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Ethnicity and Response to Drug Therapy

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Abstract

Hypercholesterolemia is a complex disorder presenting in different forms, including the familial form (FH), with varying underlying aetiology, and contributing substantially to coronary artery disease. Particularly, the FH underlies monogenic changes in genes involved in cholesterol synthesis and transport, including the low density lipoprotein receptor, proprotein convertase subtilisin/kexin type 9 and apolipoprotein B. However, hyperlipidemia is largely a complex interaction of changes in multiple genes with environmental factors, such as diet, overweight and obesity that are controllable by adopting healthy eating habits and exercise, which may vary by ethnicity. Diet alone is often not adequate to achieve the desired lipid lowering effect in individuals harbouring very high cholesterol levels, necessitating the use of lipid lowering medication or other forms of therapy. Antilipidemic drugs fall into (a) bile acid sequestrants (b) cholesterol absorption inhibitors, (c) 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, (d) fibric acid derivatives (e) proprotein convertase subtilisin/kexin type 9 inhibitors, (f) miscellaneous agents and (g) drug combinations. Mutations in their various metabolizing enzymes, particularly the cytochrome P450 family, often lead to partially/non-functional, or even rapid metabolizing phenotypes, triggering great variations in the way individuals respond to drug therapy, which in turn depends on ethnicity. This may produce unexpected outcomes such as therapeutic failure, adverse side effects and toxicity in individuals of different ethnic origin. Hence, in-depth information of the impact of ethnicity on these relationships has the huge potential of achieving optimal quality use of drugs as well as improving the efficacy and safety of antilipidemic therapeutic agents.

Keywords: cholesterol, hypercholesterolemia, ethnicity, gene polymorphism, polygenic complex disease, anti-lipidemic drug therapy, drug metabolism

1. Introduction

Cholesterol is a sterol that presents one of the three major classes of lipids synthesized and utilized by animal cells to construct their cell membranes. It also serves as a precursor of the steroid hormones, bile acids and vitamin D, and is transported in the blood plasma within lipoproteins. These lipoproteins are classified according to their density as (a) very-low-density lipoproteins (VLDLs), (b) low-density lipoproteins (LDLs), (c) intermediate-density lipoproteins (IDLs) and (d) high-density lipoproteins (HDLs) [1]. Hypercholesterolemia (also often referred to as dyslipidemia) describes a condition characterized by elevated lipid (hyperlipidemia) or lipoprotein levels (hyperlipoproteinemia) (>240 mg/dL) in circulation [2]. Such elevated levels of lipoproteins, other than HDL (also called non-HDL-cholesterol), particularly the LDL-cholesterol, are associated with an increased risk of coronary artery disease (CAD) [3]. In contrast, increased HDL-cholesterol levels are deemed protective [4]. An elevation in circulating non-HDL- and LDL-cholesterol may be triggered by diet, obesity, genetic disorders or presence of other diseases, such as diabetes and dysfunctional thyroid [2, 5]. Hyperlipidemia is one of the most important players in developing cardiovascular disease leading to high mortality [6, 7]. Hence, management of hyperlipidemia not only maintains healthy lipoprotein levels, but is also designed to avert the more deleterious consequences of CAD manifestation.

Hyperlipidemia affects humans globally with a prevalence of approximate 34 million in the USA. It occurs partly as an inheritable monogenic (Mendelian) disease, specifically the familial form, which affects 1 in 500 individuals globally, but more frequently so, as a result of an interaction of genetic changes with environmental factors, that may or may not be modifiable. Inheritable forms include the familial types, such as homozygous familial hypercholesterolemia (HOFH) or familial hyperbetalipoproteinemia (FHBL), a disorder that impairs the body's capability to absorb and transport fats. This form of the disease is characterized by early signs of cholesterol infiltrates with premature CAD, accompanied by a building up of excess cholesterol in other tissues such as the skin, tendons and coronary arteries. This, in turn, is also accompanied by growths defined as tendon xanthomas, known to affect the Achilles tendons as well as tendons in hands and fingers [8]. Other forms of cholesterol deposits also exist, such as xanthelasmata under the eyelid skin and cornealis, accumulating at the edge of the clear front surface of the cornea. The complex form of hypercholesterolemia is triggered by some interplay between genetic variants with modifiable risk factors, such as lifestyle or diet and/or unmodifiable variables, such as age, ethnicity, gender and family history. Some of the modifiable predisposing factors such as diet, overweight and obesity are controllable by adopting a healthy eating plan, staying active and managing personal weight scale. However, patients with very high cholesterol levels, such as in familial hypercholesterolemia (FH), diet alone is often not adequate to achieve the desired lipid lowering effect, necessitating the use of lipid lowering medication to reduce its production and absorption [9], as well as other therapies including LDL apheresis or surgery. Several drug families are employed targeting different components of cholesterol metabolism. The success of treatment may vary in different communities, depending on a number of contributing factors, particularly ethnicity. Importantly, while the influence of the unmodifiable risk traits is likely to be felt alike across ethnicities, their actual impact on disease will often be defined by the extent to which genetic

changes interact with these environmental factors within a given population. These risk factors can also influence drug response and toxicity, whereby the penetrance of these interactions on disease and drug therapeutic outcomes similarly depends on ethnicity, with some influence of the confounding modifiable risk factors. This chapter therefore focuses on the impact of ethnicity on interaction of these predisposing factors, particular genetic polymorphism, in the management of hypercholesterolemia.

