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Familial hypercholesterolemia and its manifestations: Practical considerations for general practitioners

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ABSTRACT

Familial hypercholesterolemia (FH) is the most common genetic disorder of lipid metabolism, affecting almost 1 in 250 individuals worldwide. It is usually inherited via the autosomal dominant way and is characterized by aberrantly high total and low-density lipoprotein cholesterol (LDL-C) concentrations from early childhood, predisposing to increased risk of premature atherosclerotic cardiovascular disease (ASCVD), mostly coronary heart disease (CHD). Despite its high prevalence in the general population and the high ASCVD risk, FH is often underdiagnosed and undertreated. Genetic diagnosis is not always necessary, since specific criteria, taking into account the patient's individual and family history, clinical signs and untreated LDL-C concentrations, may be used for prompt diagnosis. Except for CHD, which may be already evident at diagnosis, leading to increased mortality, other non-CHD morbidities, such as stroke, peripheral artery disease, carotid artery stenosis and aortic valve calcification may be also present, substantiating the need for prompt intervention. Statins

constitute the mainstay of treatment both in adults and children >8 years old. In cases of statin intolerance or not achieving the LDL-C target despite maximal tolerated statin dose, ezetimibe and/or proprotein convertase subtilisin-kexin type 9 inhibitors may be used. The advent of the recently approved medications, such as inclisiran and bempedoic acid, either as monotherapy or as add-on-therapy to statins, has further enhanced the therapeutic armamentarium in patients with FH. The purpose of this narrative review is to provide practical considerations regarding the diagnostic and therapeutic approach of patients with FH.

Key words: familial hypercholesterolemia, atherosclerosis; cardiovascular disease, xanthomas, statins, ezetimibe

INTRODUCTION

Familial hypercholesterolemia (FH) is the most common genetic disorder of lipid metabolism, characterized by very high total (TC) and low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations [1, 2]. This chronic exposure to hypercholesterolemia from early childhood predisposes the individual to increased risk for premature cardiovascular disease (CVD), mainly attributed to coronary heart disease (CHD) (hazard ratio [HR], 10.6; 95% confidence interval [CI], 9.8–11.5) [3]. Moreover, increased risk of other non-CHD complications, such as peripheral artery disease (PAD), and aortic valve calcification (AVC) and non-alcoholic fatty liver disease, has been reported in patients with FH [4, 5]. These data necessitate early pharmaceutical intervention, even from childhood, in order to forestall these complications.

The purpose of this article is to provide a brief overview of FH for the general practitioner, focusing on the epidemiology, clinical manifestations and therapeutic management of this common clinical entity.

GENETICS, EPIDEMIOLOGY AND DIAGNOSIS

In the vast majority of cases, FH is a usually a monogenic disease inherited by the autosomal dominant way (although the frequency of detectable mutations is 60%–80%) [6], mainly due to loss-of-function mutations in the LDL-receptor (*LDLR*) gene (90% of detectable cases) or apolipoprotein B (*APOB*) (5%) gene, or gain-of-function of the proprotein convertase subtilisin/kexin type 9 (*PCSK9*) (<1%) gene [1, 2, 6]. Autosomal recessive mutations in the LDLR adaptor protein (*LDLRAP1*) gene have also been reported [1, 2]. No causative mutations may be identified in ≥20% of cases, being diagnosed as FH with clinical criteria. In such cases,

a polygenic type of inheritance may be suspected, which involves multiple small-effect common variants, which raise plasma LDL-C concentrations [6, 7].

The clinical phenotype and the degree of LDL-C elevation seem to be largely dependent on the genetic background of FH and the residual LDLR activity. In particular, *LDLR* mutations are associated with higher LDL-C concentrations compared with pathogenetic variants of the *APOB* or *PCSK9* genes [8]. Of course, the presence of other cholesterol-affecting factors, as well as dietary habits also moderate the magnitude of LDL-C elevation [8].

