Critical Review

Familial Combined Hyperlipidemia: An Overview of the Underlying Molecular Mechanisms and Therapeutic Strategies

Eskandar Taghizadeh[1,2†]
Reza Jafarzadeh Esfehani[1,3†]
Amirhossein Sahebkar[4,5,6]
Seyed Mostafa Parizadeh[7]
Daryoush Rostami[8]
Mohammadreza Mirinezhad[1]
Arash Poursheikhani[1]
Majid Ghayour Mobarhan[7]
Alireza Pasdar[1,3,9*]

[1]Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Cellular and Molecular Research Center, Yasuj University of Medical Sciences, Yasuj, Iran
[3]Medical Genetics Research Centre, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[5]Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[6]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[7]Metabolic Syndrome Research Centre, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[8]Department of School Allied, Zabol University of Medical Sciences, Zabol, Iran
[9]Division of Applied Medicine, Medical School, University of Aberdeen, Aberdeen, UK

Abstract

Among different types of dyslipidemia, familial combined hyperlipidemia (FCHL) is the most common genetic disorder, which is characterized by at least two different forms of lipid abnormalities: hypercholesterolemia and hypertriglyceridemia. FCHL is an important cause of cardiovascular diseases. FCHL is a heterogeneous condition linked with some metabolic defects that are closely associated with FCHL. These metabolic features include dysfunctional adipose tissue, delayed clearance of triglyceride-rich lipoproteins, overproduction of very low-density lipoprotein and hepatic lipids, and defect in the clearance of low-density lipoprotein particles. There are also some genes associated with FCHL such as those affecting the metabolism and clearance of plasma lipoprotein particles. Due to the high prevalence of FCHL especially in cardiovascular patients, targeted treatment is ideal but this necessitates identification of the genetic background of patients. This review describes the metabolic pathways and associated genes that are implicated in FCHL pathogenesis. We also review existing and novel treatment options for FCHL. © 2019 IUBMB Life, 000(000):1–9, 2019

Keywords: familial combined hyperlipidemia; therapy; molecular pathway; hypercholesterolemia; hypertriglyceridemia

ABBREVIATIONS: *25(OH) D, 25-hydroxyvitamin D; apoB, apolipoprotein B100; apoCIII, apo lipoprotein CIII,; BAT, brown adipose tissue; CVD, cardiovascular disease; FCHL, familial combined hyperlipidemia;* GPR77, *G-protein-coupled receptor 77,; GWAS, genome-wide association studies; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HL, hepatic lipase; HSL, hormone-sensitive lipase; IR, insulin resistance; LDL, low-density lipoprotein;* LEPR, *leptin receptor gene; MTP, microsomal TG transfer protein;* PCSK9, *proprotein convertase subtilisin/kexin type 9;* PPARG, *peroxisome proliferator-activated receptor γ gene; SNP, single nucleotide polymorphisms;* SREBP2, *sterol regulatory element binding protein 2; T2D, type 2 diabetes mellitus; TRL, TG-rich lipoprotein; VLDL, very low-density lipoprotein*

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**Address correspondence to: Alireza Pasdar, MD, PhD, Department of Medical Genetics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Tel.: +98-51-38002310, Fax: +98-51-38002287. E-mail: pasdara@mums.ac.ir; Division of Applied Medicine, Medical School, University of Aberdeen Foresterhill, Aberdeen, AB25 2ZD. E-mail: a.pasdar@abdn.ac.uk*

