Management and clinical outcomes of patients with homozygous familial hypercholesteremia in Saudi Arabia

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Abstract

We report the incidence, patient characteristic with clinical outcomes in patients with homozygous familial hypercholesterolemia (HoFH) in Saudi Arabia. This is a retrospective and prospective, single center study which included 37 patients 14 years and older enrolled and followed up between 2018-2021 for three years. 46% were females, 78% were offspring of consanguineous marriage. LDLR mutation was in 78% and LDL-C/LDL-RAP in 3% of patients. Mean LDL-C at the first presentation was 14.2±3.7 mmol/L, average Dutch lipid score was 20.9±6.24. LDL apheresis was performed on 70% of patients. Most patients were on ezetimibe (92%), high-dose statins (84%) and PCSK9 inhibitors (32%); 48.6% had aortic stenosis, out of which 30% had severe aortic stenosis. Ten underwent aortic valve surgery (5 mechanical valve, 3 Ross procedure, 1 aortic valve repair, 1 bioprosthetic valve) and one had transcatheter aortic valve implantation (TAVI). Coronary artery bypass surgery (CABG) was performed on 32% and percutaneous intervention (PCI) on 11% of patients. HoFH patients have complex diseases with high morbidity and mortality, and benefit from a highly specialized multidisciplinary clinic to address their clinical needs. Although there are several therapeutic agents on the horizon, early diagnosis, and treatment of HoFH remain critical to optimize patient outcomes.

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Introduction

Familial hypercholesterolemia (FH) is a hereditary treatable lipid metabolism disorder characterized by high levels of low-density lipoprotein cholesterol (LDL-C), which leads to the development of premature atherosclerotic cardiovascular disease (ASCVD). Although therapeutic advancements have somewhat succeeded in slowing disease progression and ASCVD development, reaching target lipid levels has remained challenging [1]. FH is considered to be underestimated in many countries of the world, with less than 10% of patients formally diagnosed with the condition [2]. The prevalence of heterozygous FH (HeFH) has been historically estimated to be 1 in 500 people, and that of homozygous FH (HoFH) to be 1 in 1,000,000 [3]. Recent studies show that the prevalence may actually be much higher, with HeFH likely affecting 1 in ~200 and HoFH affecting 1 in 300,000 people [3,4].

The reported prevalence of hypercholesterolemia varies in Saudi Arabia and the Gulf region. A 2008 report highlighted that 54% of the Saudi population aged 30-70 years were found to have hypercholesterolemia [5]. A Ministry of Health survey in 2013 estimated a hypercholesterolemia prevalence of 8.5% in the Saudi population [6]. The Africa Middle East Cardiovascular Epidemiological Study estimated the prevalence of dyslipidemia in the Africa and Middle East (AfME) region to be as high as 70% [7,8]. Based on the

Arabian Gulf Region FH Registry, the prevalence of FH among adults was thrice the worldwide estimated prevalence, and target LDL-C levels were noted to be poorly achieved [9]. The same study estimated the combined prevalence of definite and probable FH cases in the Gulf region to be 1/112 or 0.9%, which is three-fold, the world estimate prevalence [9]. This can be attributed to two main reasons: consanguineous marriage [10], and a factor probably amplified by consanguinity. Consanguinity, as is common in the Gulf region, increases the chances of two parents with rare disease alleles producing offspring with pathological genetic conditions. Approximately 40% of the Saudi Arabian FH population have a mutation in exon 14 of the LDLR. This mutation is a frameshift aberration resulting in c.2027delG, p.(G676Afs*33), and appears to originate in families living in the northern and western areas of Saudi Arabia [11].

FH increases risk of cardiovascular disease (CVD) and death, especially if left untreated. HoFH is associated with very high levels - around 10 times the normal levels - of LDL-C causing severe atherosclerosis, which results in premature fatal cardiovascular disease if left untreated in early life [12,13]. Mean age of CVD onset in male patients with HeFH is 40 years and 50 years in women. HoFH is more aggressive, more often unresponsive to treatment, and the mean age for CVD onset is 20 years [14,15]. Therefore, timely diagnosis and treatment of FH, especially HoFH are essential. In the absence of a genetic test, the clinical criteria that indicates a HoFH diagnosis includes an untreated LDL-C level higher than 13 mmol/L (500 mg/dL) or treated LDL-C level of at least 8 mmol/L (300 mg/dL), together with either cutaneous or tendon xanthoma before age 10 years, or untreated elevated LDL-C levels consistent with heterozygous FH in both parents [15]. A genetic test can be used to confirm the diagnosis. A systematic review exploring FH-related mutations in the Saudi population observed that 80% of the variants were linked to the LDLR gene, and PCSK9 and APOB variations were the second most common and one of the least common, respectively [16,17].