The estimated prevalence of heterozygous FH (HeFH) is 1:200 to 1:250 individuals worldwide, with LDL-C concentrations ranging between 190 mg/dL (4.9 mmol/l) and 400 mg/dl (10.3 mmol/l). The estimated prevalence of homozygous FH (HoFH) is much lower, ranging from 1:160 000 to 1:300 000 individuals of the general population [1, 2, 6]. According to the European Atherosclerosis Society (EAS) Familial Hypercholesterolaemia Studies Collaboration (FHSC), median LDL-C levels in patients with HeFH are 206.3 mg/dl (5.4 mmol/l) (interquartile range [IQR], 163.4–254.6 mg/dl [4.3–6.7 nmol/l]) [9], whereas the respective values in patients with HoFH according to the HoFH International Clinical Collaborators registry are 558.6 mg/dl (14.7 mmol/l) (IQR, 440.8–699.2 mg/dl [11.6–18.4 mmol/l]) [10].

However, what matters most is that FH is often underdiagnosed. According to the EAS FHSC, a considerable delay in diagnosis is often observed, since the median age at diagnosis is 44.4 (32.5–56.5) years, with 40.2% of participants being <40 years when diagnosed [9]. FH should be highly suspected in cases of LDL-C >190 mg/dl (4.9 mmol/l) in adults and LDL >150 mg/dL (3.9 mmol/l) in children [8]. In any case, secondary causes of hypercholesterolemia, such as hypothyroidism, nephrotic syndrome, cholestasis, pregnancy or medication-induced (i.e., diuretics, β-blockers, corticosteroids), should be initially excluded and treated when feasible [6]. Cascade screening is recommended in adults or cases with 1st degree relative with TC >310 mg/dl (>8 mmol/l) without treatment, premature CHD, or tendon xanthomas [6]. In children, FH diagnosis is set when LDL-C is >160 mg/dl (>4 mmol/l) with positive family history for high cholesterol or premature CVD. The diagnostic cut-off for a child with a parent carrying a known genetic defect is >130 mg/dl (>3.5 mmol/l) [6].

Genetic diagnosis is not available worldwide. Therefore, the diagnosis of FH can be based on a combination of criteria, including LDL-C levels, physical signs and individual or family history of hypercholesterolemia and/or premature atherosclerotic CVD (ASCVD). The most commonly used are the Dutch Lipid Clinic Network (DLCN) criteria, which are in 85% alignment with the genetic diagnosis of the disease [11]. Briefly, these include the presence or

absence of one of the following items: (1) positive family history (LDL-C >95th percentile, premature CVD or tendon xanthomas and/or corneal arcus); (2) individual history of premature CVD; (3) physical examination (tendon xanthomas and/or corneal arcus before the age of 45 years); (4) LDL-C levels without treatment; (v) DNA analysis. Each item contributes with 1–8 points, yielding a "definite" FH diagnosis when >8 points are present, a 'probable' FH diagnosis with 6–8 points and a "possible" FH diagnosis when the patient is in the range of 3–5 points [6].

Interestingly, lipoprotein (a) [Lp(a)] concentrations, which are independently associated with increased risk of CVD, may be also increased in patients with FH, more commonly compared with the general population [12]. In particular, the estimated prevalence of Lp(a) >30 mg/dl (>72 nmol/l) or >50 mg/dl (>120 nmol/l) is 29%–40.7% and 22%–29.4% of HeFH patients [13, 14]. Vice versa, patients with Lp(a) concentrations >30 mg/dl are more likely to be diagnosed with definite/probable FH than those with Lp(a) <30 mg/dl)odds ratio [OR], 2.37; 95% CI, 1.78–3.17] [15]. Increased Lp(a) (>55 mg/dl; >132 nmol/l) independently augments ASCVD in patients with FH [14].

CLINICAL MANIFESTATIONS

Signs

During physical examination of a patient with possible or confirmed diagnosis of FH, the clinician should search for the accumulation of cholesterol at different parts of the human body. Even in apparently healthy individuals, physical examination can lead to the suspicion and/or diagnosis of FH.

