# Familial Hypercholesterolemia in Kuwait

committee members:

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**Key words:**

| | |
|---|---|
| **CVD** | Cardiovascular Disease |
| **FH** | Familial Hypercholesterolaemia |
| **DFH** | Definite familial hypercholesterolaemia |
| **DLCNC** | Dutch Lipid Clinic Network Criteria |
| **LDL-C** | Low Density Lipoprotein Cholesterol |
| **LDLR** | Low Density Lipoprotein Receptor |
| **PFH** | Probable Familial Hypercholesterolaemia |
| **CS** | Cascade Screening |
| **FHR** | Familial Hypercholesterolaemia registry |

BACKGROUND:

Cardiovascular disease (CVD) is the leading cause of death in the Western world. Atherosclerosis is the most common pathological vascular change underlying CVD. Hypercholesterolemia has been known as a major risk factor for the development of atherosclerosis and CVD. Heterozygous familial hypercholesterolemia (hFH) is a common autosomal dominant disease with a prevalence of 1:500 in the general population. hFH is caused by mutations in the low-density lipoprotein (LDL) receptor gene (LDL-R) or apolipoprotein B-100 (ApoB) gene or LDLRAP1 genes resulting in vey high blood cholesterol levels and premature CVD. The hFH is clinically characterized by early arcus cornealis and tendon xanthomata. The phenotypic presentation of hFH is relatively homogeneous. The Simon Broome or the Dutch Lipid Clinic Network FH register criteria are used to classify patients into definite, probable, or possible hFH groups (table1, 2). In contrast to many other genetic diseases, treatment in the form of lifestyle management and lipid lowering medications (eg. statin) are highly effective in preventing premature CVD in these individuals. The treatment is highly cost effective-identifying 3 hFH prevents one premature myocardial infarction. Approximately 13 million people worldwide. Employing the Dutch Lipid Clinic Network criteria (DLCN) criteria and applying it on a randomly selected sample of Kuwaiti population, we estimated the prevalence of heFH to be 1 in 250 or 0.4%. Our prevalence is higher than the commonly reported prevalence of heFH (1 in 500), which was most likely estimated based on statistics from Western societies. The current population of Kuwaitis is 1,370,013. According to our findings, the number of patients with heFH in Kuwait is approximately 5480.

Several studies were done that estimated FH prevalence, mostly in Europe and US. Our study concurs with a systematic review and a meta-analysis that pooled prevalence of FH from 19 studies including 2,458,456 individuals. Their pooled prevalence was 0.40% (95% CI 0.29% to 0.52%) which corresponds to a frequency of 1 in 250 individuals.[6] Moreover, our prevalence also agrees with the United States National Health and Nutrition Examination Survey, which showed that the FH prevalence in the U.S. was 1 in 250. Hence, most population studies estimated higher

prevalence of FH in populations than suggested earlier. Despite an international effort to improve the identification and management of patients with FH [7],[9], few countries have established large-scale programs to systematically determine the FH status of relatives of these patients [13],[14],[15],[16],[17],[18],[19],[20],[21].

Although about as common as type 1 diabetes mellitus, the current lack of recognition implies that both lay people and health professionals lack awareness of the hFH, its diagnostic features and consequences. Framingham-based cardiovascular risk assessment should exclude individuals with extreme hypercholesterolaemia but health professionals still, sometimes falsely, reassure hFH patients that they are of low global cardiovascular risk. Despite lack of awareness, there is no doubt that hFH can be hard to recognise for a number of reasons. Physical signs may be absent and sometimes there is no background family history of CHD. This usually means that affected relatives are female and have escaped events. Exercise electrocardiography can be less reliable despite the fact that surprisingly severe coronary atheroma, affecting all three vessels, is often present. In addition, laboratory confirmation is not always straightforward (7). Only around 25% of hFH patients are currently diagnosed and treated adequately and the majority remain untreated or improperly treated (2). Therefore, it is worthwhile to identify the subjects with hFH to confirm and to treat them appropriately.

**Our main mission** is to identify patients with hFH in order to identify their affected relatives. The cascade screening includes the first, second and third-degree relatives. **The ultimate goal** of this project is to reduce morbidity and mortality from heart disease in persons with hFH through early diagnosis and effective disease management. In addition, cascade screening has been shown to be a cost-effective method of identifying people with FH [3],[11],[12].