2. Ethnicity and hypercholesterolemia

Blood lipid levels are highly heritable traits. Essentially, hypercholesterolemia occurs as a result of the low-density lipoprotein receptor (LDLR) being unable to remove cholesterol effectively from circulation. This can be caused by mutations in one or more genes that regulate cholesterol metabolism and transportation. The greatest contribution to the manifestation of hypercholesterolemia and difficulties related to maintaining health circulating cholesterol levels are genetic changes in components of these pathways. While only a handful of Mendelian disease genes and founder mutations for the autosomal recessive form of the disease have been identified to date, there are many other genes that contribute to the complex form of the disease. Thus, whereas the Mendelian form is likely to exert the same impact globally, the manifestation of the complex trait will more often than not depend on the nature of the interactions between the predisposing genes and environmental factors, which may vary among various ethnicities. This, in turn, has a great impact on disease manifestation in a given society.

2.1. Ethnicity, race ancestry and disease

Ethnicity and race have traditionally been related to biological and sociological factors, respectively. Accordingly, race presumes shared biological or genetic traits and is distinguishable by the traits resulting from a shared genealogy due to geographical demarcations, while ethnicity connotes shared cultural traits and history, and possibly linguistic or religious traits. In terms of genetic undertones, therefore, individuals of the same racial background (ancestry) are likely to carry more common genetic architecture than those belonging to the same ethnicity. Hence, the impact of these two societal confounders on dyslipidemia manifestation may not always be the same. Besides, in multi-cultural societies, such as in the USA or Southern Africa, many (ethnic) admixture groups have arisen in the course of time, from different ancestral lineage, and are often placed into the one or the other ethnical group. This adds some complexity to the estimation of the depth of genetic adulteration in racial genetic texture, rendering the ancestral delineation more complex. Accordingly, the impact of intra-ethnic variations on disease might be over- or underestimated within a given community. Most importantly, the influence of ethnicity on the disease manifestation or therapeutic outcome is also often regulated by modifiable confounders as well as the depth of public awareness within a given society. Hence, the accuracy in the estimation of the depth of the influence of ethnicity on dyslipidemia and therapy thereof may depend on the constituent racial component of the given society.

2.2. Ethnicity and genetics of hypercholesterolemia

Genetically, hypercholesterolemia may occur in various forms depending on the type and genomic location of the causative mutation. This may directly be caused by a structural change in a gene involved in the transportation of the lipids. Thus, the monogenic (Mendelian) form, often manifest as familial hypercholesterolemia (FH), is triggered by changes in a single gene. To date, the monogenic form has been linked primarily to mutations in three genes, the *LDLR* [10–15], proprotein convertase subtilisin/kexin type 9 (*PCSK9*) [16–23] and apolipoprotein B (*APOB*) genes [24–28]. In most cases, individuals with FH will have inherited one or both altered copies of the gene from affected parents. In this case, the disease can be acquired in an autosomal recessive (presence of two copies of the mutated gene from both parents) such as the autosomal recessive hypercholesterolemia (ARH), or in a dominant (presence of only one copy of the mutated gene from either parent) form such as HOFH or heterozygous familial disease (HEFH). The recessive type tends to lead to the more severe form of the disease, which often appears in childhood. The HEFH is a very rare form of FH, affecting a small but noticeable percentage of individuals, yet constituting an important cause of early onset of CAD. The disease results from either biallelic pathogenic variants in one of the three genes or one pathogenic variant in each of two different genes. It is thought to account for 60–80% of FH.

However, the most common forms of hyperlipidemia are complex in nature, resulting primarily from an interaction between genetic changes and environmental factors [29]. Thus, apart from the three genes, *LDLR*, *APOB* and *PCSK9*, known to cause the monogenic disease, several others are also involved in the manifestation of the disease. The genes include the peroxisome proliferator-activated receptor- α (*PPAR- α*), cholesteryl ester transport protein (*CETP*), low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*), apolipoprotein (APO) A1 (*APOA1*), A4 and A5 complex (*APOA1/A4/A5*) and apolipoprotein E (*APOE*), 3-hydroxy-3-methylglutaryl coenzyme A reductase (*HMGCR*), lecithin cholesterolacyltransferase (*LCAT*) and lipoprotein lipase (*LPL*), just to name a few. The genes associated with the different forms of dyslipidemia are summarized in **Table 1**.

Among the genes associated with dyslipidemia to date, the *LDLR* is understandably the most well defined. This gene encodes the LDLR protein which binds to low-density lipoproteins (LDLs) particles, the primary carriers of cholesterol in the blood. This receptor resides on the outer surface of many cell types, particularly in the liver, where it picks up circulating LDL particles and transports them into the cell. Within the cell, the receptor is broken down in order to release cholesterol for utilization by the cell, storage or removal from the body. The LDLR is essential in regulating the amount of circulating cholesterol, whereby the speed at which the later gets eliminated from the system depends on the receptor expression. Hence, alteration in the structure of these receptors will lead to fundamental changes in the regulation of circulating cholesterol levels. Such mutations in the *LDLR* gene are thought to be the primary cause for FH, with a greater frequency in a population with founder mutations. Several such hyperlipidemia-related variants have been identified thus far in this gene [10–15]. These mutations have different effects on the function of the protein. For example, some of them do so by reducing the number of LDLRs produced within the cells, while others disrupt the ability of the receptors to remove the LDLs from circulation. As a result, individuals harbouring *LDLR*

mutations will have very high circulating cholesterol levels, ultimately leading to the familial form of the disease. Some of these mutations have been implicated in both the autosomal recessive (ARH) and dominant (ADH) forms of hypercholesterolemia, whereby in some ethnic populations, the ADH has been shown to exhibit allelic heterogeneity [11, 30]. Thus, genetic diversity has been described in FH [30, 31], pointing to the likelihood of differences in the extent to which these mutations may cause disease in different populations. This may be ascribable to differences in life style. It has also been suggested that the *LDLR* gene has a sex-specific pleiotropic effect, as is indicated by changes in the relationship between traits [32]. This suggests in turn that environmental factors, such as diet or even migration, may play a significant role in modulating the phenotype of heterozygous FH.