During skin examination, the most common findings are xanthomas (tendon or tuberous) and xanthelasmas [16]. Tendon xanthomas are nodules, commonly observed subcutaneously in the Achilles tendon or hands, elbows and knees (Figures 1 and 2). In subjects with HoFH, tendon xanthomas are present earlier in life, while in HeFH these usually appear during adulthood [16]. Their prevalence ranges from 5% to 20%, underscoring the importance of clinical examination in these patients [17–19]. As thickening could be observed in Achilles tendon, ultrasound (>5.8 mm for males, >5.5 mm for females) could be useful to confirm a suspicious palpation [20]. Xanthelasmas are cutaneous yellow, slightly uplifted signs, usually evident on the upper inner part of eyelid. Their prevalence (5%–9%) is less than the one reported for xanthomas [18, 21].

Regarding eye examination, corneal arcus may be found, which is characterized by a differently colored (usually gray) ring around the cornea. FH registries have reported a prevalence of up to 33%. When it is observed in patients <45 years old, further investigation is needed [21, 22].

Long-term complications

Patients, with either HoFH or HeFH are generally free of symptoms, until the development of atherosclerotic process and the presence of one or more of the following clinical manifestations [4]:

Coronary heart disease, atrial fibrillation and heart failure. Globally, CHD is the most common type of atherosclerotic CVD, involving about 17% of FH adults, with premature cases being present also at high rates (11.3%). This prevalence may be even higher (i.e., 23%) in the Japanese population, as reported in the Familial Hypercholesterolemia Expert Forum (FAME) Study [23]. In particular, the adjusted HR for CHD in patients with LDL-C >190 mg/dl (>4.9 mmol/l) compared to individuals with LDL-C <130 mg/dl (3.4 mmol/l) is 5.1 (95% CI, 1.1–21.7) and 3.1 (95% CI, 1.8–5.5) for the age range of 20–29 and 30–39 years, respectively [24]. Except for untreated high LDL-C levels, ageing and male gender are also independent risk factors for CHD in patients with FH [25]. As CHD mortality is high in FH patients (even in those treated with statins), early detection of CHD is of major importance. Therefore, detailed clinical history and clinical examination are mandatory. Electrocardiography (in rest and exercise), as well as echocardiography, have to be performed and, in case of high possibility of CHD, patients should be referred to a specialized cardiology center [26]. The need for early clinical diagnosis is getting increased, as recently data also indicate a 2-fold increased risk of hospitalization for atrial fibrillation or heart failure in FH population than in the general population [27].

Stroke. Stroke may also be a clinical manifestation of FH. Globally, its prevalence in FH population is reported to be 2.1% [25], while a recently published cohort study showed that the risk for stroke/transient ischemic attack is almost seven times higher than in the age- and sex-matched general population [3]. If clinical symptoms occur, brain computerized tomography (CT) and referral to a stroke physician are needed.

Peripheral artery disease (PAD). A recently published meta-analysis, evaluating data from more than 170 000 patients with HeFH, showed that the risk of PAD among this population is

almost 3.5 times higher than in healthy individuals [28]. Hence, the clinical evaluation of FH patients should include questions to assess possible weakness or pain after walking and physical examination to detect coldness in the lower leg or lack of arterial pulses. If any of the previous are observed, ankle-brachial index and ultrasound of the arteries of lower extremities has to be performed [26, 29]. As the probability and severity of PAD increases with age, more caution has to be taken in the elderly population [30].

Carotid artery stenosis (CAS). Patients with FH appear to be at high risk for CAS. In a recently published prospective cohort study, CAS was detected in 32% of the FH population by the use of ultrasound [31]. In the general population, the global prevalence of CAS is lower (1.5%; 95% CI, 1.1–2.1), reaching up to 6.9% (95% CI, 5.2–9.3) in males aged 75–79 years old [32]. In patients experiencing a myocardial infraction episode, carotid intima media thickness was also higher in HeFH population compared to those with mixed hyperlipidemia [33]. Thus, a careful physical examination to exclude the presence of a bruit in carotid artery is of major importance. In case of positive signs, carotid echocardiography may be considered, before referring the patient to magnetic resonance or CT angiography [26]. In case of no clinical signs, further parameters have to be taken into account when considering a patient for ultrasound. For example, women, as well as individuals with monogenic type of FH, are at a higher ASCVD risk compared with men and polygenic type of FH, respectively [34, 35].