Unfortunately, Saudi Arabia lacks a robust HoFH screening system. Additionally, accurate diagnosis of HoFH in Saudi Arabia is hindered by a general lack of disease awareness among physicians. Over 90% of responders to a survey of 294 physicians at tertiary centers in Riyadh were noted to have "poor knowledge" of FH [18]. Similar indications of poor knowledge and awareness were noted in 48.4% of the surveyed family physicians in a second survey conducted in Riyadh [19]. Although a survey based on the FH-KAP questionnaire noted reasonable knowledge of FH definition among medical interns in Jeddah, considerable gaps in knowledge on inheritance, prevalence and CAD risks were observed [20].

Treatment of hyperlipidemia includes statins, ezetimibe, LDL apheresis, PCSK9-inhibitors, lomitapide, and liver transplantation. Gene therapy is mostly in pre-clinical development, far from implementation in routine practice [21]. Due to extremely elevated LDL-C levels and poor response to standard lipid-lowering regimens, treatment of HoFH is more challenging and apheresis and liver transplantation are considered standard lines of treatment. Lomitapide is effective but cost considerations and lack of availability in most centers in the Middle East limits its wide use [22-24]. Unfortunately, development and progression of cardiovascular complications still occur, emphasizing the need for early aggressive treatment [25]. Valvular heart disease, especially involving the aortic valve, is very common in HoFH and lacks effective pharmacological management, often necessitating surgical treatment with aortic valve replacement or percutaneous aortic valve implantation [26,27].

Objective

The objective of our study was to share our experience managing patients with HoFH, discussing relevant patient characteristics, treatment modalities and clinical outcomes.

Methods

The study was a retrospective chart review with prospective follow-up conducted at King Faisal Specialist Hospital & Research Centre (KFSH&RC), Riyadh, Saudi Arabia. KFSH&RC is a prominent tertiary referral hospital in the Middle East for transplant medicine, oncology, and complex and rare diseases. We identified patients with HoFH who were referred to us from peripheral hospitals for further evaluation and management of possible FH from 2018 to 2021. We included adult patients diagnosed with FH based on the Dutch criteria [2]. Patients who were in the pediatric age group , died before study enrollment, refused enrollment, not compliant to clinic follow up and did not consent were excluded from the study.

Subjects were identified using the hospital electronic system (Cerner, Kansas City, MO, USA) and medical record numbers (MRNs). Were exported patient data into a secure spreadsheet and data on the following details were collected from the subjects' electronic records: Complete demographic information, consanguinity status, mortality, relevant past medical history including cardiovascular diseases and procedures (CABG, PCI, heart valve surgeries), medications, genetic analysis and family history, clinical features based on Dutch criteria, LDL-C level pre and post treatment, echocardiography findings and liver transplant status. Privacy and confidentiality of patients was completely respected, and data was kept in a secure place within KFSH&RC premises, both hard and soft copies. The study was approved by KFSH&RC Ethics Committee (RAC# 2191111).

We used a direct method to measure LDL levels, using a homogeneous enzymatic colorimetric assay (Roche, Basel, Swtizerland). LDL was recorded on first hospital visit (this was retrospectively recorded from the electronic chart), and last visit at our advance lipid clinic. In addition, for patients on apheresis, the LDL was measured pre- and post- the last apheresis session.

Statistical analysis

Two groups based on whether or not they were treated with Apheresis were compared using summary measures. Categorical data were presented in frequency and percentages, and Fisher's exact test was performed to compare between the two groups. Wilcoxon's rank-sum test was performed on the continuous variables as they were not normally distributed. A p-value of ≤ 0.05 was considered to be statistically significant. Analysis was performed using JMP® (version 15; SAS Institute Inc., Cary, NC, USA).