Gene	Chr locus	Protein function	Mechanism	Disorder (mutations)
APO A1	11q23.3	Promotes Chol efflux from tissue to the liver for excretion.	Cofactor for LCAT	hTG; HDL deficiencies; Tangier disease; HALP
APO A4	11q23.3	Major HDL and chylomicron component; chylomicron and VLDL secretion and catabolism	Required for lipoprotein lipase activation by ApoC-II; potent activator of LCAT	Chronic inflammatory demyelinating polyneuropathy
APO A5	11q23.3	Regulating plasma TG levels; inhibitor of hepatic VLDL production	Minor apolipoprotein associated with HDL, may activates LCAT	hTG; HLP
APOB	2p24-p23	Internalization of LDL particles by apoB receptor	Recognition signal for cellular binding; major constituent of LDL and VLDL	FHBL (>50); HL; FDB (>5), ADH
APOE	19q13.2	Ligand for LDLR and specific apo-E receptor (chylomicron remnant) of hepatic tissues	Mediates binding, internalization and catabolism of lipoprotein particles	Polygenic HL; HLP type II and III
CETP	16q21	Transfer of neutral lipids, e.g. cholesteryl ester and triglyceride among lipoprotein particles	Allows net movement of cholesteryl ester from HDL to TG-rich VLDL and TG and vice versa	HALP; hTG, Low HDLC
LDLR	19p13.2	Intracellular cholesterol transfer and transport in blood	Binding to bile acids in intestines	FH (>1000)
LDLRAP1	1p36.11	LDL binding and internalization; endocytosis	Adapter protein for LDLR endocytosis in hepatocytes and lymphocytes	HL (>10)
PCSK9	1p32.3	Regulation cholesterol homeostasis	Binds to LDLRs, VLDLR, APOER, APOER2	Familial HBLP
PPAR-α	3p25.2	Key regulator of lipid metabolism	Binds to peroxisome proliferators, e.g. hypolipidemic drugs	

ADH, autosomal dominant hypercholesterolemia; ApoB, apolipoprotein B; APOER, apolipoprotein receptor; CETP, cholesteryl ester transport protein; FDB, familial defective apoB-100; Chol, cholesterol; Chr; chromosomal position; FH, familial hypercholesterolemia; FHBL, familial hyperbetalipoproteinemia; HALP, hypoalphalipoproteinemia; HBLP, hypobetalipoproteinemia; HDLC, high-density lipoprotein-cholesterol; HMG-CoA; 3-hydroxy-3-methylglutaryl coenzyme A reductase; HLP, hyperlipoproteinemia; hTG, hypertriglyceridemia; LCAT, lecithin cholesterol acyltransferase; LDLR, low-density lipoprotein receptor; LDLRAP1, low-density lipoprotein receptor adaptor protein 1; LPL, lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; PPAR-α, peroxisome proliferator-activated receptor-alpha; VLDL, very-low-density lipoprotein.

Table 1. Gene polymorphisms currently known to contribute to hypercholesterolemia.

One other important gene involved in HL is that encoding the apolipoprotein B (apoB) proteins. This gene encodes two versions of the protein: a shorter version (apoB-48) and a longer version (apoB-100). Both isoforms are involved in transporting fat-like particles, including cholesterol, in the blood. They are synthesized primarily in two organs, whereby the apoB-48 is produced in the intestines, while the apoB-100 is synthesized primarily in the liver. The former functions as a component of the chylomicron lipoproteins and is important for the absorption of certain fat-soluble vitamins, such as the vitamins A and E. The apoB-100, on the other hand, constitutes a component of other forms of lipoproteins, specifically the VLDLs, IDLs and LDLs, all of which are involved in the transportation of fats and cholesterol in the blood. Accordingly, apoB facilitates the LDL binding to their receptors in the liver cell surface. This in turn enables the transportation of these lipoproteins into the cell, where they are broken down to facilitate the release of cholesterol. Thus, mutations in the *APOB* gene can cause familial hyperbetalipoproteinemia (FHBL) or hypercholesterolemia by triggering the production of abnormally short forms of the protein, and therefore a reduction or lack of dietary fat and cholesterol transportation and ultimately the body's ability to absorb fats and fat-soluble vitamins from the diet. The severity of the disease depends on the length of the abnormal protein. Accordingly, a resultant protein that is longer than the apoB-48 will not hamper its production; hence, it should still be capable of forming chylomicrons. On the other hand, a similar product of the apoB-100 in the liver will not be able to produce LPLs efficiently. Hence, protein products that are shorter than the apoB are associated with more severe symptoms than in cases where some normal apoB-48 is produced. *APOB* mutations may also trigger the familial ligand-defective apoB-100 (FDB) [27] and ADH conditions [26]. These states are characterized by the presence of very high circulating cholesterol levels and therefore increased risk of disease. The impact of genetic changes in *APOB* on hypercholesterolemia is, however, less described than that of the *LDLR* gene. Besides, there has been some inconsistencies in reports on the impact of some of these mutations in different populations [10], pointing to its variation by ethnicity [33, 34].