Calcium deposition. The development of aortic valve calcification (AVC) is quite common in the FH population due to the increased LDL-C levels. In particular, the reported prevalence of AVC in patients with HoFH may reach up to 100%, whereas it varies between 3% and 61% in those with HeFH [36–38]. As so, coronary artery calcium score could be measured and referral to a cardiologist — especially in homozygous cases — is more than necessary for echocardiographic assessment and, in case of pathological findings, further management/follow-up is recommended [26, 39]. In patients with confirmed AVC, Lp(a) should also be measured, since high levels (>50 mg/dl; 120 mmol/l) may further increase the AVC and ASCVD risk in patients with FH [4, 40].

Aortic disease. In general, a positive association between FH and aortic disease (defined either as aortic stenosis or aortic aneurysm) has been described in the literature. However, studies are limited, are of small sample size and could not confirm causality [41]. The strongest determinants of this association seem to be ageing and higher values of recorded blood pressure

[41, 42]. Therefore, guidelines recommend X-ray and abdominal ultrasound, especially in the elderly FH patients, on this regard [26].

Renal artery disease and chronic kidney disease. Regarding the association between FH and renal artery or chronic kidney disease, a positive correlation has been shown, although data are again limited, mainly emerging from studies with small sample size [4, 41]. Therefore, there is no evidence to support further evaluation of this aspect in FH population, unless other symptoms or risk factors co-exist. However, taking into account the cost-effectiveness of the estimated glomerular filtration rate (eGFR) calculation, this could be used during follow-up visits of FH patients, especially in the elderly.

THERAPEUTIC MANAGEMENT

Dietary and lifestyle measures should be addressed in all patients with FH, but most frequently multidrug treatment will be required to achieve the therapeutic targets of LDL-C. These measures include not only hypolipidemic diet and regular exercise, but also counseling on the importance of not smoking or vaping, as well as maintaining a healthy body weight. Of course, cardiovascular risk factors and comorbidities (e.g. hypertension, diabetes mellitus [DM]) should be treated accordingly.

Statins

Statin therapy is the initial pharmaceutical approach for the management of hypercholesterolemia in FH patients. Indeed, current guidelines recommend treatment with the maximal tolerated dose of a high potency statin [6]. However, the recommended LDL-C levels (i.e., <70 mg/dl [1.8 mmol/l] and <55 mg/dl [1.4 mmol/l] in FH patients without and with established ASCVD, respectively) are commonly not attained with statin monotherapy.

The most fundamental mechanism of statin action is the increased hepatic expression of LDLR. Therefore, homozygous FH patients with null mutations on LDLR gene would not be expected to respond to statin therapy. However, they do respond to statins, but to a lesser extent compared with (double) heterozygous FH patients, as statins appear to exert alternative mechanisms of action, such as very low-density lipoprotein (VLDL) (and subsequently LDL) synthesis reduction [43]. Specifically, a reduction of approximately 20% in LDL-C has been demonstrated in such patients [44].

Based on current guidelines, children with FH should start statin therapy from the age of 8–10 years, initially with low doses and subsequently with higher doses aiming to reach the

recommended LDL-C levels [6]. Statins have proven safety and efficacy in children [45], while evidence suggests a reduced risk of CVD in adulthood in statin-treated FH children [46, 47]. Overall, statins are very safe and are currently used by millions of patients. True statin intolerance, due to transaminase or creatine kinase (CK) elevation and/or myalgias is not frequent [48] and usually patients can tolerate at least a low dose of one or more statins even in alternate days [49]. Before the initiation of a statin, it is prudent to measure baseline transaminase and CK levels; therapy should be withheld in patients with transaminase >3 times the upper limit normal (ULN) or CK >5 ULN. Regarding the increased risk of new-onset DM, this is indeed a consistent, dose-related effect of (mainly potent) statin treatment [50]; however, the absolute cardiovascular risk reduction in high-risk patients clearly outweighs this small increase in the incidence of DM [51].