Results

Demographics and clinical characteristics

Over the three-year period (2018-2021), 40 patients were screened to be followed in the clinic. Among these, 3 patients were excluded as one patient died before enrollment from surgical complications in another hospital, one patient refused enrollment and one was lost to follow up). Therefore, 37 patients with

HoFH were enrolled in the study. Sixteen patients (43.24%) were female, while 56.7% were male. Mean age was 26.8±7.9 years. Consanguineous marriage was identified in 29 patients (78%), and genetic confirmation was conducted in 31 (84%) patients. Average Dutch Lipid Clinic Network criteria score was 20.9. Out of all patients, 29 patients (78%) had an LDL-C gene mutation. One patient carried a compound heterozygous LDL-C mutation, and one carried LDL+ LDLRAP mutation. Mortality rate was 2.70% (one patient) who died from complication due aortic valve surgery. Two patients had hypertension, no patients admitted to smoking, and no patients had diabetes mellitus. Further details on demographics, clinical characteristics and cardiovascular events can be found in Tables 1 and 2.

LDL-C management

All patients were treated with statins. Thirty-two patients (86%) were treated with high intensity statins, 35 patients (95%) with ezetimibe, 12 patients (32.4%) with PCSK9-inhibitor (evolocumab), and 26 patients (70%) underwent LDL apheresis (Figure 1). At pres-

Table 1. Baseline characteristics and genetic confirmation

Characteristics	All patients (n=37)	On plasmapheresis (n=26)	Not on plasmapheresis (n=11)	p-value
Age, mean ± SD	26.8±7.9	28.1±7.2	23.7±8.9	0.08
Consanguinity, % (n)	78 (29)	84.6 (22)	72.7 (7)	0.4
Male, % (n)	54 (20)	57.7 (15)	45.5 (5)	0.71
Genetic confirmation, % (n)	83.8 (31)	88.5 (23)	72.7 (8)	0.33
LDLR* + LDLRAP** genetic type, % (n)	2.7 (1)	3.8 (1)	0.0 (0)	1
LDLR* genetic type, % (n)	78.3 (29)	80.7 (21)	72.7 (8)	1
Compound LDLR*** genetic type, % (n)	2.7 (1)	3.8 (1)	0.0 (0)	1
FH of CAD, % (n)	84.9 (28)	95.7 (22)	60 (6)	0.01
FH of dyslipidemia, % (n)	89.2 (33)	88.5 (23)	90.9 (10)	1
Arcus cornealis, % (n)	27 (10)	19 (5)	45.5 (5)	0.11
Xanthomas, % (n)	59.5 (22)	50 (13)	81.8 (9)	0.06
DLCN score, mean ± SD	20.9±6.24	20.38±6.4	22±6.07	0.48
HTN, % (n)	5.4 (2)	3.8 (1)	9.1 (1)	0.51
First presentation LDL (mmol/L), mean ± SD	14±3.8	14.3±3.8	13.6±3.95	0.49
Last LDL measured at last clinic visit (mmol/L), mean ± SD	7.2±4.2	5.57±2.8	10.96±4.74	0.00

LDLR, low density lipoprotein receptor; FH, familial hypercholesterolemia; CAD, coronary artery disease; DLCN, Dutch Lipid Clinical Network; HTN, hypertension; LDL, low-density lipoprotein.

Table 2. Cardiovascular outcomes.

Characteristics	All patients (n=37)	On plasmapheresis (n=26)	Not on plasmapheresis (n=11)	p-value
Mortality, % (n)	2.7 (1)	0 (0)	9.0 (1)	0.3
Aortic valve stenosis, % (n)	48.6 (18)	46.2 (12)	54.5 (6)	0.83
Mild, % (n)	16.67 (3)	16.7 (2)	16.67 (1)	0.73
Mild to moderate, % (n)	NA	NA	NA	
Moderate, % (n)	22.22 (4)	16.7 (2)	33.33 (2)	
Moderate to severe, % (n)	61.11 (11)	66.67 (8)	50 (3)	
Supra aortic valve stenosis, % (n)	37.8 (14)	34.6 (9)	45.5 (5)	0.54
Aortic valve intervention, % (n	29.7 (11)	30.77 (8)	27.3 (3)	1
Ross procedure*, % (n)	27.27 (3)	25.00 (2)	33.33 (1)	
Mechanical valve**, % (n)	45.46 (5)	37.50 (3)	66.67 (2)	
Repair**, % (n)	9.1 (1)	12.50 (1)	NA	
TAVI, % (n)	9.1 (1)	12.50 (1)	NA	
Bioprosthetic valve**, % (n)	9.1 (1)	12.50 (1)	NA	
CABG, % (n)	32.4 (12)	34.6 (9)	27.3 (3)	0.66
PCI, % (n)	10.8 (4)	15.4 (4)	0 (0)	0.3
Aortic root replacement (Bentall procedure), % (n)	10.8 (4)	11.5 (3)	9.1 (1)	1
Carotid artery stenosis, % (n)	32.4 (12)	42.3 (11)	9.1 (1)	0.03
Mitral valve surgery, % (n)	8.1 (3)	11.5 (3)	0 (0)	0.54
CAD, % (N)	59.5 (22)	61.5 (16)	54.5 (6)	0.69