†Contributed equally

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INTRODUCTION

Familial combined hyperlipidemia (FCHL) is the most common inherited form of dyslipidemia (1), which is estimated to affect about one person per 100 (2). The genetic aspects of FCHL have not been fully understood (3). Some metabolic defects accompany FCHL such as malfunctioning of adipose tissue, impaired metabolism of lipoprotein particles, reduced clearance of apolipoprotein B100 (apoB), hepatic fat accumulation, overproduction of very low density lipoprotein (VLDL) in the liver and insulin resistance (IR) (2). This polygenic lipid metabolism disorder is characterized by different phenotypes such as high cholesterol or triglyceride (TG) levels or combination of both hypercholesterolemia and hypertriglyceridemia, increased apoB levels in plasma, preponderance of atherogenic small dense low-density lipoprotein (LDL) particles, and decreased concentration of high-density lipoprotein cholesterol (HDL-C) within at least two members of one family to be classified as FCHL; however, lipid phenotypes commonly change over time (4). The exact molecular defect that occurs in FCHL is still unclear. FCHL appears to be associated with metabolic syndrome and a number of cardiometabolic abnormalities such as IR, type 2 diabetes, obesity, and hypertension (1, 5). It has been reported that metabolic syndrome is an independent marker of cardiovascular disease (CVD) risk in those who have FCHL. Likewise, IR is another feature of FCHL that is associated with lipid phenotypes, indicating that impaired in insulin sensitivity can result in lipid metabolism abnormalities (6). Therefore, patients with FCHL are at a high risk of premature atherosclerotic coronary artery disease (CAD) and myocardial infarction (4, 6–8). The prevalence of CAD in patients with FCHL younger than 60 years has been estimated to be about 15% (4, 9, 10). With respect to male gender as a CAD risk factor, CAD prevalence is almost five-fold higher in FCHL men compared to older, predominantly postmenopausal FCHL women (11). Since there is a lack of robust biomarker for definite diagnosis of FCHL, many FCHL patients remain undiagnosed despite being at a high CVD risk (12). In this review, we tried to comprehensively search the extant literature to present an updated picture of the disorder.

METABOLIC AND MOLECULAR PATHWAYS RELATED TO FCHL

Previous studies have identified some molecular pathways that are involved in FCHL. These pathways are described in the following sections (Fig. 1) (3, 13, 14).

DYSFUNCTIONAL ADIPOSE TISSUE

The evidence for dysfunctional adipose tissue in FCHL subjects is abundant (Fig. 2) (14, 15). Arner et al. demonstrated that the turnover of TG is reduced in the adipose tissue of patients with FCHL (14). There is a list of genes with suggested roles in adipose tissue dysfunction (Fig. 1). Lipolysis involves hydrolysis of TGs into glycerol and free fatty acids and occurs in adipose tissue (16). Hormone-sensitive lipase (HSL) is encoded by the *LIPE* gene and has a key role in the lipolysis. Hence, it is a candidate gene in FCHL pathogenesis (17, 18). *PNPLA2*, which encodes patatin-like phospholipase domain-containing protein 2, is another gene with a role in the lipolysis of TGs and is implicated in adipose tissue dysfunction (19, 20). One of the main genes that has been shown to have some important roles in FCHL pathogenesis is *USF1* (21, 22). *USF1* has several important target genes with key roles in lipid and glucose metabolism. Gene variants in *USF1* are associated with catecholamine-induced lipolysis that are mediated by phosphorylation of *HSL* and *PNPLA2* genes. *USF1* regulates the expression of many genes involved in lipid metabolism and lipolysis (23, 24). In a study by Laurila and colleagues in 2016, inactivation of *USF1* in mice led to protection against diet-induced dyslipidemia, hepatic steatosis, IR, obesity, and atherosclerosis. Increased HDL-C and decreased TGs were accompanied by increased energy expenditure due to the activation of brown adipose tissue (BAT) (25). It was also observed that *USF1* inactivation could enhance plasma TG clearance. In mice lacking *USF1* or with silenced *USF1*, a direct effect of *USF1* on BAT activation was confirmed following an amplified adrenergic response in brown adipocytes and augmented norepinephrine-induced thermogenesis after *USF1* silencing (25). A variant in G-protein-coupled receptor 77 (*GPR77*) genes is associated with TG storage in adipocytes. Individuals with this variant have decreased TG storage in adipocytes and high levels of plasma lipids, indicating that some forms of FCHL are monogenic (26).

LepR is encoded by the leptin receptor gene (*LEPR*) and is usually produced by the adipose tissue. This protein is involved in the regulation of energy metabolism and appetite. It was reported that Gln223Arg polymorphism in the *LEPR* gene is associated with increased risk of FCHL (27).

Peroxisome proliferator-activated receptor γ gene (*PPARG*), which encodes a nuclear receptor and transcription factor, regulates adipocyte differentiation and glucose homeostasis. *PPARG* is another gene with a probable role in the dysfunction of adipose tissue. (28).