The proprotein convertase subtilisin/kexin type 9 (PCSK9) functions by enhancing the regulation of circulating cholesterol levels, thereby possibly controlling the number of LDLRs on the cell surface. It probably acts by breaking down the LDLRs before they reach the cell surface. A few hypercholesterolemia-related mutations have been reported in the PCSK9 to date [16, 35], and have been linked mainly to ADH [20–23]. Accordingly, the mutations responsible for the disease are termed 'gain-of-function' mutations as they enhance the protein activity or lead to the protein acquiring new atypical functions. Serum lipoprotein Lp(a) is thought to be elevated in FH as a result of such PCSK9 gain-of-function mutations [18, 19], for example. The overactive protein significantly reduces the number of LDLRs on the surface of the liver cells, possibly by triggering faster breakage of the LDLRs. Thus, the attenuated production of the receptors leads to more cholesterol accumulation, and therefore the possibility of the disease occurring. Other mutations in the gene defined as 'loss-of-function' mutations reduce blood cholesterol levels (hypcholesterolemia) by decreasing the PCSK9 activity or reducing its amount in the cell. These mutations lead to an increase in the number of LDLRs on the surface of liver cells. Harboring of such mutation has been linked to a significantly lower than average risk of developing heart disease. Furthermore, elevated

PCSK9 levels are thought to be detrimental for patients carrying either non-FH or HEFH [36], since they tend to correlate with LDL-cholesterol levels [37].

The PPAR- α , - β/γ are ligand-activated transcription factors serving as the primary regulators of several activities including glucose, fatty acid and lipoprotein metabolism, energy balance, cell proliferation and differentiation, inflammation and atherosclerosis. Thereby, the PPAR- α activates the lipoprotein lipase (LPL) to ultimately reduce the formation of VLDL-cholesterol and triglycerides as well as increasing HDL-cholesterol. The genes have been collectively implicated in hypertriglyceridemia [38], possibly through gene-gene interactive mechanisms, and may modulate the risk of CAD by influencing both fasting and postprandial lipid concentrations [39]. Together with the PPAR- γ , the PPAR- α has also been implicated in HL [40–43] and low HDL levels [44, 45].

As the name denotes, the function of cholesteryl ester transfer protein (CETP) is to transfer neutral lipids, such as cholesteryl ester, forming cholesterol among lipoprotein particles. Specifically, it controls the net influx of cholesteryl ester from HDL to triglyceride-rich VLDL and the equimolar transport of triglyceride from VLDL to HDL. Thus, it regulates the reverse cholesterol transport through which the lipid is removed from peripheral tissue and returned to the liver for elimination. Defects such as *CETP Taq1B* polymorphism in the encoding gene have been implicated in harbouring of low HDL-cholesterol [46, 47] and hypertriglyceridemia [48].

The low-density lipoprotein receptor adaptor protein 1 (*LDLRAP1*) acts essentially by influencing the function of the LDLRs. Hence, mutations in this gene would either prevent the cell from making functional receptors or alter their function. It probably interacts with the LDLRs thereby removing them together with the attached LDLs from the cell surface to the interior of the cell to facilitate the breaking down of the latter and the release of cholesterol. In the absence of a functional LDLRA1 protein, LDLR particles cannot be transported into the cell, even if they bind normally to them. This triggers the retention of the lipids in circulation, therefore leading to abnormally high cholesterol levels. Mutations in the gene have been associated with ARH [49–52]. This is thought to be a result of the gene producing an abnormally small, non-functional version of the protein or preventing the cell from making the functional protein.

The apolipoprotein A-1 promotes cholesterol efflux from tissue to the liver for excretion. It is also a co-factor for lecithin cholesterol acyltransferase (LCAT), which is responsible for the formation of the majority of cholesteryl esters. Some recent reports indicate that the increase in HDL-cholesterol on statin treatment may also be influenced by *APOA1* genotypes. The *APOA1* gene is closely linked to three other apolipoprotein genes, *APOA4*, *APOA5* and *APOC3* in a cluster form of *APOA1/C3/A4/A5* on chromosome 11. This complex has been associated with hypertriglyceridemia in various ethnic groups [53, 54]. The *APOA4* gene is a major component of HDL and chylomicrons, but not so much associated with VLDL. It is thought to be a potent activator of LCAT. It may play a role in chylomicrons and VLDL secretion and catabolism, and is needed by the apoC-II for efficient activation of LPL. The apo A5 regulates plasma triglyceride levels by acting both as a potent stimulator of triglyceride hydrolysis by apoC II-mediated LPL activity and as an inhibitor of hepatic VLDL production. However, its

activation of LCAT is weak and does not enhance the efflux of cholesterol from macrophages. The *APOA5* gene polymorphism has been associated with hypertriglyceridemia and hyperlipoproteinemia type 5 [54].

The apolipoprotein E (*APOE*) polymorphism is regulated through three common alleles, epsilon 2, 3 and 4, coding for proteins that differ in lipoprotein receptor binding activity or their catabolism. This lipoprotein contains two different polypeptides apoB-100 and the (lipoprotein) Lp(a) glycoprotein. The latter exhibits a genetic polymorphism that is regulated by a series of autosomal alleles at a single locus and is associated with lipoprotein plasma concentrations. This suggests that the same gene locus is involved in determining Lp(a) glycoprotein phenotypes and its plasma concentrations. Hence, variability in apolipoprotein genes related to the normal variance of lipoprotein concentrations play a major genetic role in multi-factorial forms of HL such as hTG, familial type III HL, polygenic HL [55] and ADH [24].