Ezetimibe

Ezetimibe is the second agent which is used on top of statins in patients with FH if the LDL-C therapeutic goal is not achieved. This drug inhibits the intestinal uptake of dietary and biliary cholesterol, thus reducing the amount of cholesterol which is delivered to the liver. Consequently, hepatic LDLR expression is upregulated, leading to increased clearance of LDL from the circulation. Importantly, the absorption of fat-soluble nutrients is not affected by the administration of ezetimibe. When added to ongoing statin therapy, ezetimibe further reduces LDL-C levels by approximately 21%–27% [52], although its LDL-C lowering capacity is smaller as monotherapy. The complementary mechanisms of action of these drugs probably explain why they work in synergy.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

About eight years ago, a game changer in the pharmacological management of lipid disorders, PCSK9 inhibitors, were added to our therapeutic armamentarium. The monoclonal antibodies alirocumab and evolocumab have been consistently shown to induce robust reductions in LDL-C levels by simultaneously achieving a significant decrease in cardiovascular events [53, 54]. Patients with FH who have very high baseline cholesterol levels very often require these agents to reach LDL-C target levels as they do not attain them with the combination of statin with ezetimibe.

More recently another PCSK9 inhibitor, inclisiran, which is a small interfering RNA, was also approved for patients with HeFH as well as for patients with established ASCVD who do not attain their LDL-C treatment targets with maximally tolerated statin with or without ezetimibe.

Specifically, inclisiran was approved by the EMA in December 2020 and by the FDA in December 2021 [55, 56]. This agent has been found to effectively lower LDL-C levels and has a favorable safety profile [57, 58], whereas a recent analysis of the major inclisiran clinical trials suggests potential benefits for major adverse cardiovascular events reduction [59].

Bembedoic acid

Quite recently, a novel agent which also impedes cholesterol biosynthesis at the liver, bembedoic acid, was approved for the treatment of hypercholesterolemia. This agent inhibits adenosine triphosphate-citrate lyase, i.e., it acts at a previous level in the cascade of cholesterol biosynthesis compared with statins [58, 60]. It is a prodrug for oral administration with intracellular activation, mainly in liver and to a lesser extent kidney cells, being absent from the adipose tissue and muscle cells. Therefore, it lacks the muscle-related side effects of statins [60]. It was recently approved both by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as a lipid-lowering drug in combination with diet, statins or other hypolipidemic drugs in patients with hypercholesterolemia (including FH subjects), mixed dyslipidemia, statin intolerance or contraindication to statins.

Overall, we should aim to achieve each patient's LDL-C treatment target with any of the aforementioned available agents or their combinations, beginning with statin with or without ezetimibe and adding PCSK9 inhibitors accordingly. In very high risk patients, i.e. those with a second ASCVD event within 2 years, a treatment goal of LDL-C <40 mg/dl may be considered [6].

Pharmaceutical options for Lp(a) lowering

As previously mentioned, patients with FH frequently have increased Lp(a) levels; this population has even greater risk for ASCVD. Phase II studies with antisense oligonucleotides and small interfering RNAs targeting apolipoprotein (a) have demonstrated remarkable reductions in Lp(a) levels of up to 80% [61, 62]. Currently, phase III studies with cardiovascular outcomes are ongoing and are eagerly awaited.

Therapeutic options in patients with HoFH

LDL apheresis. LDL-C apheresis should be considered in all patients with HoFH with LDL-C >300 mg/dl (7.76 mmol/l) and started as soon as possible, ideally at the age of three and not later than eight years, depending on appropriate venous access [63]. Limitations of this treatment include variable access, high cost and a time-consuming procedure affecting the

patients' quality of life, while LDL-C levels acutely decrease and then rebound following apheresis [63].