DELAYED CLEARANCE OF TG-RICH LIPOPROTEINS

An overview of TG-rich lipoprotein (TRL) metabolism is illustrated in Figs. 1 and 2. The causes of delayed clearance of TRLs are complex (29, 30). Previous studies have demonstrated that TRLs and their remnants can lead to the progression of atherosclerosis and CVD both directly and indirectly (31, 32). In the circulation, lipoprotein lipase, which is encoded by the *LPL* gene, hydrolyzes TG molecules. These TG molecules are carried in VLDL particles. Some TG molecules in VLDL particles that are less TG-rich are hydrolyzed by hepatic triacylglycerol lipase encoded by the *LIPC* gene (3, 31). Patients with FCHL have a delayed clearance of chylomicron remnants and VLDL

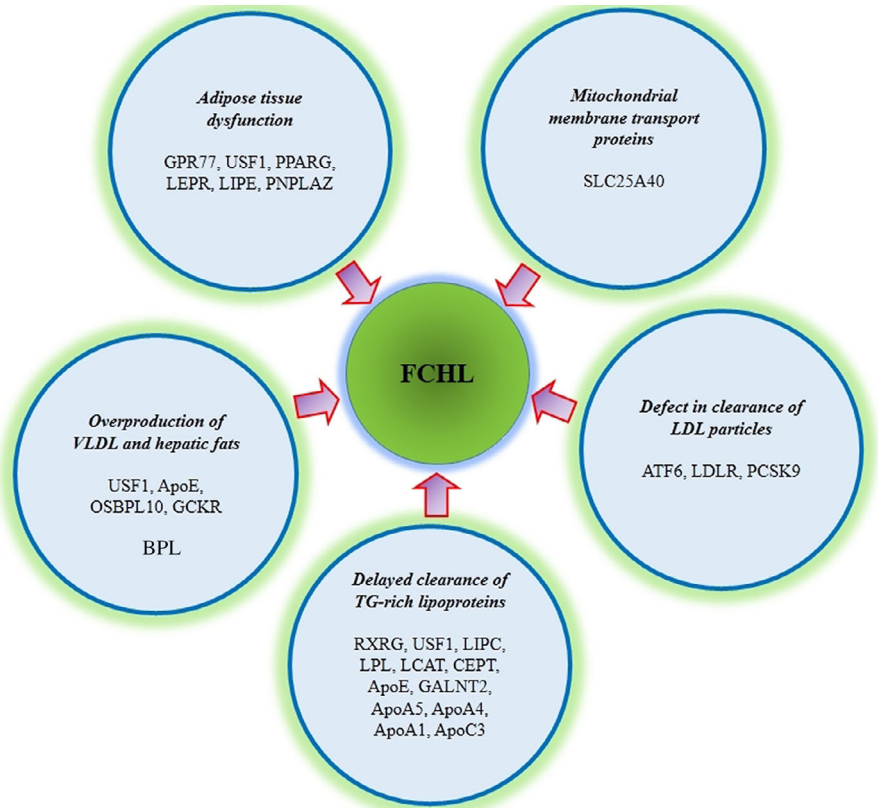

FIG 1 *Metabolic pathways and related genes involved in FCHL.*

particles (33). Using candidate gene approach, linkage data, and genome-wide association studies (GWAS), several genes with a possible role in the clearance pathways of TRLs have been identified (34–36). These include the *LPL* gene on 8p22 chromosome, *LIPC* gene on 15q21-23 chromosome, *apoC-II* and *apoE* on 19q13, and *apoC-III* and *APOA1/C3/A4/A5* gene cluster on 11q23–24 chromosome. The apolipoprotein CIII impedes TG hydrolysis and TG remnant clearance, and may exert pro-atherogenic activities. This gene has also been linked to IR and type 2 diabetes mellitus, both of which being frequent in FCHL. Other genes affecting TRL clearance include the *GALNT2* gene on 1q41-42 chromosome, *LCAT* gene on 16q22 chromosome, *RXRG* gene on 1q22-23 chromosome, *USF1* gene on 1q22-23 chromosome, and *CETP* gene on 16q21 chromosome (3, 37–41) (Fig. 2).

OVERPRODUCTION OF VLDL AND HEPATIC FATS

There are numerous studies showing overproduction of apoB in FCHL patients (Fig. 2) (42, 43). Increased free fatty acid flux to the liver, hepatic de novo lipogenesis, and beta-oxidation defects cause hepatic fat accumulation. Previous studies in diabetic patients have demonstrated that VLDL production is increased by a high amount of hepatic fat and IR (44–46). Several genes and variants in these genes that are involved in this pathway can play a role in FCHL pathogenesis. *GCKR* inhibits glucokinase in the liver and pancreatic islet cells, and some variants in this locus have been associated with de novo lipogenesis, β oxidation, and plasma TG levels (47, 48). *ApoE* gene, a ligand for LDL receptor and apoE, may lead to VLDL overproduction (49). *OSBPL10* gene that is an intracellular receptor for lipids is involved in the suppression of hepatic lipogenesis and VLDL production. Mutations in this gene can lead to a defect in the mentioned processes (50). Another gene, which looks very important, is the upstream transcription factor or *USF1* gene that regulates transcription of several genes including the genes related to lipid and glucose metabolism (51, 52).

