

Familial hypercholesterolaemia reduces the quality of life of patients not reaching treatment targets

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ABSTRACT

INTRODUCTION: Familial hypercholesterolaemia (FH) is the most common monogenic disorder associated with premature cardiovascular disease. If untreated, life expectancy in heterozygous FH patients is shortened by 20-30 years compared with the general population. Nevertheless, treatment goals are only met in approximately 50% of patients. This comparative study examined the quality of life (QoL) impact of FH in patients who had and had not reached the target of treatment.

METHODS: Two qualitative focus group interviews were carried out with a total of ten FH patients. A semi-structured interview guide included questions identified in a preceding literature study. The data were analysed using a medical anthropological approach.

RESULTS: While having FH did not have much impact on well-treated patients' QoL, patients who had not reached the treatment target had markedly more concerns. They had experienced severe side-effects and worried about their own and their relatives' health. They were concerned about the long-term impact of not being effectively treated including the risk that coronary heart disease could cause their premature death or disability and inability to care for their children, in particular. The women had issues with stigma and self-efficacy.

CONCLUSIONS: The QoL impact of FH is related to treatment efficacy. These findings need to be addressed in the management of FH patients. Particular attention should be paid to those who are not presently reaching the target of treatment.

FUNDING: The study was funded by a research grant from Amgen.

TRIAL REGISTRATION: not relevant.

Familial hypercholesterolaemia (FH) is a genetic condition most often caused by mutations in the low-density lipoprotein (LDL) receptor. This results in increased levels of plasma LDL cholesterol which predisposes to atherosclerotic cardiovascular disease (CVD). If untreated, the life expectancy in heterozygous FH patients is shortened by 20-30 years compared with that of the general population [1]. Around 50% of untreated 50-year-old men and 30% of untreated 60-year-old women develop coronary heart disease [2]. Recently, the prevalence of FH has been estimated at 1:225 (0.4%)

[3]. The autosomal dominant inheritance of FH implies that 50% of first-degree relatives of FH patients may have FH. Early detection of affected relatives allows for initiation of treatment and hence reduction or even elimination of the risk of CVD. In Denmark, it is recommended that adult patients with LDL levels ≥ 5 mmol/l and children below the age of 16 years with LDL levels ≥ 4 mmol/l are referred to a lipid clinic for further examination, specialist treatment and family screening for identification of affected relatives. Work-up for the FH diagnosis is also recommended in patients with premature arcus cornea, xanthoma tendinosum and with a family history of premature CVD [3-7]. Yet, only a small fraction of the estimated 10,000-20,000 Danish FH patients have been diagnosed [8].

FH treatment consists of a combination of lifestyle counselling and cholesterol-lowering medication, primarily high-potency statins that may be supplemented with cholesterol absorption-inhibitors [3]. This combination usually reduces LDL levels by 50-70%. Less commonly, anion-exchange inhibitors, nicotinic acid or LDL-apheresis are used. The goal in primary prophylactic treatment is LDL ≤ 3.5 mmol/l in children and < 2.5 mmol/l in adults. However, due to high initial LDL values ($\geq 7-8$ mmol/l) or treatment intolerance, these goals are not reached in approximately 50% of FH patients [2, 5, 8].

A literature study showed that FH patients identified before the presence of manifest CVD mostly regard themselves as healthy and consider FH a manageable condition with no major impact on their health-related quality of life (QoL), i.e. the physical, emotional and social well-being connected with their condition [2, 9-16]. One study showed that receiving the FH diagnosis could cause temporary anxiety [9], but to many the diagnosis came as a relief and brought promise of specialised treatment [2, 9, 11, 13, 15]. Many patients were already aware of having high levels of cholesterol and a family history of CVD [10, 12]. While some patients became distressed when nearing the age of close relatives' premature death [1, 9, 15], they were often more concerned with the risk of CVD in relatives with FH than in themselves. The risk of passing on FH to children was a particularly common concern [2, 9, 10, 13, 15]. Finally, some studies have shown that FH patients believe more in the efficacy of medication than in dietary control to

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Dan Med J
2016;63(5):A5224

reduce their cholesterol levels [15, 16]. Still, many feel they have an obligation to lead a healthy lifestyle [2, 10, 15, 17].