Although FH is thought to be monogenic to a greater part, some inter-ethnic differences have been reported in the prevalence of the disease. In the USA, for example, dyslipidemia is thought to be highly prevalent among Hispanics (Latinos), with Cubans appearing to be particularly at risk, possibly explained by socio-economic status and acculturation [56], while increased African ancestry has been apparently linked to a decrease in triglyceride and LDLC as well as increased HDLC levels [57]. Also, lower odds for combined hyperlipidemia have been demonstrated for African-Americans compared to whites, despite higher body mass index (BMI) and abnormal adiposity, while Hispanics had slightly higher and Asian no difference odds to whites [58]. These differences may to a greater part be due to variations in the genetic modifiers among ethnic groups, a subject that continues to be unravelled. Similarly, the prevalence of the CEPT polymorphism appears to vary among ethnic groups as suggested by a Singaporean study reporting highest prevalence in Indian and lowest in the Malays with the Chinese showing an intermediate value, while African-American veterans exhibited higher blood pressure, LDL-cholesterol and protein A1c levels than Whites [59]. Differences have also been reported in the distribution of the *APOA5* gene variants in various ethnic groups in China [54] and Singapore [59]. These variations have been partly linked to the existence of population admixture [60]. It has also been observed that some polymorphic gene locus controls the concentrations of Lp(a) lipoprotein complex in plasma which may vary very widely between individuals. Hence, variability in apolipoprotein genes related to the normal variance of lipoprotein concentrations play a major genetic role in multi-factorial forms of HL such as hTG, familial type III HL and polygenic HL [55], as well as ADH [24]. Furthermore, the effects of the *APOE* alleles on the phenotypic variance of plasma lipoprotein concentrations have been found to differ significantly among ethnic groups. This has been explained by the fact that *APOE* polymorphism encodes different proteins with different binding properties. However, to date, most of the large-scale studies have been performed primarily in individuals of European descent, but many other ethnic groups have not been exhaustively studied yet. Importantly, due to lack of studies in such populations, we might be missing important data relevant in the influence of ethnicity of the manifestation of the disease. For example, it is quite likely that because of consanguinity among ethnic Arab populations, their prevalence would rank among the highest in the world. Therefore, data needs to be collected on such populations

to define more precisely the impact of ethnicity on the relationship between gene polymorphism and HL manifestation, which is likely to be unique for that particular ethnic group. Nonetheless, these data furnish support to the notion of the inter-ethnic variations in lipid traits being linked to genetic variants that exhibit differences in frequencies in individuals of African, Asian and European ancestry [61]. Besides, differences in lifestyle, such as leisure time, smoking and pedantic life style, for example, will also exert an impact on the disease manifestation, as demonstrated by the different levels of awareness of health risks among urban population compared to rural ones. Therefore, their ultimate effect on disease manifestation may vary between different ethnic groups, even within a given society.

2.3. Confounders for ethnicity interactions with hyperlipidemia disease

As stated above, in the majority of cases, HL is a product of an interaction of a combination of lifestyle choices with structural alterations in a multiple of genes, rather than a result of a single inherited condition. The disease penetrance will be dependent on the prevalence of various risk factors, including diet, exercise and tobacco smoking, but more importantly gender and age. The latter are also important determinants of the influence of dyslipidemia and other diseases, such as diabetes and obesity, on the manifestation of CAD. Ultimately, the impact of these interactions on dyslipidemia varies by ethnicity. The impact of ethnicity on HL manifestation is, in turn, also greatly influenced by these lifestyle confounders, particularly the modifiable variables, such as obesity, diet and lifestyle. According to the World Health Organisation (WHO), obesity is a condition in which the body accumulates fat to the extent that the health and well-being of the individual are adversely affected [62]. The primary causes for this disorder are sedentary lifestyle and high-fat energy-rich diets. This is a result of fundamental adaptive changes involving the societal and behavioural patterns of modern communities, attributable mainly to increased urbanization and industrialization at the cost of the fading or disappearing traditional ways of living. These traits are themselves significantly influenced by other risk factors, such as BMI, which exhibits great inter-ethnic variability. To begin with, BMI is determined by the distribution of the body fat, which in turn depends on age and sex. The average body fat is known to differ among ethnic populations, as suggested by studies demonstrating that most Asian ethnicities have higher average body fat percentage than whites of the same age and BMI [63–65], for example. These variations appear to be a result of the distribution of body fat for a given BMI. A study in the Singaporean population established differences among its ethnic subpopulations in the association of the CETP variants, Taq1B and -629C>A, with plasma HDL-cholesterol in which the BMI was uniformly linked to disease [59]. The adverse health outcomes associated with these variations are often accompanied by additional complexities, especially since the depth of their relationships can also differ by ethnicity. To add to the intricacy of the problem, the relationship of BMI and such adverse health outcomes involves additional complexities of displaying intra-ethnic variations. For example, among white populations, Europeans have been reported to have a higher percentage of body fat at a given BMI than whites in the USA [63, 66], and a study in the Chinese showed lower average BMI levels among rural compared to urban populations [64, 67]. Thus, the BMI levels may also differ considerably among subpopulations within an ethnic group because of prevailing environmental and lifestyle conditions. Given

the variations in the ratios of body fat for a given BMI [64–66], some of these studies have led to the notion that Asians may be predisposed to a greater risk of clinical events, such as acquiring hypertension and cardiovascular disease, despite having lower BMI levels than Caucasians [63, 67–70]. Taken together, these data imply that the global impact of obesity on hyperlipidemia is similar across ethnicity, while that of the BMI may differ considerably even within an ethnic group, since the relationship between BMI and percentage of body fat depends on age and sex, and differs across ethnic groups [63, 65]. Gender has also been implicated, whereby for example, female veterans have been shown to display higher LDL-cholesterol than males [71]. Hence, the penetrance of their influence is ultimately dependent on their distribution by ethnicity. Differences in lipid profiles, prevalence of dyslipidemia and their risk factors can also be explained as product of combined effects of lifestyle and genetic factors [72]. Such inter-ethnic differences in the prevalence of obesity, cholesterol, hypertension and diabetes have similarly been ascribed to socio-economic effects and lifestyle changes [73]. The direct influence of the different risk traits on dyslipidemia can also vary within an ethnic group in presence of racial admixturing. All these variations will affect the appropriateness of managing dyslipidemic disorders in an ethnicity-dependent fashion.