DEFECT IN THE CLEARANCE OF LDL PARTICLES

LDLs are complexes of apoprotein B-100 and lipids including cholesterol esters, free cholesterol, triacylglycerol, and phospholipids (53). LDL receptor binds to LDL and clears LDL from the blood (54). Genetic defects in LDLR lead to elevated circulating levels of LDL as the major cholesterol-carrying lipoprotein of plasma. Impairment of LDL transportation into cells by

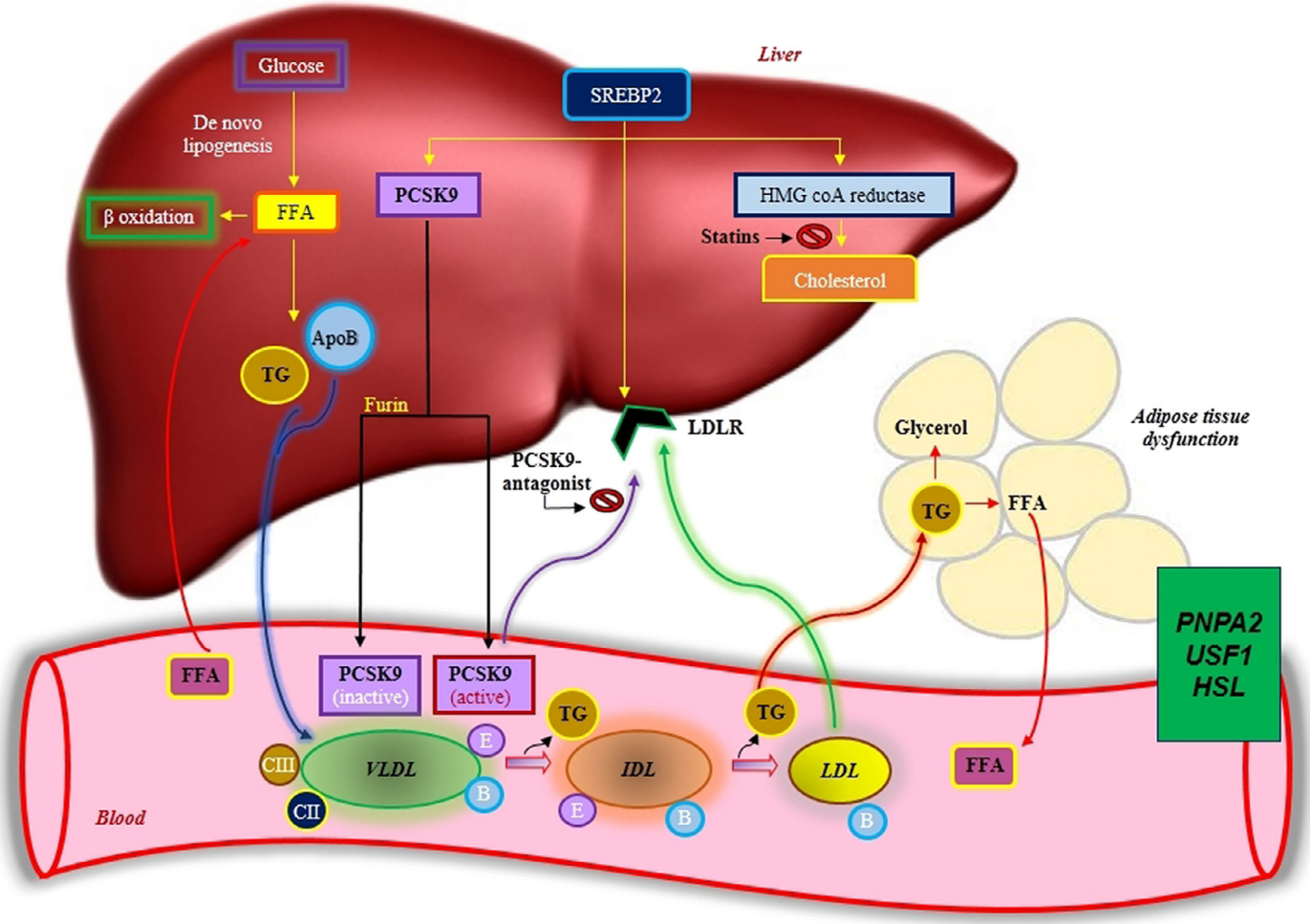

FIG 2

Pathogenic mechanisms of familial combined hyperlipidemia including dysfunctional adipose tissue, delayed clearance of TG-rich lipoproteins, overproduction of VLDL and hepatic fats, defect in clearance of LDL particles. Adipose tissue dysfunction increases the amount of free fatty acids in the liver. Liver FFAs and FFAs synthesized by de novo pathway from glucose in liver are secreted into the bloodstream as VLDL accompanied by apolipoproteins (Apo). In the blood VLDL, IDL (intermediate density lipoprotein) and then LDL are formed. LDL particles are cleared from plasma by the LDL receptor (LDLR). Dysfunction in any of these steps can cause FCHL. Abbreviations: FFA, free fatty acid; TG, triglycerides; apo, apolipoprotein; LDL, low density lipoprotein.

endocytosis may leads to FCHL (55, 56). *ATF6* gene on 1q22-23, a sensor of ER stress response, is another gene with a suggested role in the clearance of LDL in FCHL subjects. Proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene is involved in cholesterol homeostasis and differentiation of cortical neurons related to the FCHL phenotype (57, 58). There is also an interaction between sterol regulatory element binding protein 2, *LDLR* expression, cholesterol synthesis, and *PCSK9* expression in the hepatocytes (Fig. 2) (13, 59–61).