NA, not available; TAVI, transcatheter aortic valve implantation; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CAD, coronary artery disease.

entation, mean LDL-C was 14±3.8 mmol/L (540.54±146.72 mg/dL) in all patients, 14.3±3.83 mmol/L (552.12±147.88 mg/dL) in patients treated with LDL apheresis and 13.6±3.95 mmol/L (525.10±152.51 mg/dL) in patients not treated with LDL apheresis. Last mean LDL-C was 7.2±4.2 mmol/L (277.99±162.16 mg/dL) in all patients, 5.57±2.8 mmol/L (215.06 108.11 mg/dL) in patients on LDL apheresis and 10.96±4.74 mmol/L (423.17±183.01 mg/dL) in patients not on LDL apheresis.

Mean LDL-C pre-apheresis was 12.2 mmol/L (471.04 mg/dL), mean LDL-C post-apheresis was 5 mmol/L (193.05 mg/dL), with a median LDL-C of 8.6 mmol/L (332.05 mg/dL). Median LDL-C of non-apheresis patients was 12.3 mmol/L (474.90 mg/dL). For the seven patients (19%) on both PCSK9-inhibitor and apheresis, mean pre-treatment LDL-C was 11.25 mmol/L (434.36 mg/dL) and mean post-treatment LDL-C was 4.28 mmol/L (165.25 mg/dL), p<0.01, respectively (Figures 2 and 3). One patient had a liver transplantation at the age of 6 years. Since then, she had had two acute rejections, but these were treated medically. Prior to liver transplantation her LDL was 20.6 which went down dramatically to 3.0 post-transplantation. However, over the course of 10 years, her LDL level increased steadily to 5.4 requiring the addition of high dose statin therapy (rosuvastatin 20 mg) reducing her LDL to 2.3. Two patients were started on lomitapide, one for 3 months in 2015 where he was able to get off apheresis and had an LDL of 4.6 (his LDL pre-apheresis was 14.9 and post-apheresis was 2.95). Another patient in 2016 was on lomitapide for 5 months, and her LDL decreased to 5.5 (her LDL pre-apheresis was 17.8 and post-apheresis was 6.7) However, due to cost and drug availability issues, the drug was discontinued for both patients and they were placed back on apheresis.

In our patient group, patients on LDL apheresis had a significantly lower last mean LDL-C level (5.57 *vs* 10.96 mmol/L, p<0.01), more likely to have carotid artery stenosis (42.3% *vs* 9.1%, p=0.03) and more likely to have a family history of CAD (95.7% *vs* 60%, p=0.01).

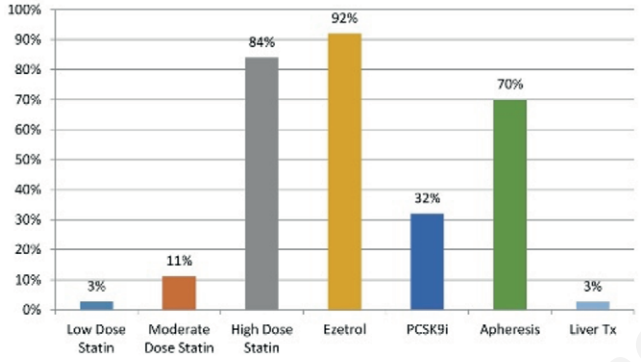

Figure 1. Percentage of patient on different treatments.

Cardiovascular disease and interventions

Twenty-eight patients (76%) had a family history of CAD, and 33 patients (89%) had a family history of dyslipidemia. Aortic stenosis was seen in 18 patients (48.6%), with eleven patients (30%) having moderate to severe or severe AS, and no patients had mitral stenosis, but 3 patients had severe mitral regurgitation (8.1%). Ten patients (27.02%) underwent aortic valve replacement; three patients underwent Ross procedure, five underwent mechanical aortic valve replacement (AVR), one underwent bioprosthetic valve replacement and one underwent aortic valve repair. One patient underwent percutaneous aortic valve replacement (TAVI) Aortic root replacement was done in four patients (11%). Carotid artery stenosis was found in 12 patients (32%) and CAD was found in 22 patients (59%). Percutaneous coronary intervention (PCI) was done in 4 patients (11%) and Coronary artery bypass surgery (CABG) in 12 patients (32%). One patient underwent liver transplantation (Table 2).