Lomitapide. Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), an enzyme responsible for the synthesis of VLDL in the liver and chylomicrons in the intestine. This agent has been approved by the FDA and EMA for the treatment of hypercholesterolemia in adult patients with HoFH. Lomitapide reduces LDL-C levels by around 40% in these patients on top of statin treatment with or without LDL apheresis. It has an acceptable safety and tolerance profile, with gastrointestinal symptoms being the most frequent adverse events, which, however, decrease in frequency with long-term treatment (58, 64). Of note, an increase in liver fat may occur with lomitapide therapy; therefore, screening for liver steatosis, steatohepatitis and fibrosis should take place before treatment initiation (58, 64).

Angiopoietin-like protein 3 (ANGPTL3) inhibitors. The ANGPTLs are a family of proteins consisting of members 1–8 of the angiopoietins. ANGPTL3, ANGPTL4 and ANGPTL8 are essential for the metabolism of triglyceride-rich lipoproteins, i.e., chylomicrons and VLDL, as they inhibit the activity of lipoprotein lipase (LPL) [65]. ANGPTL3 also reduces the activity of endothelial lipase, which hydrolyzes the phospholipids of high-density lipoproteins [66]. The inhibition of ANGPTL3 is a novel therapeutic option for the reduction of both LDL-C and triglyceride reduction. Evinacumab, a fully monoclonal human antibody, has been shown to induce reductions of >50% in LDL-C with a favorable safety profile [58, 67] and was approved by the FDA and the EMA in 2021 for the treatment of patients ≥12 years with HoFH [68]. Studies with small interfering RNAs targeting ANGPTL3 are also under way.

The aforementioned treatments are usually provided by specialized centers for FH with experience on their use.

The LDL-C lowering capacity of the aforementioned treatment options are summarized in Table 1.

CONCLUSIONS — PRACTICAL CONSIDERATIONS

FH is the most common genetic disorder which, however, is worldwide underrecognized and undertreated. Patients with FH are at increased risk for premature ASCVD; therefore, timely treatment initiation is of major importance. Physicians should always suspect FH in patients with very high LDL-C levels. In such cases, a careful family history and physical examination are often adequate for diagnosis. In less clear cases, genetic testing may be required. Cascade screening is very important to detect as many individuals with FH as possible and treat them

accordingly. Potent statins usually combined with ezetimibe are the cornerstone of treatment. PCSK9 inhibitors are frequently also required for the achievement of therapeutic targets. Patients with HoFH should better be referred to specialized lipid clinics for treatment and follow-up.

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Drug Class		**Compound**	**LDL-C reduction**
Statins	Low potency	Lovastatin (20–40 mg)	24%–27%
		Pravastatin (10–40 mg)	20%–29%
		Pitavastatin (1–4 mg)	33%–46%
		Fluvastatin (80 mg)	33%
		Simvastatin (10–80 mg)	28%–47%
		Rosuvastatin (5–40 mg)	45%–63%

High potency	Atorvastatin (10–80 mg)	37%–50%
Intestinal Cholesterol Absorption Inhibitor	Ezetimibe	18%–20% as monotherapy +21%–27% of statin-achieved reduction
PCSK9 inhibitors		
Monoclonal antibodies	Evolocumab Alirocumab	55%–75% 46%–63%
siRNAs	Inclisiran	40%–51%
ACL blocker	Bempedoic Acid	22%
MTP Inhibitor	Lomitapide	40%
ANGPTL3 inhibitors	Evinacumab	47%
ASO against apolipoprotein (a)	Pelacarsen	35%–80% reduction in Lp(a)

Table 1. Low-density lipoprotein cholesterol lowering capacity of currently available lipid lowering agents and drugs under development