3. Drug therapy of hypercholesterolemia

3.1. Anti-lipidemic agents

Anti-lipidemic agents are entities that are employed to enhance the reduction of circulating lipid levels. These agents can reduce LDL-cholesterol level and/or triglyceride levels, or facilitate the elevation of HDL-cholesterol, thereby preventing both the primary and secondary symptoms of CAD. These agents fall into one of the following categories: (a) bile acid sequestrants, (b) cholesterol absorption inhibitors, (c) 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, (d) fibric acid derivatives, (e) proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and (f) miscellaneous agents (**Table 2**).

3.1.1. Bile acid sequestrants

Bile acid sequestrants are a group of polymeric ion exchange resins that disrupt the enterohepatic circulation of cholesterol-containing bile acids by combining with bile components and preventing their re-absorption from the gut. These drugs are not absorbed following oral administration. They also do not undergo hydrolysis by digestive enzymes or become adsorbed into systemic circulation, but rather bind to bile acids in the intestines and prevent their reabsorption into the body. Hence, they are employed to reduce LDL-cholesterol levels by binding to cholesterol-containing bile acids in the intestines. Since the bound complex is insoluble, it is excreted in faeces. Accordingly, the liver is triggered to produce more bile acids, subsequently reducing the levels of circulating LDL-cholesterol. A decrease in bile leads to an increase in hepatic synthesis of bile acids from cholesterol, and a depletion of cholesterol increases LDLR activity, therefore increasing the removal of LDL-cholesterol from circulation.

Class	Drugs (examples)	Function	Mechanism	Metabolizing pathways/ enzymes
Bile acid sequestrants	Cholestyramine Colesevelam Colestipol	Binding to bile acids in intestines leading to LDLC reduction	Prevent resorption, decrease in bile acid; increase in hepatic synthesis of bile acids	P-glycoprotein; currently no CYP450-related information available
Cholesterol absorption inhibitors	Ezetimibe	Reduce dietary and biliary cholesterol absorption through the intestines	increased hepatic LDLR activity, thereby leading to increase clearance of LDLC	UGT-glucuronidation; Currently no CYP450-related information available
Fibric acid derivatives	Bezafibrate Clofibrate Gemfibrozil Fenofibrate Cinofibrate	Decrease formation of VLDL -cholesterol and triglycerides and an elevation in HDLC	Activating PPARs inducing transcription of gene that facilitate lipid metabolism	Hepatic, CYP3A4; P-glycoprotein; UDP-glucuronosyltransferases
Statins (HMG-CoA reductase inhibitors)	Atorvastatin Fluvastatin Pravastatin Lovastatin Simvastatin Rosuvastatin	Increase in LDL membrane receptors, and therefore clearance of LDLC from blood	inhibit the function of the HMG CoA enzyme; P-glycoprotein substrates	Hepatic; CYP3A4; CYP3A5; CYP2C9; CYP2C19; CYP1A1; CYP2C8; CYP2D6; UGT-glucuronidation
PCSK9 inhibitors	Alirocumab Evolcumab	Antibodies, preventing LDLR destruction	inhibits PCSK9 Increase LDLR availability	Reticuloendothelial system? Currently no CYP450-related data
Nicotinic acid agents	Niacin Niacor Slo-Niacin	Reduction in LDLC and increase in total HDL; decrease ApoB-100 levels	Precursors for NAD and NADP involved in hydrogen transfer processes	Hepatic; currently no CYP450-related information available
CETP inhibitors	Torcetrapid Anacetrapid Evacetrapid	Blocking all major plasma CETP lipid transfer functions	Induction of non-productive enzyme complex with HDL	Currently no CYP450-related information available

ApoB-100, apolipoprotein B-100; CETP, cholesteryl ester transport protein; CVD, atherosclerotic cardiovascular disease; HEFH, heterozygous familial hypercholesterolemia; HDL, high-density lipoprotein; HDLC, high-density lipoprotein-cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HOFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDLC, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; NAD, nicotinamide adenine dinucleotide; NADP, NAD phosphate; PCSK9, proprotein convertase subtilin/kinase subtype 9; PPARs, peroxisome proliferator-activated receptors; TG, triglycerides; UGT, uridine 5'diphosphate-glucuronosyltransferase.

Table 2. Summary of the function, functional mechanism and metabolic pathways of anti-lipidemic drugs.

3.1.2. Cholesterol absorption inhibitors

Cholesterol absorption inhibitors, such as ezetimibe, belong to a group of chemicals known as monobactams. They decrease the amount of intestinal cholesterol that is delivered to the liver by reducing the absorption of dietary and biliary cholesterol through the intestines. Thus, these

drugs exert their effects by lowering both LDL-cholesterol and total cholesterol. Specifically, ezetimibe selectively inhibits the intestinal absorption of cholesterol and related phytosterols, thereby leading to a decrease in cholesterol clearance from the blood. It does not, however, inhibit cholesterol synthesis in the liver. A reduction in cholesterol levels delivered to the liver results in increased hepatic LDLR activity. This, in turn, enhances the clearance of LDL-cholesterol. The use of ezetimibe is called for especially in individuals who cannot take statins or as additional drug in cases where a need arises to maintain a low statin drug dose because of side effects. Ezetimibe is primarily metabolized via glucuronide conjugation.

3.1.3. *Fibric acid derivatives*

Fibric acid derivatives are broad-spectrum lipid lowering drugs, whose main action leads not only to a decrease in triglyceride levels, but also a reduction in LDL-cholesterol levels, thereby contributing to the elevation of HDL-cholesterol. The drugs are believed to activate the peroxisome proliferator-activated receptor alpha (PPAR- α). This protein activates the lipoprotein lipase, ultimately resulting in decreased formation of VLDL cholesterol and triglycerides and an elevation in HDL-cholesterol. The three drugs, bezafibrate, clofibrate and gemfibrozil, are hepatically metabolized. Clofibrate is metabolized and rapidly de-esterified in the gastrointestinal tract or through first pass metabolism to its active form clofibrate acid (chlorophenoxy isobutyric acid). Gemfibrozil undergoes UDP-glucuronidation (oxidation) through different isoforms of the UDP-glucuronosyltransferase to gemfibrozil 1-b-glucuronide, to eventually form a hydroxymethyl and a carboxyl metabolite. However, the enzymes responsible for bezafibrate metabolism have not been identified yet. Currently, no metabolic pathway has been defined for fenofibrate and cinnofibrate yet.

