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CHARACTERIZING THE ROLE OF ABCG5/G8 IN SITOSTEROLEMIA: DIAGNOSTIC CHALLENGES IN DIFFERENTIATING FROM FAMILIAL HYPERCHOLESTEROLEMIA

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Abstract

Introduction. Sitosterolemia is a rare genetic disorder directly associated with dysfunction of ABCG5 and G8 genes. The data obtained was used to analyze the cellular mechanisms and the role of transporters in absorption and excretion of serum sterols. Thus, to understand the influence of mutations on the development of cardiovascular disease.

Aim. To investigate the clinical manifestation between sitosterolemia and familial hypercholesterolemia (FH), focusing on how dysfunctions of transporters lead to the misdiagnosis of sitosterolemia as FH.

Research Strategy. The data collection was conducted by searching research papers in English based on lipidology. The search strategy identified 118 papers, of which 42 were selected that meet established inclusion criteria: full-text publications in English, meta-analyses, cohort studies, experiments on mice, whereas established exclusion criteria: research papers in other languages, promotional articles, conferences, short reports. The research papers reviewed the span from 1970 to 2022.

Results. Inactivation of genes causes the dysregulation of sterols. FH is characterized by elevated low-density lipoprotein cholesterol (LDL-C), whereas sitosterolemia presents with moderate elevation in LDL-C but dramatic increase in phytosterols. The phenotypic overlap between sitosterolemia and FH complicates detection. Both disorders manifest cardiovascular complications with elevated total cholesterol (TC) levels. The lipid profile distinguishes these conditions, necessitating HPLC, GC-MS tools. Genetic testing for mutations is essential for confirmation. The findings suggest that sitosterolemia mimics the FH state. FH is managed primarily with statins, while sitosterolemia requires ezetimibe. In addition, dietary modifications that reduce the intake of plant sterols are recommended.

Conclusion. This review highlights ABCG5 and ABCG8 mutations that impair sterol transport, causing plant sterol accumulation. The condition often leads to xanthomas and early coronary artery disease. A major diagnostic challenge is the overlap with FH, as similar lipid abnormalities can obscure proper diagnosis.

Key words: *ABCG5, ABCG8, Lipid profile, Sitosterolemia, Familial Hypercholesterolemia, phytosterol.*

Резюме

ХАРАКТЕРИСТИКА РОЛИ ABCG5/G8 ПРИ СИТОСТЕРОЛЕМИИ: ДИАГНОСТИЧЕСКИЕ ТРУДНОСТИ В ДИФФЕРЕНЦИАЦИИ ОТ СЕМЕЙНОЙ ГИПЕРХОЛЕСТЕРИНЕМИИ

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Введение. Ситостеролемия - это редкое генетическое заболевание, непосредственно связанное с дисфункцией генов ABCG5 и ABCG8. Полученные данные использовались для анализа клеточных механизмов и роли транспортёров в абсорбции и выведении стеролов из организма. Таким образом, целью исследования является понимание влияния мутаций на развитие сердечно-сосудистых заболеваний.

Цель. Изучить клинические проявления ситостеролемии и семейной гиперхолестеринемии (СГ), с акцентом на то, как дисфункции транспортёров приводят к ошибочной диагнозу ситостеролемии как СГ.

Стратегия поиска. Сбор данных осуществлялся путём поиска научных статей на английском языке, посвящённых липидологии. В ходе поиска было выявлено 118 публикаций, из которых 42 статьи соответствовали установленным критериям включения: полнотекстовые публикации на английском языке, метаанализы, исследования пациентов, эксперименты на мышах. Исключались статьи на других языках, рекламные материалы, материалы конференций и краткие отчёты. Обзор охватывал исследования, опубликованные в период с 1970 по 2022 годы.