Whole exome sequencing has determined a new gene in a large FCHL pedigree. This gene, *SLC25A40*, is a casual factor for hypertriglyceridemia. It represents a new metabolic pathway that is very important as a potential therapeutic target (62, 63) (Fig. 2). In addition, GWAS and linkage studies have determined several genes that can contribute to the pathogenesis of the FCHL (3). These genes are listed in Table 1 and require additional studies to clarify their exact role.

CONVENTIONAL AND NOVEL TREATMENTS

Different treatments have been suggested for FCHL from decades ago. The need for FCHL treatment is mostly because of its well-known complications. Recently, Skoumas et al. completed a long follow-up study on both FCHL and heterozygous familial hypercholesterolemia (HeFH) patients treated with statins. It was reported that statins will not increase the risk of developing diabetes mellitus in aging FCHL patients. According to their results, statin therapy will prevent cardiovascular

TABLE 1 *Reported FCHL-associated genes with uncertain roles*

Gene product	*Gene*	*Location*	*References*
Adducin 1	*ADD1*	4p16	(64)
ApoB mRNA editing enzyme, catalytic polypeptide 1	*APOBEC1*	12p13	(65)
WW domain-containing oxidoreductase	*WWOX*	16p23-24	(64)
Unknown	*rs1424032*	16p21	(65)
TNF receptor superfamily, member 1B	*TNFRSF1B*	1p36	(66)
Transcription factor 7-like 2 (T-cell specific, HMG-box)	*TCF7L2*	10q25	(67)
Ceramide synthase 4	*CERS4*	19p13	(68)
Paraoxonase 1	*PON1*	7q21	(69)
Protocadherin-related 15	*PCDH15*	10q21	(70)
Hepatocyte nuclear factor 4α	*HNF4A*	20q13	(21, 71)
Fatty acid desaturase 3	*FADS3*	11q12-13	(22, 64)
Forkhead box C2	*FOXC2*	16q24	(22, 64)
Galanin prepropeptide	*GAL*	11q13	(72)
Cellular retinoic acid-binding protein 2	*CRABP2*	1q21-23	(64)