3.1.4. *The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors*

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (HMGCR) inhibitors, also known as statins, are drugs that reduce cholesterol synthesis in the liver by competitively inhibiting the HMGCR activity. A decrease in cholesterol production leads to an increase in the number of membrane LDLRs, which enhances the clearance of LDL-cholesterol from circulation. This, in turn, leads to an increased hepatic LDLR expression and greater uptake of LDL-cholesterol from plasma, thereby reducing the production of very low-density lipoprotein (VLDL), the precursor of LDL. The net statin dose-dependent reductions in LDL cholesterol are 20–60%, accompanied by some reductions in plasma triglyceride and a small rise in HDL-cholesterol.

The most commonly used statins are simvastatin and atorvastatin. Until recently atorvastatin was considered the most effective statin available for decreasing LDL given in daily doses of 10–80 mg. Furthermore, the higher dose was shown to decrease serum triglycerides by 45% in individuals with hypertriglyceridemia. However, rosuvastatin appears to be even more effective than atorvastatin in lowering LDL-cholesterol over its licensed dose range of 10–40 mg, although there appears to be no significant difference between 40 mg rosuvastatin and 80 mg atorvastatin in this respect. The advent of statins into anti-lipidemic therapy was triggered by the discovery and deciphering of the role of the LDLR in FH. They were soon found not

only to lower the LDL-cholesterol levels, but also to effect a significant reduction in cardiac events and mortality. They are probably the most effective drugs in lowering LDL-cholesterol available to date. They lower both the LDL-cholesterol and risk for cardiovascular disease in a concentration-dependent fashion.

3.1.5. Proprotein convertase subtilisin/kexin type 9 inhibitors

The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, alirocumab and evolocumab, are human monoclonal antibodies, which act by inhibiting the PCSK9 function to increase the LDLR availability. They are employed primarily for treating adults with HEFH, HOFH or clinical atherosclerotic cardiovascular disease taking other cholesterol lowering medication, but requiring additional lowering of cholesterol. Inhibition of PCSK9 function holds significant promise as a therapeutic option especially for reducing cardiovascular risk.

3.1.6. Cholesteryl ester transport protein inhibitors

The cholesteryl ester transport protein (CETP) inhibitors apparently function by blocking all of the major lipid transfer functions of plasma CETP through an induction of a non-productive complex between the transfer protein and HDL. By inhibiting the CETP function of transferring HDL-cholesterol to the VLDLs or LDLs, they increase the HDL levels and reduce that of the LDLs.

3.1.7. Nicotinic acid agents

The nicotinic acid agents, such as the nicotinic acid (niacin) itself, are water-soluble vitamin B derivatives, which increase the lipoprotein levels in high doses, lower total cholesterol, LDL-cholesterol and triglyceride levels, while raising HDL-cholesterol level. Niacin is a precursor to nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are co-factors to several enzymes. These agents are hepatically metabolized. The mechanism involved in their lipid lowering actions is not fully understood yet. It appears to involve several actions, such as a decrease in esterification of hepatic triglycerides.

3.1.8. Combinations and miscellaneous agents in anti-lipidemic therapy

As described above, some of the anti-lipidemic agents target the lowering of LDL-cholesterol, some aim to reduce triglyceride levels, while others assist in raising HDL-cholesterol. They can prevent both primary and secondary symptoms of CAD. However, some patients who are statin-resistant or intolerant do not respond to or do so very weakly for single drug treatment. Combinations of different anti-lipidemic agents, such as niacin or ezetimibe with statins, can lead to significant reduction in the levels of LDL-cholesterol and triglycerides in blood. Treatment with ezetimibe-bile acid sequestrants and statin-gemfibrozil is also available [74]. Anti-lipidemic agents are also available in combination with anti-hypertensive agents. This is consistent with the concept that taking one tablet of such a combination of agents makes it more conducive and easier for patients to take their medications, which in turn increases compliance. Apart from the above-mentioned classes of drugs, several other agents are also

employed to treat patients for lowering of LDL-cholesterol and triglycerides as well as raising HDL-cholesterol.

3.2. Influence of ethnicity on patient response to anti-lipidemic therapy

The response (efficacy) of a drug is a product of both its pharmacodynamic and pharmacokinetic characteristics. However, genetic factors also have a significant, albeit less well documented, impact on how individuals respond to drug therapy. Pharmacodynamics is a discipline that characterizes the biochemical and physiological effects of drugs, the mechanisms of drug action and the relationship between drug concentrations and effect. Pharmacokinetics, on the other hand, relates to the interaction of a drug with the body with respect to absorption, distribution, metabolism and excretion (ADME) properties. Hence (pharmacodynamically, the effect of the drug will be influenced by structural changes, particularly to receptor proteins and signalling transduction entities, while (pharmacokinetically, these effects will be modulated by modifications in entities, particularly enzymes, involved in the bioavailability or excretion of the drug. Hence, polymorphisms in genes encoding proteins that mediate the effects of the anti-lipidemic drugs, such as receptors, as well as in the cholesterol biosynthetic pathways exert a significant impact on the therapeutic outcome of these drugs in a given population. With respect to hyperlipidemia, in particular, structural changes in the majority of the genes involved in the binding of cholesterol to its vehicles, such as the LDLR or apoA1, for example, would affect the dynamics, while those that are involved in its different ADME phases would influence the kinetics. For example, the ARH individuals appear to be more responsive to lipid lowering drugs. Furthermore, patients with ARH resulting from LDLRAP1 mutations are likely to have more severe cardiovascular involvement than the hypercholesterolemia homozygotes, and will also present with lower LDL-cholesterol and higher HDL-cholesterol levels. It is also generally thought that patients with HOFH do not respond well to lipid lowering therapy with statins because they cannot respond to an increased demand for hepatic cholesterol through the up-regulation of the LDLR activity. Variation in response to anti-lipidemic agents has also been linked to polymorphisms in the *CETP*, *APOE*, *HMGCR*, *CLMN* and *APOC1* genes, whereby, for example, *APOE* genotypes have been associated with differential response to treatment with fenofibrate [75].