The majority of existing studies assessed the perspective of FH patients receiving successful treatment. However, evidence relating FH patients' QoL to the efficacy of their treatment is limited, and no studies have examined the QoL of the many FH patients who do not reach treatment goals. To bridge this gap, the present study aimed to compare the perspectives of FH patients with different treatment experiences: 1) patients having reached the treatment target, and 2) patients to whom treatment had not yet proved successful. Due to the explorative nature of the study and to generate in-depth insights into the patients' experiences, a qualitative research approach was applied. We thus aimed to enhance our understanding of the possible correlations between efficacy of treatment and QoL and in FH patients.

METHODS

To examine existing knowledge about the QoL impact of FH, a literature search was carried out in Medline, Embase and Psycinfo. Of 112 selected articles, 22 were included in the literature study. The results of the literature study guided the construction of a semi-structured interview guide to be applied in two qualitative focus

group interviews including a total of ten patients. The interview guide began with an enquiry into the participants' conceptualisation of FH, their reactions to the diagnosis and initial treatment expectations. The interviews then focused on the participants' perceptions of the risk and severity of FH and of the means of controlling FH through lifestyle behaviour and medicine. Next, their experiences with medical treatment were discussed. Finally, the patients were asked about any physical, emotional, relational, social or professional QoL impacts that FH may have had on their lives.

With the focus groups we aimed to create confidential settings in which participants with comparable experiences could openly discuss the QoL impact of having FH. We included 18-72 year-old patients who had confirmed heterozygous FH diagnosis through genetic testing at Rigshospitalet's Centre of Inherited Cardiovascular Disease. The participants had been diagnosed for a minimum of one year. They had no significant co-morbidity or history of CVD that might affect their experience with FH. Group A consisted of patients whom the treating specialist considered had reached their treatment target, while group B were patients who had not reached their treatment targets (Table 1).

The focus group interviews were moderated by G Lee Mortensen. They were recorded, transcribed verba-

TABLE 1

Participant characteristics.

Patient	Age, yrs	Time of diagnosis		Treatment, daily	LDL concentration, mmol/l	
		with high cholesterol concentration	FH		at FH diagnosis	at latest control
<i>Group A: patients having reached the treatment goal</i>						
F1A	72	1994	2011	Atorvastatin 40 mg Ezetrol 10 mg	— ^a	2.7
M1A	40	2010	2011	Atorvastatin 80 mg Ezetrol 10 mg	7.8	2.7
M2A	20	2010	2012	Atorvastatin 40 mg	4.1	2.5
M3A	40	2010	2011	Atorvastatin 80 mg	5.9	2.3
M4A	68	1996	2014	Simvastatin 40 mg	— ^b	2.5
<i>Group B: patients having not reached the treatment goal</i>						
F1B	50	1976	2011	Crestor 40 mg	6.6	3.4
F2B	42	2002	2014	Ezetrol 10 mg Crestor 20 mg	6.7	2.9
F3B	63	2009	2011	Zarator 80 mg Ezetrol 10 mg	6.0	3.9
M1B	38	1999	2012	Atorvastatin 80 mg Ezetrol 10 mg	6.8	4.0
M2B	65	2012	2014	Atorvastatin 20 mg	8.7	7.0

F = female; FH = familial hypercholesterolaemia; LDL = low-density lipoprotein; M = male.

a) Unknown, total cholesterol concentration > 10.0 mmol/l. b) Unknown, total cholesterol: 9.6 mmol/l.

tim and analysed using Nvivo (QSR) and a medical anthropological constructivist approach [18, 19]. This approach was used to create clusters of meaning from the diverse participant statements. The approach involves an examination of the terminology used to address the topic and how it is narratively related to other topics. This produced a pattern of the participants' perceptions of FH and its QoL impacts on their everyday lives.

Trial registration: not relevant.

RESULTS

Disease perceptions and quality of life impact of familial hypercholesterolaemia

Prior to the FH diagnosis, all focus group participants knew that high cholesterol levels ran in their families. Many also knew that this was due to FH and told about older relatives with heart attacks at 50-60 years of age. In most cases, this had motivated the participants to be tested for FH. The majority also had at least one sibling and younger relatives with FH, including grown children; others had young children who had not yet been tested. For these reasons and because some participants already took cholesterol-lowering medication, getting a positive FH diagnosis came as no surprise to most. Still, some (M1A and F1B) reacted with shock as their physician had presented the diagnosis with gravity, conveying a high risk of premature death. M1A described this as a "near death experience" with lasting impact on his feeling of robustness.