Результаты. Инактивация генов приводит к дисрегуляции транспорта стеролов. Для СГ характерно повышение уровня липопротеинов низкой плотности (ЛПНП), в то время как ситостеролемия сопровождается умеренным увеличением ЛПНП, но значительным повышением уровня фитостеролов. Фенотипическое сходство между ситостеролемией и СГ затрудняет их диагностику. Оба заболевания сопровождаются сердечно-сосудистыми осложнениями и повышением общего холестерина (ОХ). Липидный профиль позволяет различать эти состояния, для чего требуются такие методы, как ВЭЖХ и ГХ-МС. Генетическое тестирование на наличие мутаций является необходимым для подтверждения диагноза. Полученные данные показывают, что ситостеролемия имитирует состояние, схожее с СГ. Основной метод лечения СГ — использование статинов, тогда как для ситостеролемии требуется назначение эзетимиба. Кроме того, рекомендуется изменение рациона с ограничением потребления растительных стеролов.

Вывод. Обзор подчеркивает, что мутации в генах ABCG5 и ABCG8, нарушающие транспорт стеролов, вызывают накопление растительных стеролов. Заболевание часто приводит к развитию ксантом и раннему поражению коронарных артерий. Основной диагностической проблемой является сходство с СГ, так как схожие липидные нарушения затрудняют постановку правильного диагноза.

Ключевые слова: *ABCG5, ABCG8, Липидный профиль, ситостеролемия, семейная гиперхолестеринемия, стерол.*

Түйіндеме

СИТОСТЕРОЛЕМИЯДАҒЫ ABCG5/G8 РӨЛІНІҢ СИПАТТАМАСЫ: ОТБАСЫЛЫҚ ГИПЕРХОЛЕСТЕРИНЕМИЯДАН АЖЫРАТУДАҒЫ ДИАГНОСТИКАЛЫҚ ҚИЫНДЫҚТАР

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Кіріспе. Ситостеролемия – ABCG5 және ABCG8 гендерінің дисфункциясымен тікелей байланысты сирек кездесетін генетикалық ауру. Алынған деректер жасушалық механизмдер мен стеролдардың сіңуі мен шығарылуындағы тасымалдаушылардың рөлін талдауға пайдаланылды. Осылайша, мутациялардың жүрек-қан тамырлары ауруларының дамуына әсерін түсінуге болады.

Мақсат. Ситостеролемия мен отбасылық гиперхолестеринемияның клиникалық көріністерін зерттеу, соның ішінде тасымалдаушылардың дисфункциялары ситостеролемияны отбасылық гиперхолестеринемия ретінде қате диагностикаға қалай әкелетінін талдау.

Іздеу стратегиясы. Мәліметтер жинау липидология саласындағы ағылшын тіліндегі ғылыми мақалаларды іздеу арқылы жүзеге асырылды. Іздеу нәтижесінде 118 жарияланым анықталып, олардың 42-сі іріктеу критерийлеріне

сәйкес келді: толық мәтінді ағылшын тіліндегі мақалалар, метаанализдер, когорттық зерттеулер, тышқандармен эксперименттер. Іріктеу критерийлеріне сәйкес келмегендер: басқа тілдердегі зерттеулер, жарнамалық материалдар, конференция материалдары және қысқаша есептер. Зерттеулер 1970-2022 жылдар аралығын қамтыды.

Нәтижелер. Гендердің инактивациясы стеролдардың реттелуін бұзады. Отбасылық гиперхолестеринемия кезінде төмен тығыздықтағы липопротеидтердің (ТТЛП) деңгейі жоғарылайды, ал ситостеролемия кезінде ТТЛП деңгейі орташа деңгейде болса да, фитостеролдардың күрт өсуі байқалады. Ситостеролемия мен отбасылық гиперхолестеринемия арасындағы фенотиптік ұқсастық олардың диагностикасын қиындатады. Екі ауру да жалпы холестериннің (ЖХ) жоғарылауымен және жүрек-қан тамырлары асқынуларымен сипатталады. Бұл жағдайларды ажырату үшін липидті профиль қажет, ол үшін HPLC және GC-MS әдістері қолданылады. Диагнозды растау үшін мутацияларға генетикалық тестілеу жүргізу өте маңызды. Алынған деректерге сүйенсек, ситостеролемия отбасылық гиперхолестеринемияға ұқсас жағдайды имитациялайды. Отбасылық гиперхолестеринемияны емдеуде статиндер негізгі құрал болып табылады, ал ситостеролемия жағдайында эзетимиб тағайындалады. Сонымен қатар, өсімдік стеролдарын тұтынуды шектеуге бағытталған диета ұсынылады.