events in patients with familial hyperlipidemia (73). According to the latest ESC/EAS guidelines for the management of dyslipidemias, elevated LDL-C levels, which are associated with elevated TG levels, will bear a greater risk for developing CVD. Therefore, statins will be more beneficial in those with higher TG levels. Patients with atherogenic profile including metabolic syndrome and diabetes mellitus can benefit from statin therapy alone or in combination with ezetimibe. Besides their putative cholesterol-lowering activity, statins possess numerous lipid-independent pleiotropic effects (74–79). Patients who suffer from chronic kidney disease should receive statins with caution especially if they have glomerular filtration rate less than 30 mL/min (80). For both FCHL and non-FCHL patients, reduction of TG will result in postprandial lipidemia improvement. Reducing plasma VLDL levels can enhance chylomicron catabolism and, therefore, facilitate postprandial lipoprotein clearance (81). Asztalos et al. conducted a study on the effective dose of statins in dyslipidemic patients. High doses of both atorvastatin and rosuvastatin were effective in altering HDL subpopulation phenotype though the effect of rosuvastatin was more favorable (82). Karlson et al. also reported that each dose of rosuvastatin is 3–3.5 times higher than equal doses of atorvastatin (83). Monotherapy or combination therapy with statins and fibrates are two cornerstones of therapeutic strategies in FCHL patients. However, controversy surrounds the superiority of the drug of choice for FCHL treatment. A common drug from statin family is atorvastatin, which is known to inhibit VLDL secretion and reduce fasting plasma TGs (81, 84). Even healthy subjects can benefit from improvement in postprandial lipidemia after treating with atorvastatin (85). Cabezas et al. demonstrated that atorvastatin is more efficacious in reducing the cholesterol rather than TG content of TRLs. Other researchers have provided different results in patients with dyslipidemias other than FCHL and concluded that reduction of TRL could only be seen in FCHL patients (30, 81). Moreover, Cabezas et al. demonstrated that the most prominent effect of atorvastatin therapy would be on hepatic TRLs but there is no major effect on intestinal TRLs. The authors clarified the need for another lipid-lowering agent to improve the clearance of postprandial TRLs in FCHL patients treated with atorvastatin (81). Aside from statins, other important drugs in FCHL are fibrates that are used either as monotherapy or in combination with statins from decades ago. One of the first studies to evaluate the combination of different drugs in FCHL was conducted by Bredie et al., who used the combination of gemfibrozil (as a fibrate) and simvastatin. Although none of these two drugs could completely normalize the lipoprotein profile in monotherapy, a higher efficacy can be achieved upon combination (86). Another study, which indicated the effectiveness of combination therapy in FCHL patients, was done by Zambon et al. In patients with elevated apoB lipoproteins and reduced HDL-C, lovastatin could lower LDL-C and gemfibrozil could affect HDL-C and VLDL. It was reported that only a minority of patients benefited from monotherapy while combination therapy was safe and superior (87). Athyros et al. provided valuable evidence about the long-term effects of combination treatment with statins and fibrates in FCHL patients. Decreased LDL-C, total cholesterol, and apoB as well as a significant increase in HDL-C were observed with combined treatment. It was concluded that the combination therapy is safe in refractory FCHL patients with or without CAD (88). Despite various studies about the superiority of combination therapy, some researchers have recently tried to establish

a first-line therapy rather than starting with combination therapy for FCHL. Arca et al. provided evidence showing that atorvastatin (average dose of 20 mg/d) is superior to fenofibrate (200 mg/d) in treating hyperlipidemia in FCHL patients (89). There are also several novel therapies for the management of hypertriglyceridemia that might find applications in future, either alone or in combination with other agents, for the management of FCHL (90, 91).