Abbreviations: ACL, adenosine triphosphate-citrate lyase; ANGPTL3, angiopoietin like protein 3; ASO, antisense oligonucleotide; LDL-C, low density lipoprotein cholesterol; Lp(a), lipoprotein (a); MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA

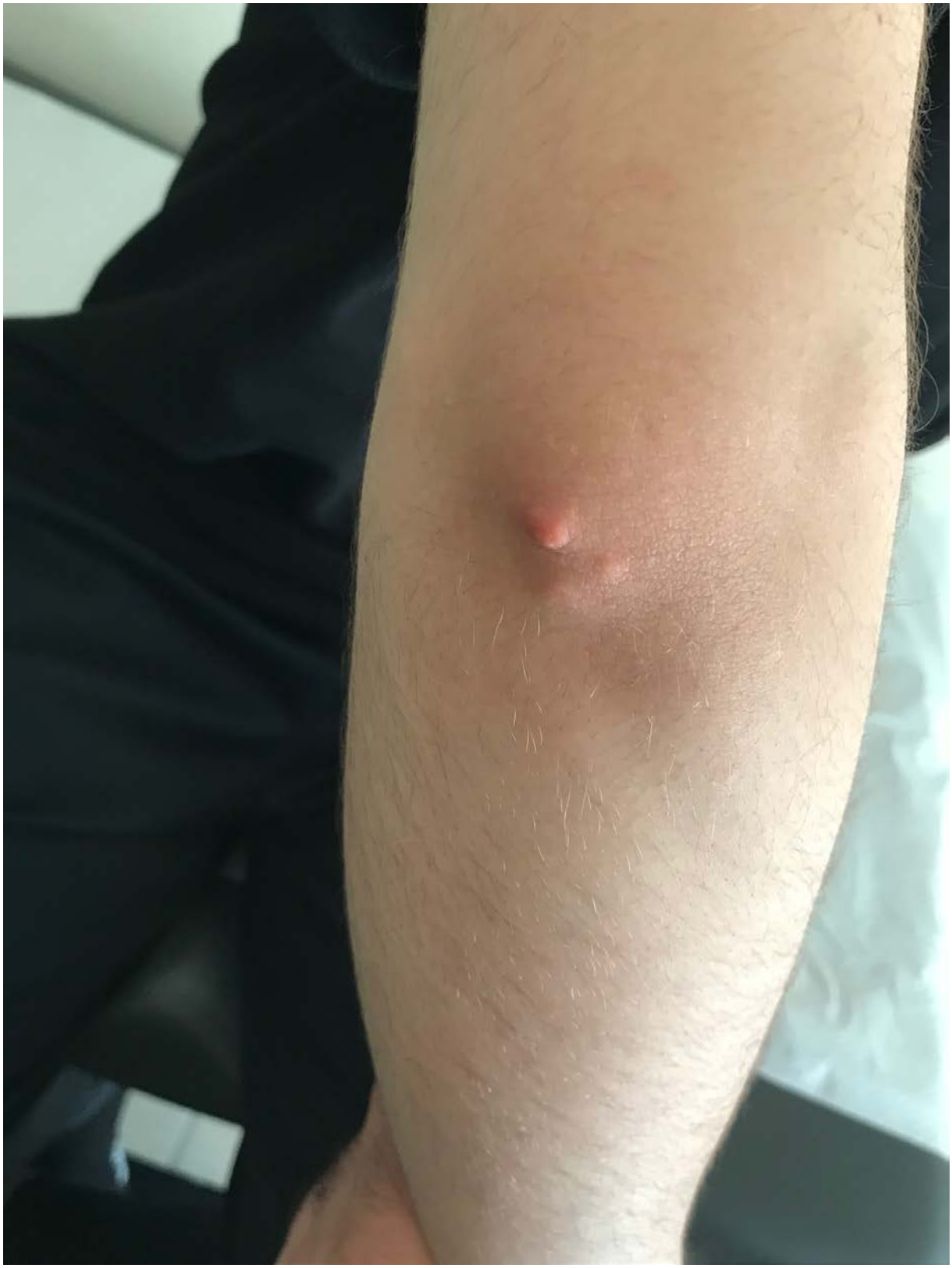

Figure 1. Tendon xanthoma of the elbow in a patient with familial hypercholesterolemia