Қорытынды. Бұл шолу стеролдардың тасымалдануын бұзатын ABCG5 және ABCG8 гендеріндегі мутациялар өсімдік стеролдарының жиналуына әкелетінін атап көрсетеді. Ауру ксантоманың пайда болуына және жүрек артерияларының ерте зақымдануына жиі себеп болады. Негізгі диагностикалық қиындық – бұл отбасылық гиперхолестеринемиямен ұқсастығы, өйткені ұқсас липидті өзгерістер дұрыс диагноз қоюды қиындатады.

Түйін сөздер: *ABCG5, ABCG8, липидті профиль, ситостеролемия, отбасылық гиперхолестеринемия, фитостерол.*

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Introduction

Sterols are essential building blocks of cellular membrane and act as a precursor for steroid hormones [2]. One type of sterol, phytosterols are structurally similar to cholesterol and compete for absorption in the intestines [41], effectively lowering the LDL cholesterol level. The transport of phytosterols is regulated by ATP-binding cassette subfamily G5 and G8, encoding “sterolin-1” and “sterolin-2” proteins, respectively [17]. These genes products primarily form heterodimeric complex, which is responsible for homeostasis for sterols and non-cholesterol sterols, such as xenosterol and sitosterol.

The ABCG5 and ABCG8 genes are located together in STSL locus on 2p21 chromosome [11,16,21]. Both genes share several common transcription factors. They are regulated by Liver X Factor (LXR), Farnesoid X Factor (FXR) and Hepatocyte Nuclear Factor 4 alpha (HNF4α) [35,22,13]. According to the recent studies that were conducted by cryo-electron microscopy, the structures of ABCG5/G8 genes reveal unique dimer interface, which is crucial for their transport cycle [15]. The nucleotide binding domains of the heterodimeric complex exhibit several networks of interactions that are essential for ATP hydrolysis. It provides evidence that the ATP hydrolysis powers the sterol transport processes.

ABCG5 and G8 dysfunction disrupts normal sterol transport. Meaning that inactivation of heterodimers leads to increased intestinal absorption of plant sterols in the tissues [6]. This issue alters the lipid homeostasis, contributing to the sitosterolemia disease [28].

Sitosterolemia is a rare autosomal recessive disease characterized by excessive absorption of dietary sterols in the intestines and reduced elimination of these sterols through bile [28,16]. It is worth noting that patients with sitosterolemia have a high absorption rate of cholesterol, which is the possible reason for xanthomas and premature coronary artery disease development [31]. It is worth noting that there are other clinical signs. Elevation of phytosterols and incorporation into erythrocytes may lead to the development of stomatocytes, thrombo- and macrothrombocytopenia [27]. Other clinical signs may occur, such as hematologic abnormalities, including the presence of stomatocytes, thrombocytopenia, and macrothrombocytopenia, which can be the result of accumulated plant sterols and their incorporation into red blood cells and platelets, leading to abnormal morphology and function [25,38].

Non – cholesterol sterols are obtained mostly from plants and fish. It is known that xenosterols have poor bioavailability. Healthy human body absorbs < 5% of xenosterols with effective biliary elimination [27]. Since sitosterolemia leads to poor biliary excretion and intestinal hyperabsorption, patients with sitosterolemia show a 30 to 100 – fold increase in the serum phytosterols [33,18]. According to Wang et al. (2015), liver-specific [*L-G5G8*(−/−)], intestine-specific [*I-G5G8*(−/−)], and total [*G5G8*(−/−)] double knock-out mice had > 90-fold higher β-sitosterol concentrations in tissues than in wild-type mice [37].