The participants' perceptions of the risk and severity of FH depended on whether they had reached the treatment target (group A) or not (group B). While group A mostly considered FH a relatively harmless "programming error" – just like myopia – the participants in group B felt at risk of developing CVD and some worried this might kill or disable them at an early age. These concerns also extended to relatives with FH. While parents in group A believed their young children would receive an early diagnosis and effective treatment, parents in group B were more worried about this. Similarly, having a parent who had passed away at age 50-60 years was associated with personal worries to some participants in group B. To them, reaching the age of death of a parent with FH was anticipated with fear of having a heart-attack themselves – surpassing such age was a corresponding relief.

The women in group B and M1A felt that having high cholesterol was stigmatising. To F2B, FH is an "embarrassing condition" that she preferred to conceal to others; F3B described it as "not as posh as other diseases". However, participants in both groups said they always described FH as a hereditary condition to underline that their cholesterol issues were not due to un-



PATIENT QUOTES

Patient quote 1

"I got a really bad case of gout from the pills [statins]. I didn't feel bad before, but I certainly did then. I eventually got another kind of pills and since then I have had no problems. It [his cholesterol level] has not been entirely "knocked down" but I don't plan to do anything about that. I have been through enough experiments, and with the pain it involved – both with the muscular pain and the gout – I'm not going to do anymore of that. I do not want more of the same, or of anything else" (M1B).

Patient quote 2

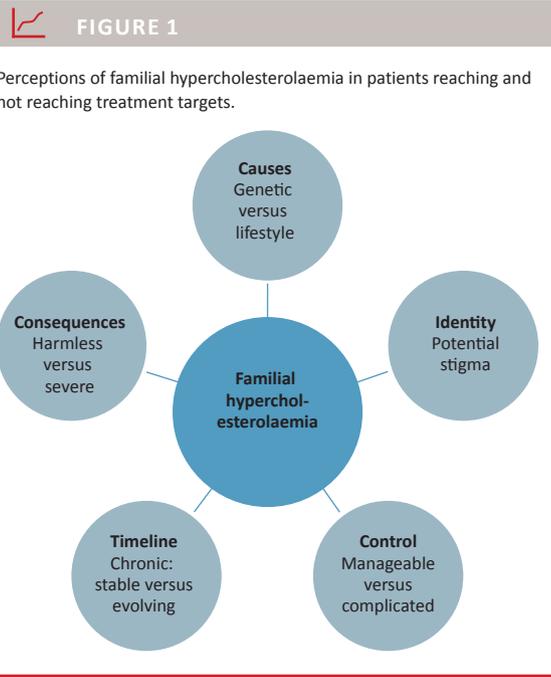
"I cannot say one main area where it [having FH] has affected me most because there are several areas. Feeling guilty about not doing more myself is definitely one. Then there are the worries about my children. I don't mind taking the medication, but I'm afraid that one day, I may develop side effects because I know that many others have severe side effects from what I'm taking. It is the only kind of statins that do not make me nauseous and that make my everyday life liveable. That's why I was extremely alert when I got muscle pain because that "what if" is always present in me. Do I then have to switch to something that makes me nauseous round the clock? ... I guess I have a feeling that one day, this will happen" (F2B).
"If you were to have nausea all the time, what would you choose: to be nauseous and well treated or to not receive treatment? Say it took 40 years before the FH would make you ill ... 40 years of nausea weighed against having a heart attack, well, I'd have my doubts" (M2B).

healthy lifestyle. M1A noted that it was important to his self-perception that FH is a genetic disorder: "I didn't eat myself to this; I'm not to blame". To stress the distinction from other patients with high cholesterol levels, F1A compared FH to having type 1 diabetes as opposed to type 2 diabetes. In general, the women felt more responsible for taking care of their health – and blamed themselves when they did not.

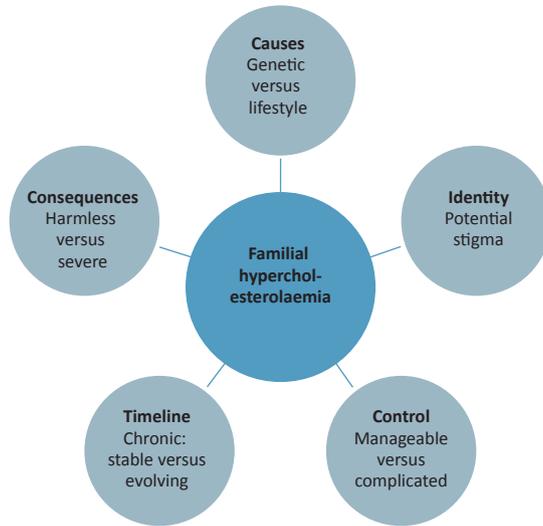
At diagnosis, most participants thought that their cholesterol levels could be sufficiently lowered with medication. Overall, group A had good experiences taking statins, though M3A and M4A presented muscle pain from the old statins. In contrast, realising that medical treatment did not sufficiently lower their cholesterol level had a negative impact on Group B participants' experiences. They had tried several types of medication in order to find an effective treatment without unacceptable side effects. All but M1B had experienced severe cases of flu-like symptoms, muscle aches and fatigue, nausea, flushing or gout in response to treatment.