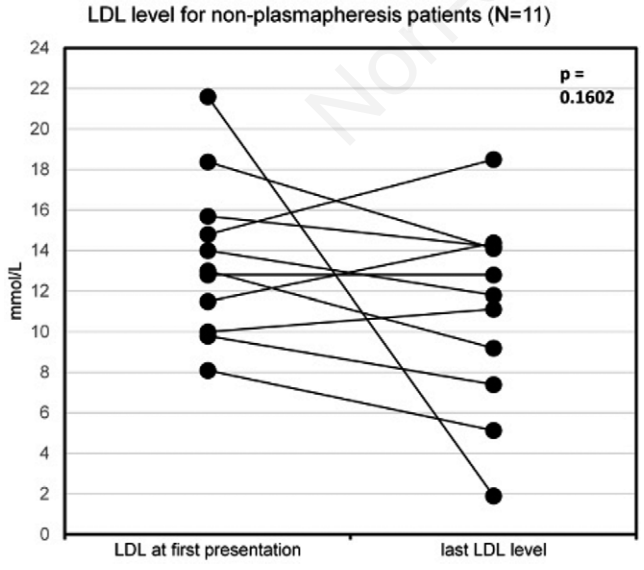

Figure 2. LDL level on non-plasmapheresis group at presentation and at the last visit (for individual patients). LDL, low-density lipoprotein.

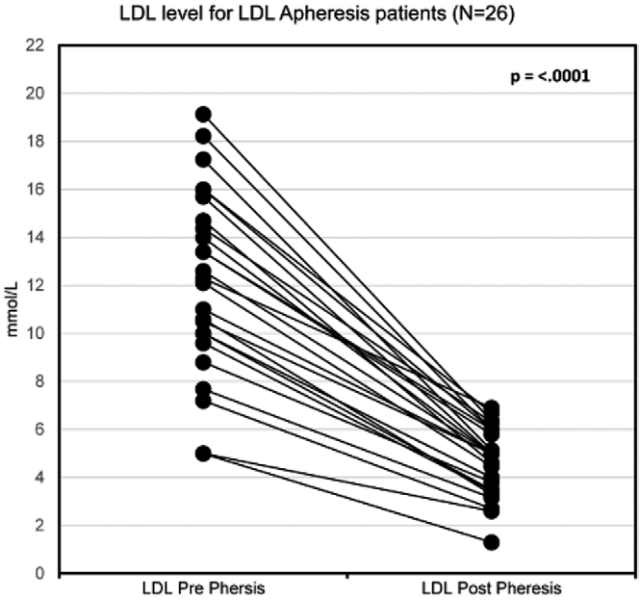

Figure 3. LDL levels in LDL apheresis group before and after last session of apheresis (for individual patients). LDL, low-density lipoprotein.

Discussion

This paper reports the experience of a prominent Middle Eastern tertiary referral and clinical characteristics and outcomes of managed HoFH patients over a three-year follow-up. HoFH patients are a high-risk group with multiple cardiovascular risk factors, contributing to significant morbidity and mortality. With HoFH, cardiovascular events can start occurring in adolescence, and untreated LDLR-negative HoFH patients rarely survive beyond the second decade of life [28]. Therefore, early diagnosis and treatment becomes critical in optimizing patient outcomes and reducing risk of further complications. Previous studies have highlighted the importance of primary prevention of fatal CAD, yielding better outcomes than secondary interventions [21,25]. In patients who have progressive coronary disease despite maximal statin treatment or who are statin intolerant, PCSK9 inhibitors can play an important role in LDL-C control, used in 32.4% of our patients who demonstrated considerable improvement in LDL-C levels but only those who were on LDL apheresis ($p<0.01$).