This problem illustrates the importance of studying the disease among Kazakhstanis. Since there is a lack of data, it is impossible to conclude analyze the spread of sitosterolemia in Kazakhstan. On the other hand, some ABCG5/G8 mutations mimic familial hypercholesterolemia, worsening detection and therapy. In the laboratory, enzymatic colorimetric techniques for measuring cholesterol levels are not suitable for detection of sitosterolemia. The only possible solution is the use of high-pressure liquid chromatography, gas chromatography and gas chromatography/mass spectrometry that can correctly distinguish phytosterols from cholesterol [7].

The aim of this research study is to investigate the clinical manifestation between sitosterolemia and Familial Hypercholesterolemia (FH), focusing on how dysfunctions of heterodimeric compex of sterolins 1 and 2 can lead to the misdiagnosis of sitosterolemia as FH. Since both conditions present similar symptoms but differ significantly in their corresponding molecular mechanisms and treatment approaches.

Through the study, the following research questions were examined:

- What is the role of ABCG5/G8 genes in lipid metabolism?
- What is the cellular mechanism of sterol transportation?
- How do mutations in ABCG5/G8 contribute to the phenotypic overlap between sitosterolemia and Familial Hypercholesterolemia?

This study is directed to identify the role of ABCG5/G8 gene variants in alteration of sterol homeostasis, particularly the abnormal absorption of non-cholesterol sterols in sitosterolemia and compare it with the cholesterol metabolism dysfunctions seen in FH. Thus, the study will examine the implications of misdiagnosis, as treatment of sitosterolemia requires a different approach to that of familial hypercholesterolemia.

The data analysis seeks the understanding of how genetic mutations affect lipid transport can influence cardiovascular risk and provide guidance for clinicians in accurately diagnosing and managing patients with these rare lipid disorders.

Objective of this Review

The aim is to explore the molecular mechanisms of heterodimeric ABCG5/G8 transporter dysfunction, its contribution to lipid metabolism, and the clinical challenges posed by the phenotypic overlap between sitosterolemia and FH. Molecular diagnostics and personalized treatment approaches hold great importance for people affected by this disorder and particularly benefit regions like Kazakhstan where data on the prevalence and effect of sitosterolemia remain unknown. This review aims to promote better cardiovascular health outcomes and address the gap in genetic lipid disorder diagnosis in Kazakhstan.

This goal requires full understanding of cellular mechanisms of ABCG5/G8 gene expression. By obtaining this data, it is possible to examine the relationship between heterodimeric transporters and lipid homeostasis. Furthermore, correct monitoring techniques can be applied to monitor lipid profiles.

Research strategy

The data collection was conducted by searching research papers in English based on lipidology, which are aimed at studying the role of sterols. The following databases were used:

- Google Scholar (https://scholar.google.com/)
- Scopus (https://www.scopus.com/search/form.uri?display=basic#basic)
- ScienceDirect (https://www.sciencedirect.com/)
- NU library (https://library.nu.edu.kz/)

The challenging factor is limited number of available literature because ABCG5/G8 mutations are associated with a rare sitosterolemia condition. Sitosterolemia is considered as a rare disease since only about 100 cases are reported around the world [13]. Thus, much of the data comes from small sample sizes or case reports. On the other hand, some papers do not provide WES data, so it is hard to assess whether it is due to ABCG5/G8 mutations or other gene alterations.

Our search strategy identified 118 papers, of which 42 were selected that meet established inclusion criteria: full-text publications in English, meta-analyses, cohort studies, experiments on mice. These inclusion criteria were set to ensure a high level of evidence and scientific validity. We had to choose those literatures where the cause of this morbidity in cohorts is due to mutation of the ABCG5/G8 genes. Thus, established exclusion: research papers in other languages, promotional articles, conferences, short reports. The research papers reviewed the span from 1970 to 2022. The reason for a broad timeframe is the low volume of research relevant to this direction with specific experimental approaches.