While statins can lower plasma cholesterol and fibrates can lower both plasma cholesterol and TGs, there is a need for drugs, which can improve LDL phenotype as well (92). Therefore, searching for novel therapies with efficacies beyond statins and fibrates in FCHL is an ongoing attempt. Calabresi et al. evaluated the impact of administration of omega-3 fatty acids in FCHL patients and reported beneficial effects of these fatty acids on CHD risk. The administration of omega-3 fatty acids did not change plasma cholesterol but reduced TGs and increased HDL2 subfractions as well as antioxidant enzyme paraoxonase (93). Long-chain n-3 fatty acids' effects in FCHL patients are not yet understood. Docosahexaenoic and eicosapentaenoic acids (DHA and EPA), which are present in fish oil can reduce TGs in hyperlipidemic patients. Omacor, which consists of esters of EPA and DHA, has been tested in FCHL patients in Europe. Calabresi et al. provided their patients with four Omacor capsules per day for a period of 8 weeks in a randomized double-blind study. Significant reductions in plasma TGs and VLDL-cholesterol were achieved but the total cholesterol did not change. After 8 weeks, plasma LDL particles in the Omacor group were enriched in cholesterol but the abnormal size of LDL remained unchanged. The authors concluded that the LDL size is mostly controlled by genetic factors in an independent manner from plasma lipoprotein levels (94). Nutraceuticals and phytochemicals are another class of agents that have emerged as lipid-modifying agents (95, 96). Gentile et al. evaluated the effects of Armolipid Plus (combination of red yeast rice, policosanols, astaxanthin, coenzyme Q, folic acid, and berberine) on serum LDL-C levels of FCHL patients. This nutraceutical combination could reduce LDL score (proportion of small dense LDL particles [subfractions 3–7] to the whole LDL area [subfractions 1–7]) and increased LDL particle size in FCHL patients (97). It is noteworthy to mention that routine use of fish oil or fibrates is better to be reserved for selective patients and those whose TG levels remain high and/or their HDL-C level remains very low despite receiving appropriate statin treatment (80). The same as other diseases, single nucleotide polymorphisms (SNPs) play an important role in patients' response to drug therapy in FCHL. Microsomal TG transfer protein (MTP)-493G/T polymorphism affects postprandial apo B48 and apo B100 contents of TRLs in FCHL patients. MTP has a major role in the secretion and intracellular lipidation of apoB in both liver and intestine. Treating patients with T allele with atorvastatin will result in significantly greater postprandial and fasting TG reduction. Klop et al. reported that atorvastatin in T allele carriers of the mentioned SNP can decrease postprandial TG in FCHL patients (98). FCHL patients have also low concentration of vitamin D, which is directly related to their atherogenic dyslipidemia. This deficiency is resolved by dyslipidemia treatment though the mechanism is as yet unknown (99). Miñambres et al. reported that FCHL patients will have lower 25(OH) D, higher TG, and lower HDL-C and LDL-C concentrations. The main difference of this study with others is consideration of different lipid-lowering regimens. Their patients were treated with monotherapy or combination therapy with statins and fibrates. According to the results, statin therapy was more effective in increasing 25(OH)D concentration. Changes in lipid parameters were not correlated with vitamin D concentration alterations (99). MTP inhibitors are another therapeutic option. Lomitapide is an MTP inhibitor, which prevents chylomicron synthesis and its efficacy in lowering VLDL and LDL in familial hypercholesterolemia has been shown (100, 101). Along with their gastrointestinal adverse effects, these drugs are still not evaluated in other hyperlipidemias such as FCHL. Mipomersen as an antisense oligonucleotide inhibitor of apoB synthesis is another therapeutic option. This injectable drug can effectively reduce LDL and lipoprotein(a) in patients with HeFH (102).

FUTURE DIRECTIONS FOR APPROPRIATE TREATMENT

Treatment of FCHL has been evolving since its discovery. As mentioned earlier, treatment was started from monotherapy with different lipid-lowering agents and continued toward different combination therapies. Several pharmacological and nutraceutical approaches have been suggested and used successfully in treating FCHL patients. Lupattelli et al. showed that primary hyperlipidemias respond differently to statins (59). Recently, PCSK9 has become an area of interest for those who need more aggressive cholesterol-lowering therapies (103). PCSK9 plays an important role in regulating cholesterol hemostasis (104). Abifadel et al. proposed that PCSK9 variants might be responsible for FCHL phenotype and hypothesized that these patients can also benefit from targeting PCSK9 (105). Various strategies have been put forward for PCSK9 inhibition (106, 107). PCSK9 antagonist therapy in combination with statins may become a superior therapy for FCHL patients though further research is warranted (Fig. 1). Moreover, given the recent developments in personalized medicine, it seems that treatment of FCHL patients may also become more dynamic in different populations. There is still a long way toward complete understanding of the role of different SNPs responsible for individual responses to different therapies in different populations suffering from FCHL.

CONCLUSIONS

FCHL has a polygenic background, and until now, many genes have been identified to be related to this type of hyperlipidemia. Considering that FCHL is the most common type of genetic hyperlipidemia and is one of the main causes of CVD, treatment of this disease is very important. Currently, combination therapy

with statins and fibrates along with dietary and lifestyle control are the basis of disease management but newer therapies are in the pipeline and expected to improve disease management. For example, combination of statins and PCSK9 antagonizing drugs is an appropriate therapy to reduce LDL-C in FCHL patients (13, 108). With this view, it seems necessary to perform more studies in future to find more genes related to FCHL pathogenesis and associated pathways. This will allow more rational, target based, and individualized therapies to be used in FCHL patients.

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