OBJECTIVES:

1. Using the Dutch database (reference), we will identify patients with hFH (definite, probable by Simon Broome or the Dutch Lipid Clinic Network FH register criteria) using hospitals laboratory database to establish their hFH status
2. Using the Dutch database (reference), we will screen 1°- 3° relatives of hFH patients (definite, probable by Simon Broome or the Dutch Lipid Clinic Network FH register criteria) to establish their hFH status (positive, negative, unknown) and their current management.

SPECIFIC AIMS:

1. To review charts of patients diagnosed with hFH in the hospitals and establish the diagnosis by the Broome and the Dutch Lipid Clinic Network category.
2. We are going to create a web site showing facts about hFH; this site may also serve as a self-referral system.

Roles of the committee:

1. Review of the subjects data
2. Identification number of patients who are known to have the disease and treated adequately
3. Identification number of relatives who are known to have the disease and treated adequately and number of relatives who are not known to have the disease or not diagnosed or not treated adequately.
4. Creation of web site showing facts about hFH

SIGNIFICANCE:

The goal of our committee is to reduce cardiovascular morbidity and mortality in persons with hFH through early diagnosis and effective management. We will also educate and increase awareness of hFH in both patient population and physicians dealing it.

1. It has shown that cascade screening reduces the average age at which FH patients are diagnosed [3].
2. Cascade screening has also resulted in increased percentages of people with FH on statins and has, subsequently, resulted in decreased lipid levels in these people [3],[27],[30].
3. Statin use has been shown to reduce both total cholesterol and LDL cholesterol in adults with FH; and early detection and treatment with statins have been shown to reduce morbidity and mortality among those with heterozygous FH [3],[4],[11].
4. Statin treatment has been shown to decrease total and LDL cholesterol concentrations in children with FH [3],[33],[34],[35],[36],[37],[38]. However, there is no evidence of the long-term health benefits of statin treatment in children with FH (such as delayed onset of, or reduced risk for, CHD), nor evidence of any benefits compared to the detection and treatment of the disorder in adulthood [35],[39]. Nevertheless, there are studies that support cholesterol lowering in children based on surrogate markers of cardiovascular disease [such as carotid intima-media thickness (IMT)] [40],[41],[42],[43], some of which note a significant deviation in carotid IMT from the age of 12 years in children with FH (compared to unaffected siblings) [42]. Increased carotid IMT is reversible by statins, though we lack information regarding when such changes become irreversible.

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**the Dutch lipid Network criteria**

| | Score |
|---|---|
| **Family History** | |
| First degree relative with known premature coronary and vascular disease (Men < 55 years, Females < 60 years),<br>OR<br>First degree relative with known LDL cholesterol above the 95th percentile for to age and sex. | 1 |
| First degree relative with tendinous xanthomata and/or arcus cornealis,<br>OR<br>Children aged less than 18 years with LDL cholesterol above the 95th percentile for age and sex (See Figure 10 for LDL percentiles) | 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 age 45 years | 4 |
| LDL cholesterol (mmol/L) | |
| LDL-C ≥ 8.5 | 8 |
| LDL-C 6.5-8.4 | 5 |
| LDL-C 5.0-6.4 | 3 |
| LDL-C 4.0-4.9 | 1 |
| DNA analysis - Functional mutation in the *LDLR*, *APOB* or *PCSK9* gene | 8 |
| **STRATIFICATION** | **Total Score** |
| Definite FH | ≥8 |
| Probable FH | 6-7 |
| Possible FH | 3-5 |
| Unlikely FH | <3 |

## Simon Broome criteria

| Definite FH | Possible FH |
|---|---|
| Cholesterol >6.7 mmol/L (LDL >4.0 mmol/L) in children under 16 **or** >7.5 mmol/L (LDL >4.9 mmol/L) in adults | |
| **Plus either**<br>Tendon xanthomata in patient or 1st or 2nd degree relative | **Plus either**<br>Family history of myocardial infarction <50 years in 2nd degree relative or <60 years in 1st degree relative |
| **Or**<br>DNA confirmation | **Or**<br>Family history or cholesterol >7.5 mmol/L in 1st or 2nd degree relative |

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