In group B, four of the five participants said that their main FH-related worries had to do with their medication. M1B preferred having elevated cholesterol levels rather than suffering from severe side effects, as previously (Patient quote 1). F1B and F3B saw the medicine as poison that was detrimental to their health; F2B's greatest concern was to one day run out of effective treatment options that had no side effects (Patient quote 2). Group B thus had less confidence in the ability to medically control FH. Compared with group A, they more frequently attended controls that served as much to monitor possible side-effects as their cholesterol levels.

The participants in group A stated that they were leading healthy lifestyles, but said this was not related to


FIGURE 1

Perceptions of familial hypercholesterolaemia in patients reaching and not reaching treatment targets.



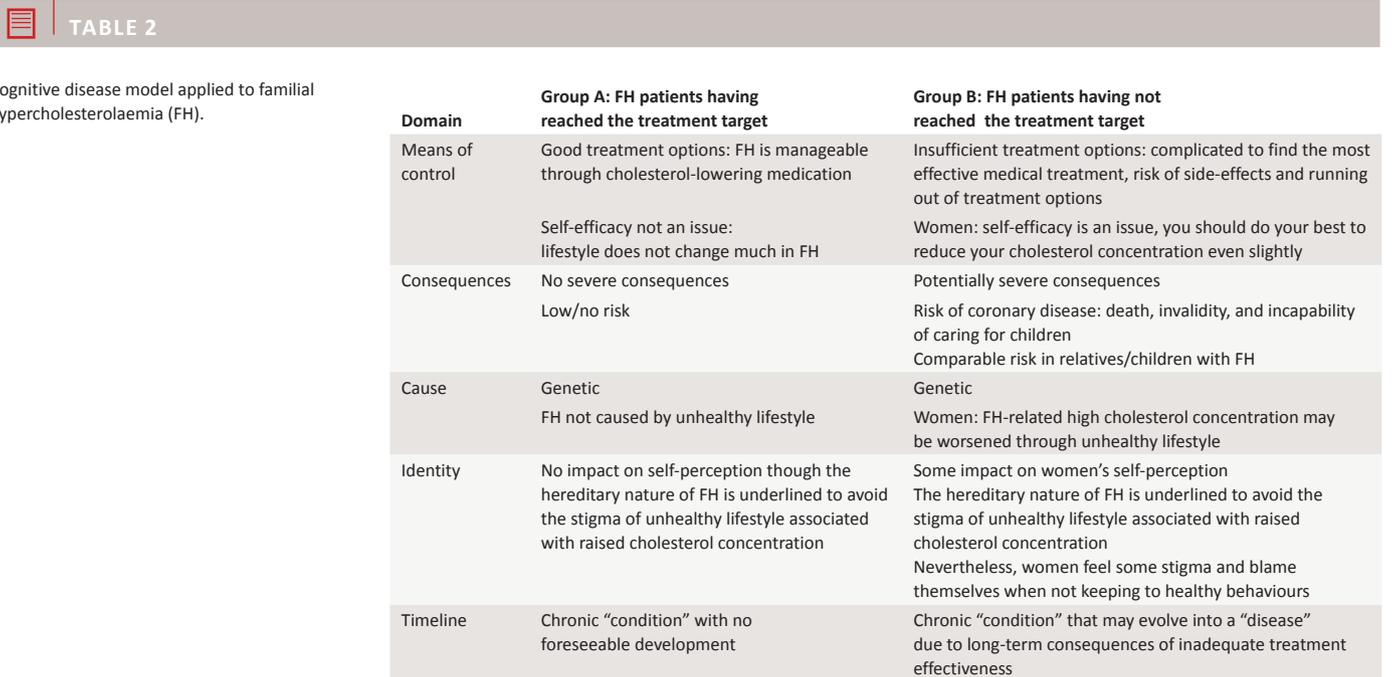
their FH. In contrast, the women in group B felt responsible for also trying to bring down their cholesterol themselves, even though they knew that healthy living may have only a small impact on their cholesterol level. F1B kept to a strict diet, F2B felt guilty for not living healthily enough, and F3B felt stigmatised for not taking better care of herself. Still, most participants in group B

felt that consuming some unhealthy foods was part of their QoL. They did not want their FH to be an issue at social gatherings, but tried to go for the “healthier alternatives” and make up for it by compensating at other times to reach a reasonable result “in the big picture”.