Results and Discussion

Sterol Metabolism

Sitosterolemia is a disease associated with ABCG5 and G8 genes. Sterolin-1 and sterolin-2 form heterodimeric complex which acts as a sterol transporter. After digestion, free cholesterol (FC) and fatty acids (FA) enter the intestinal enterocytes in micelles.

As shown in figure 1, in the enterocytes, FC is reformed into cholesteryl esters (CE) and incorporated into chylomicrons (CM) with the help of the microsomal triglyceride transfer protein (MTTP).

The cholesterol-rich CMs are secreted into lacteals and enter venous circulation. Similar to cholesterol, xenosterols are absorbed in micelles, but most are exported back to the intestinal lumen. Meaning that phytosterols compete for Niemann-Pick C1-Like 1 (NPC1L1) for uptake. This process decreases the absorption of cholesterol preventing serum sterol elevation.

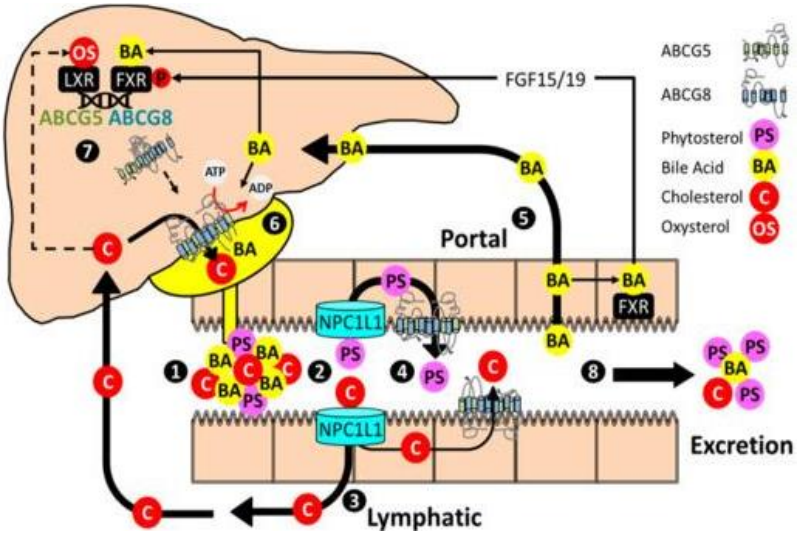

Figure 1. Enterohepatic sterol flux and regulation of *ABCG5* and *ABCG8* [39].

The ABCG5/G8 transporters form heterodimers that play a crucial role in secreting xenosterols back into the lumen. Xenosterols that remain may either be incorporated into CMs and enter circulation or be incorporated into high-density lipoproteins (HDL) with FC. Xenosterols are found in all lipoproteins, with the highest concentrations in low-density lipoproteins (LDL) and high-density lipoproteins (HDL).

In the liver, cholesterol is primarily absorbed via HDL receptors and chylomicron remnants via LDL receptors (LDLR) and LRP1. While cholesterol is incorporated into VLDL for peripheral tissue delivery, xenosterols are preferentially excreted via ABCG5/G8 into bile for intestinal elimination.

Plant sterols are known for their cardiovascular benefits, especially in reducing LDL cholesterol by competing with dietary and biliary cholesterol for absorption in the intestines. However, it is worth noting that at high concentrations, they can contribute to conditions like sitosterolemia, where elevated xenosterol levels lead to symptoms such as xanthomas, liver disease, platelet dysfunction, and atherosclerosis. It is usually misdiagnosed as Familial Hypercholesterolemia.