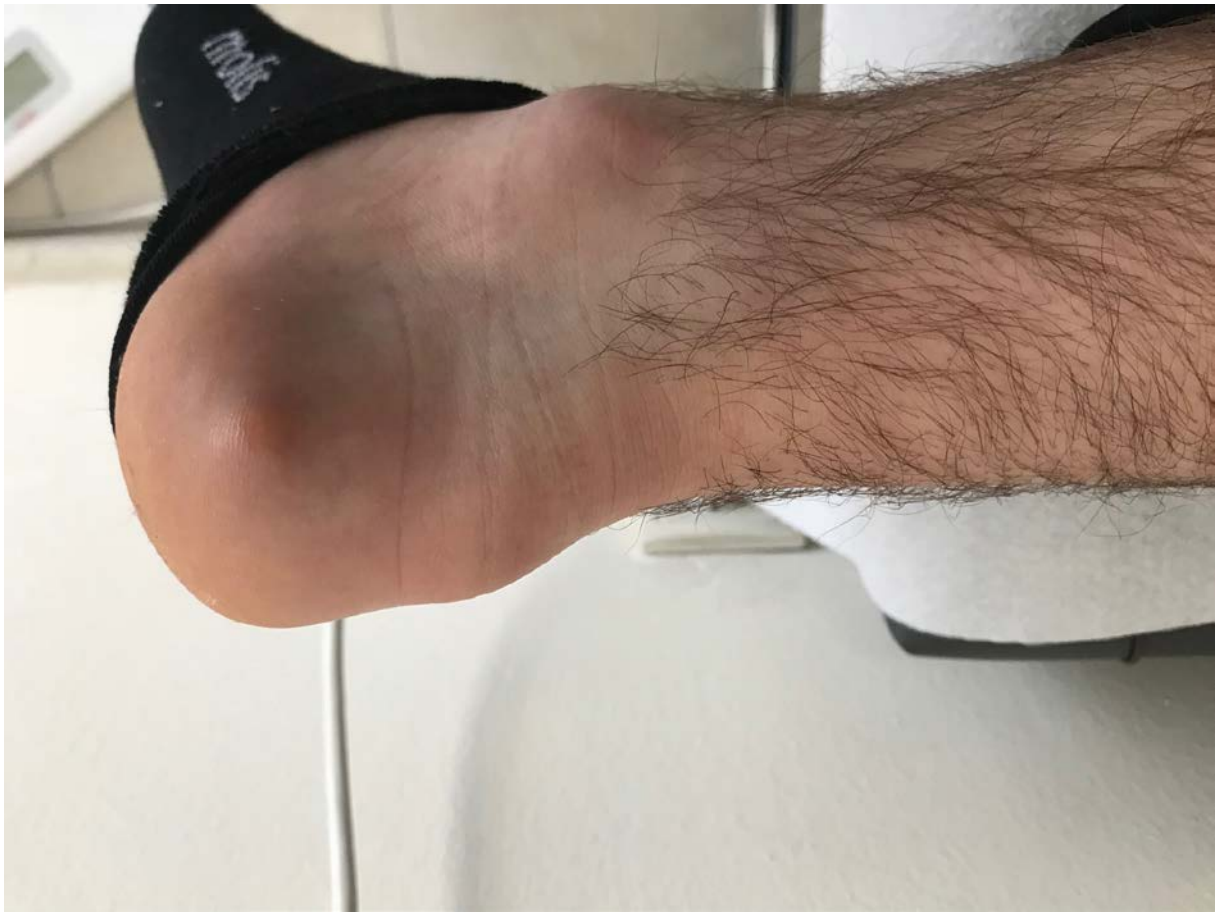

Figure 2. Achilles tendon xanthoma in a patient with familial hypercholesterolemia