DISCUSSION

Contrary to well-treated FH patients, whose perspectives are also described in the literature, the patients in this study who had not reached the treatment target had sustained FH-related concerns. Their expectations of successful treatment had not been met. The main QoL impact of this was emotional and seen only in the participants in group B who considered FH to be a serious condition entailing the risk of premature death or invalidity. Not being able to care for their children, or that their children should have FH, was particularly distressing. The doctors’ presentation of FH did, however, influence all patients’ perceptions of the risk and severity of the diagnosis.

Apart from treatment-related side-effects, the participants had not suffered physically from their FH. While group A had a high acceptability of cholesterol-lowering medication, group B had more negative experiences with side effects. In addition, the women in group B had issues with stigma and self-efficacy that were related to lifestyle. It was, however, important to all participants to present their high cholesterol as a hereditary disorder, indicating a general perception that cholesterol disease is shameful. They all verbally distanced


TABLE 2

Cognitive disease model applied to familial hypercholesterolaemia (FH).

Domain	Group A: FH patients having reached the treatment target	Group B: FH patients having not reached the treatment target
Means of control	Good treatment options: FH is manageable through cholesterol-lowering medication Self-efficacy not an issue: lifestyle does not change much in FH	Insufficient treatment options: complicated to find the most effective medical treatment, risk of side-effects and running out of treatment options Women: self-efficacy is an issue, you should do your best to reduce your cholesterol concentration even slightly
Consequences	No severe consequences Low/no risk	Potentially severe consequences Risk of coronary disease: death, invalidity, and incapability of caring for children Comparable risk in relatives/children with FH
Cause	Genetic FH not caused by unhealthy lifestyle	Genetic Women: FH-related high cholesterol concentration may be worsened through unhealthy lifestyle
Identity	No impact on self-perception though the hereditary nature of FH is underlined to avoid the stigma of unhealthy lifestyle associated with raised cholesterol concentration	Some impact on women’s self-perception The hereditary nature of FH is underlined to avoid the stigma of unhealthy lifestyle associated with raised cholesterol concentration Nevertheless, women feel some stigma and blame themselves when not keeping to healthy behaviours
Timeline	Chronic “condition” with no foreseeable development	Chronic “condition” that may evolve into a “disease” due to long-term consequences of inadequate treatment effectiveness

themselves from other patients whose high-cholesterol levels were seen as self-inflicted.

The key differences between FH patients who reach and do not reach treatment targets may be understood using Bishop's cognitive disease model [20]. From a constructivist point of view, disease does not affect patients' QoL in a uniform or objective manner, but rather in relation to how it is construed in the context of personal experiences. According to Bishop's model, patients' perceptions of five core factors has a decisive impact on their disease experiences: 1) the means of controlling the condition, 2) its consequences, including risk and severity, 3) its causes, 4) its impact on identity, and 5) the timeline, i.e. whether its limited, chronic or evolving (Figure 1 and Table 2). We found that the two FH patient groups differed in all these respects, presenting differing disease narratives involving contrasting QoL impacts.

Using qualitative methods allowed us to openly explore patient perspectives on FH. In contrast to quantitative QoL instruments, the focus group interview format meant that FH patients in comparable situations could introduce and discuss topics of relevance and relate them in ways that were meaningful to them. The qualitative approach also carried certain limitations, however. While the approach produced analytically valid results, the limited number of participants does not allow for statistical generalisation. The study may thus benefit from being followed up among a larger sample of patients. It may also have biased the results that group A only had one female participant. Especially, it would be interesting to examine if stigma is a more general issue in well-treated women. Still, this comparative study confirms that FH has no major QoL impact on well-treated patients. More importantly, we have added to the existing body of knowledge by finding that the approximate half of FH patients who do not reach treatment targets may have a markedly poorer QoL. There is a need for improvement in FH treatment modalities to reduce the patient-experienced burden of the disease.

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ACCEPTED: 17 February 2016

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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