Transcriptional and Post Transcriptional Regulation

The transcriptional and post-transcriptional regulation of ABCG5/ABCG8 transporters plays a critical role in maintaining cholesterol and sterol homeostasis. The regulation of sterolins is tightly controlled by the actions of transcriptional factors, known as Liver X Receptor (LXR), Liver Receptor Homolog 1 (LRH1), GATA-4 and Hepatocyte Nuclear Factor 4α (NHF4α) [35,22,23]. It is seen that LXR elevates the mRNA and protein levels of sterolins in the liver and intestines, respectively. The process is triggered in response to dietary cholesterol. This is driven by the accumulation of oxysterols, which activate LXR and promote transporter expression [35,23,26,39].

Besides it, FXR agonists with the help of bile acids regulate the expression of ABCG5/G8. However, the activation of FXR depends on the action of Fibroblast Growth Factor 15/19 (FGF15/19), which is secreted in response to bile acids [35,39,40]. The suppression of expression is led by Constitutive Androstane Receptor (CAR) agonists [39,30]. This process is incorporated due to the elevation of bile acid levels.

Meanwhile, thyroid hormones also participate in regulation of ABCG5/G8 expression. According to recent studies, the hormones increase mRNA levels and enhance biliary cholesterol secretion [8].

There are several uncertain factors during post-transcriptional regulation, since not much has been studied in this direction. The formation of heterodimeric complex requires proper protein folding, which is facilitated by lectin chaperones, including Calnexin and Calreticulin [39,10]. Dysfunction of those chaperones leads to assembly failure. Thus, proteins will be degraded within the endoplasmic reticulum.

Both ABC transporters contain two nucleotide-binding composite sites. In this site, the Walker A motif of one NBD is bound to the motif of the other NBD [12,42]. Since the ATPase activity of the sterolins is central to their sterol transport, mutations in these regions alter the function of the transporters. Surprisingly, the mutation Walker A or Walker B in ABCG5 inactivates biliary sterol secretion, whereas corresponding mutations in ABCG8 do not affect secretion [36].

In fact, females have higher biliary cholesterol levels and increased transporter expression in comparison with male. In recent studies on mice, ovariectomy caused a reduction of ABCG5/G8 mRNA levels [5]. Thus, estrogen replacement therapy restored these levels. The research highlights the influence of estrogen on cholesterol metabolism.

Missense mutations in ABCG5/G8 interfere with dimer formation, stability and ability for transport. According to VarSome platform, for the total of 685 known mutations of ABCG5, 61.80% labeled as uncertain significance. The same goes for ABCG8, among 766 known gene variants 62.30% labeled as uncertain significance [14]. The lack of studies in this direction dramatically increases the relevance of research area.

Phenotypic Overlap in Sitosterolemia and FH

Familial Hypercholesterolemia (FH) is a genetic condition which is attributed to further development of coronary heart disease, including myocardial infarction [20]. The persistently high level of low-density lipoprotein (LDL) cholesterol is a primary cause of this disease. The reason for serum LDL cholesterol elevation is directly associated

with deleterious mutations of LDL receptor (LDLR), protein convertase subtilisin/kexin type 9 (PCSK9) and apolipoprotein B (APOB) [34,9,17]. It is clear that ABCG5/G8 genes action indirectly related to FH associated genes. However, there is a correlation between sitosterolemia and FH. Since mutations of sterolins mimic the FH phenotype [3]. This problem complicates the detection, clinical manifestation and dietary requirements. According to the recent studies conducted by Tada (2019), comparison of lipid profiles classified into four groups based on their genetic background ("No mutation", "ABCG5/ABCG8 mutation carriers", "Monogenic FH", "ABCG5/ABCG8-oligogenic FH"), there is an association between mutations of ABCG/G8 and FH phenotype [32].

Table 1.

Summary of comparison of clinical features, diagnostic markers, and treatment outcomes in sitosterolemia patients with FH condition.