LDL apheresis is a valuable therapeutic modality in patients whose cholesterol levels are not adequately controlled pharmacologically, with our patients on LDL apheresis demonstrating significantly lower last mean LDL-C level (5.57 *vs* 10.96 mmol/L, $p<0.01$) compared to those not on LDL apheresis. However, in the context of resource costs associated with LDL apheresis, appropriate patient selection is important, to improve efficiency, resource utilization and patient experience [26,29]. A recent study exploring lipoprotein apheresis in HoFH patients acknowledged its safety and effectiveness in lowering LDL-C levels, but highlighted room for improvement with regards to treatment onset, frequency to optimize LDL apheresis use in HoFH [30]. LDL apheresis not only removes LDL-C, but it has also been observed to have pleiotropic effects in preventing atherosclerosis through removal of cell adhesion molecules, coagulation factors, and inflammatory cytokines [31-33].

While statins, ezetimibe and PCSK9 inhibitors all act by enhancing LDL receptor activity, MTP inhibitors such as lomitapide act independent of LDL receptor activity [34-37]. Although this medication had been successfully used in two of our patients, due to cost and limited drug availability, it was used for only a short period of time with likely limited lifelong therapeutic effect. Our patient who had a liver transplantation did have a dramatic reduction in the levels of LDL but required lifelong immunosuppressive therapy with episodes of rejection and eventually needed to be placed on statin therapy. This pattern has been seen previously where even after liver transplantation; LDL levels start to increase requiring medical therapy [28]. Therapeutic options for HoFH remain limited and clinical management continues to be challenging, paving the way for novel therapeutic agents including medications targeting non-LDLR pathways and gene-editing techniques [38]. These include agents such as inclisiran, an siRNA drug that inhibits translation of PCSK9, evinacumab, an anti-ANGPTL3 antibody, and mipomersen, an antisense drug for the APOB gene [22-24,39].

Eleven (30%) of our patients had moderate to severe or severe aortic stenosis out of the 18 with aortic stenosis, with ten undergoing aortic valve surgery and one undergoing TAVI. Three had mitral valvulopathy. Cardiac valvulopathy in HoFH remains poorly studied, and exact prevalence is unknown. Calcific aortic valvulopathy seems to be the most reported, with little literature on hypercholesteremic mitral valve disease. Notably, several randomized controlled trials have observed no improvement of aortic valve calcification with lipid-lowering therapy, highlighting a possible role of molecular mechanisms related to other downstream effects of the genetic mutation independent of LDL-C levels [40-42]. A study based on the Lebanese FH Registry noted that patients with valvulopathy were older and were more likely to be on apheresis but with lower intima-media thickness compared to patients without valvulopathy [43]. Kolansky *et al*. reported that aortic regurgitation could be the earliest manifestation of valvulopathy in HoFH, with 8 out of their 39 HoFH patients (21%) having mild-to-moderate aortic regurgitation, while another study reported aortic valve stenosis or regurgitation in 8 out of 10 HoFH patients [42,44].

The study may be viewed in light of a few limitations. Given its retrospective nature and single center setting, the data quality relied on the accuracy and completeness of information recorded in patients' hospital medical records. Although the sample size was limited at 37 patients, the general rarity of the disease and Middle Eastern setting offers a unique and valuable insight into HoFH management and important patient outcomes. Our study offers insight into contemporary HoFH treatment trends in a real-world setting. Given the small sample size and lack of randomization, this study is not meant to compare treatment modalities or to draw associations between treatments and outcomes.

Early diagnosis and treatment of FH remains essential in preventing premature death, morbidity and reducing healthcare costs [45,46]. Universal screening of lipid levels has been trialed in some parts of the world, in addition to cascade screening, which is able to identify at-risk family members and allows for prompt diagnosis and treatment.

Conclusions

Homozygous familial hypercholesterolemia is a complex disease with significant morbidity and mortality. A comprehensive approach as offered at KFSH&RC that integrates different services and offers genetic testing, advanced medical and surgical therapies and transplantation is essential to deliver the highest level of care. Our study is a call for improvement in screening and management of patients with HoFH in Saudi Arabia and the region. Early diagnosis and treatment remain essential to optimize patient outcomes in HoFH, with appropriate patient selection recommended for LDL apheresis therapy and liver transplantation. Patients benefit from specialist cardiovascular care addressing various disease-related comorbidities including CAD and cardiac valvular disease.

Future directions

Long term follow up is essential in a controlled clinic setting facilitating the development of a clinical registry to determine the long-term outcomes of medical treatment modalities and surgical techniques in this high-risk patient population. We will follow up the patient who underwent transcatheter aortic valve implantation (TAVI) for extended period of time to assess natural history of TAVI in this group of patients.

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