.6 kg BMI, and 96 bpm pulse rate. The other two were men, 24 and 23 years old, with 110/70 BP, 65 kg Bw, 172 cm Ht, 22 kg BMI & 72 bpm pulse rate, and 120/80 BP, 135 kg Ht, 43.6 kg BMI, and 80 bpm pulse rate respectively.

The patient in the case study by **Yuan *et al.* [35]** had an acute myocardial infarction (MI) when he was 33 years old. Two and a half months following his MI, his blood TC and LDL-C values were 5.36 and 3.76 mmol/L respectively. Nine months later, they were 4.23 and 2.90 mmol/L, respectively. At 9 months, atorvastatin was replaced with 40 mg of rosuvastatin. His TC and LDL-C values were 4.05 and 2.50 mmol/L respectively, at 12 months post-MI (i.e., 3 months later). At 15 months, they were 4.28 and 2.46 mmol/L, respectively. Physical examination results showed that he was 110 kg, 192 cm tall, 30 kg/m^2 obese, and 120/80 mm Hg blood pressure. Molecular evidence for the clinical diagnosis of HeFH was supplied by the fact that no additional mutations were detected, confirming that the patient was a simple heterozygote.

Limitations: Small sample size because of time and financial constraints.

RECOMMENDATIONS

Additional research is required in other centres around the nation. Considering the severe form of the disease, Hepatocellular Haemorrhagic Fever (HoFH), which is characterised by therapy resistance, catastrophic cardiovascular consequences, and a substantial financial burden on the Ministry of Health (MOH) budget, it is critical to incorporate LDL-c into premarital tests in order to identify couples who are both HeFH and at risk of having a HoFH child (international experts are in agreement on this point). As they are the premarital couples of tomorrow, it is essential to initiate the pediatric FH screening programme at an age recognised by the paediatric panel in order to identify children early and treat them appropriately in accordance with established criteria (Launched in Egypt by an order from the president on October 2022, after printing the draft).

CONCLUSIONS

Among 600 individuals who were contemplating matrimony, 3 (or 0.5 %) had potential HeFH.

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- **Conflict of Interest:** Nil.

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