Characteristic	Sitosterolemia	Familial Hypercholesterolemia (FH)
Definition	Rare autosomal recessive disorder due to mutations in the ABCG5/ABCG8 genes, leading to excessive absorption of plant sterols.	Common autosomal dominant disorder, often due to mutations in the LDLR, APOB, or PCSK9 genes, leading to elevated plasma LDL-C levels.
Inheritance	Autosomal recessive	Autosomal dominant
Key Mutation	ABCG5/ABCG8 genes (responsible for sterol excretion)	LDLR, APOB, PCSK9 genes (involved in LDL receptor function)
Typical Sitosterol level	30-100 times higher than normal levels (Normal: <1 μg/mL)	Normal sitosterol levels (< 1 μg/mL)
LDL-C level	Can be normal to moderately elevated (often 200-300 mg/dL)	Significantly elevated (>190 mg/dL in heterozygous FH, >400 mg/dL in homozygous FH)
Total Cholesterol Level	Normal to mildly elevated (often 200-400 mg/dL)	Markedly elevated (often >300 mg/dL in heterozygous FH, >600 mg/dL in homozygous FH)
High-Density Lipoprotein	Normal or slightly decreased	Typically normal or reduced
Key Biomarker	Elevated sitosterol (>5 μg/mL)	Elevated LDL-C (Low-Density Lipoprotein Cholesterol)
Clinical Presentation	Tendon xanthomas, premature atherosclerosis, arthralgia, hemolytic anemia	Tendon xanthomas, premature atherosclerosis, arcus corneae, xanthelasmas
Risk of Cardiovascular Disease	Elevated due to excessive plant sterol absorption and subsequent cholesterol dysregulation	High due to long-standing elevated LDL-C levels
Other Associated Conditions	Hemolytic anemia, arthralgia, hepatosplenomegaly, joint pain	Coronary artery disease, peripheral artery disease, stroke
Diagnostic Clues	Highly elevated sitosterol levels in blood; genetic testing confirming ABCG5/ABCG8 mutation; normal or mildly elevated LDL-C.	Markedly elevated LDL-C in the absence of secondary causes, positive family history, genetic testing confirming LDLR, APOB, or PCSK9 mutation.
Treatment Approach	Ezetimibe to block sterol absorption; Bile acid sequestrants (cholestyramine, colesevelam); Statins; Low-sterol diet.	Statins to lower LDL-C; ezetimibe; PCSK9 inhibitors; lifestyle and dietary modifications.

It is worth noting that significant differences are seen in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels across these groups. Group 3, characterized by monogenic FH, displays the median total cholesterol at 310 mg/dL, whereas median TC level of ABCG5/ABCG8 carriers at 290 mg/dL. The same trend is shown with LDL-C. Group 3 shows the median levels at 234 mg/dL, whereas the median level of ABCG5/G8 carriers at 199 mg/dL. While high-density lipoprotein cholesterol (HDL-C) levels remain relatively consistent across all groups. This analysis indicates that ABCG5/G8 mutations result in a less severe FH phenotype compared to monogenic FH. However, the slightly lower LDL-C and TC levels in ABCG5/G8 carriers still show a significant risk factor for cardiovascular disease. The findings suggest that ABCG5/G8 mutations exacerbate lipid dysregulation and contribute to elevated serum sterol levels. Thus, the data supports the hypothesis that ABCG5/G8 mutations mimic the hypercholesterolemic state. While oligogenic inheritance involving ABCG5/G8 mutations leads to a more pronounced disruption in cholesterol metabolism. Since the median TC level reaches 370 mg/dL, and the median LDL-C level at 266 mg/dL, respectively.

This analysis indicates that ABCG5/ABCG8 mutations result in a less severe hypercholesterolemia phenotype compared to monogenic FH. However, the slightly lower LDL-C and TC levels in ABCG5/ABCG8 carriers still represent a significant risk factor for cardiovascular disease. The findings suggest that although ABCG5/ABCG8 mutations do not drive cholesterol levels as high as monogenic FH, they exacerbate lipid dysregulation and contribute to an elevated cardiovascular risk profile, likely

due to combined effects of sterol accumulation and cholesterol metabolism disruption.

Furthermore, this research provided the analysis of sitosterol levels (μg/ml) across the same groups [32]. The subjects of group 1 are without any mutations showing the median sitosterol level of 2.89 μg/ml, serves as a baseline. While group 4, which consists of both FH and ABCG5/G8 mutations, exhibits the highest median sitosterol level at 4.06 μg/ml, which is almost twice higher than group 1. The difference between groups highlights the critical role of ABCG5/G8 mutations in disrupting the regulation of serum sterols, which accumulate to dangerously high levels in patients.

Meanwhile, group 2, characterized by ABCG5/ABCG8 mutations without an FH mutation, also displays elevated sitosterol levels, with a median of 3.96 μg/ml. This finding shows that ABCG5/ABCG8 mutations alone are sufficient to cause a marked increase in sitosterol, independent of an FH mutation. The similarity in sitosterol levels between Groups 2 and 4 suggests that the ABCG5/ABCG8 mutations are the primary drivers of plant sterol accumulation in both oligogenic and monogenic cases of FH.

Clinical features

Patients suffering from pathologies caused by mutations in the ABCG5 and ABCG8 sterolins face several clinical problems. These conditions are associated with a wide range of severity. Diseased cohorts may show increased plant sterol absorption by 3-12-fold. This leads to elevation of serum sterol levels by 30-100-fold [33,18]. There are different cases including mild symptoms such as fatigue to more serious conditions such as tendon xanthomas, dyslipidemia, premature atherosclerosis. In clinical practice, this creates difficulties in diagnosis.

Laboratory diagnosis relies on measuring elevated levels of plant sterols like sitosterol and campesterol, often detected using gas chromatography (GC) or high-performance liquid chromatography (HPLC). More advanced techniques such as LC-MS/MS are used for higher diagnostic sensitivity. Genetic testing for mutations in ABCG5 and ABCG8 is also used to confirm the diagnosis. Sitosterolemia is a rare sterol condition, the lack of standardized treatment methods worsens the therapeutic approaches due to some deleterious and missense mutations mimic familial hypercholesterolemia phenotype, worsening detection and therapy.

NPC1L1 is a membrane protein located in the small intestine and liver. It absorbs cholesterol by transporting dietary and biliary cholesterol from intestinal lumen into enterocytes. Treatment of sitosterolemia involves the use of ezetimibe, which blocks sterol uptake in the intestine by targeting the NPC1L1 transporter [29,4]. Statins also are used as a treatment. However, the NPC1L1 inhibitor ezetimibe is the most effective cure for this disease. This medication significantly reduces both cholesterol and plant sterol levels [24]. In extreme cases, hepatic transplantation has been shown to normalize sterol levels by restoring proper function to *ABCG5* and *ABCG8* in the liver [19].

Conclusion

This review has provided examination of the pathophysiology and molecular processes of sitosterolemia. The focus was largely on ABCG5 and ABCG8 gene mutations that dysregulate sterol transport. These mutations disrupt the balance between dietary sterol absorption and excretion. Inactivation of transporters leads to excessive accumulation of serum plant sterols. This type of disruption mostly results in the formation of xanthomas and premature coronary artery disease.

The significant diagnostic challenge is its clinical overlap with Familial Hypercholesterolemia. The similarities in lipid profile abnormalities between these conditions can obscure the correct diagnosis.

One of the key issues raised in this review is the lack of attention to sitosterolemia in Kazakhstan, where lipid metabolism disorders are not comprehensively studied. Traditional cholesterol measurement methods are not capable of examining plant sterol levels, necessitating the use of tools like high-pressure liquid chromatography, gas chromatography-mass spectrometry.

Thus, the findings underscore the critical need for increased awareness, improved diagnostic capabilities, and further research into the prevalence and impact of sitosterolemia and FH.

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