The efficacy of a drug is determined not only by its pharmacodynamic state, but also by its pharmacokinetic (ADME) properties. Accordingly, drug metabolism passes through three phases. These include the modification of the drug through interaction with the CYP450 family of enzymes (phase I) to introduce a reactive or polar group. This is followed by the conjugation of the altered substance to a polar compound in phase II reactions. This is then catalysed by a transferase enzyme, such as glutathione S transferases. In the final stage (phase III), the conjugated product may be further processed prior to recognition by efflux transporters and removed from the cells. Hence, the metabolic rate usually determines the duration and intensity of the pharmacological action of an agent.

The CYP450s constitute a multi-gene family of primarily membrane-associated proteins that are expressed in most organ systems and play important roles in the synthesis and biotransformation of hormones, cholesterol and vitamin D, among others, and are engaged in a large

and diverse range of enzymatic activities, including the catalysis of organic substrate oxidation [76–78]. Specifically, they constitute the most important metabolizers for anti-lipidemic agents, particularly the HMGCR inhibitors (statins) [79]. The most important CYP450 phase I enzymes in the metabolism of anti-lipidemic drugs are the CYP2C and CYP3A subfamily as well as the CYP2D6 and CYP1A1 enzymes. **Table 3** gives examples of some of the important CYP variants in anti-lipidemic therapy. These enzymes vary in the extent of their involvement in drug metabolism, whereby some metabolize a limited cohort while others process multiple substrates. Thus, for example, atorvastatin is metabolized through at least two CYP450s, CYP3A4 and CYP3A5, to the ortho- and parahydroxylated metabolites, all of which are capable of inhibiting the HMGCR activity, while fluvastatin is metabolized hepatically via hydroxylation to the 6-hydroxyfluvastatin, 5-hydroxyfluvastatin and N-deisopropylfluvastatin by the CYP2C9, but is also thought to be metabolized to a lesser extent to the 5-hydroxyfluvastatin by a number of other subtypes including the CYP1A1, CYP2C8, CYP2D6 and CYP3A4. It undergoes glucuronidation via the uridine diphosphate glucuronyltransferase (UGT) enzyme system. Pravastatin appears to be hepatically metabolized by CYP2C9, CYP2D6 and CYP3A4 with no notable effect on its overall activity and elimination. Simvastatin is similarly hepatically metabolized to its β -hydroxyacid metabolite through CYP3A4. Rosuvastatin is only slightly metabolized to the rosuvastatin 5 S-lactone by CYP2C9 and N-desmethylosuvastatin by the CYP2C9 and CYP2C19. Lovastatin is hepatically metabolized primarily to the β -hydroxyacid, through as yet undefined enzymes, and undergoes glycosylation by the P-glycoprotein pathway. In the presence of a genetic change in the metabolizing enzymes, these intended therapeutic end-point may be adversely affected leading to lack of activity or even enhanced side effects of the drugs.

The activity of each enzyme encoded by the combination of CYP450 alleles is categorized as one of five possible phenotypes: normal (NM), poor (PM), intermediate (IM), rapid (RM) and ultra-rapid (URM) metabolizers [80]. Alleles that lead to defective, qualitatively altered, diminished or enhanced rates of drug metabolism have been identified for most of the CYP450s. Defective alleles are usually a product of gene deletions, or conversion, whereby pseudo-gene and single nucleotide polymorphisms cause frameshift, mis-sense, nonsense or splice site mutations. Thereby, homozygous forms lead to a total absence of an active enzyme and impaired ability to metabolize drugs. The PM phenotype is caused by ‘loss-of-function’ alleles, while URM are a result of a duplication or amplification of an active gene, and IM are often heterozygous or carry alleles with mutations that decrease enzyme activity only moderately. Star nomenclature is commonly used in describing the various allelic subtypes of the enzyme. Accordingly, the *1 is designated as normal (commonly referred to as wild-type or fully functional) and subsequent variant alleles are numbered in the order that they are identified and characterized. Each pharmacogenetic allele may include several SNPs in form of a haplotype, rather than a single site mutation. Thus, functional changes in the encoding genes lead to enzymes with decreased/increased activity or lack of enzyme expression/activity through various molecular mechanisms. Furthermore, the incidence of a poor or slow metabolizer phenotype for a given enzyme triggered by allelic variants may vary significantly between populations.

Gene	Common name	RS ID	Arabs	Eur	CEU	Jap	Chin	Afr	Asians
CYP1A1	CYP1A1*2C_2454A>G(I462V)	rs1048943	0.061	0.031	0.232	0.209	0.232	0.036	0.256
	CYP1A1*4_2452C>A (T461N)	rs1799814	0.829	0.030	0.025	0.011	0.000	0.003	n.a.
	CYP1A1_134G>A (G45D)	rs4646422	0.001	0.000	0.000	0.168	0.139	0.000	0.14
	CYP1A1_1412T>C (I286T)	rs4987133	0.965	n.a.	0.004	0.000	0.012	0.000	n.a.
CYP1A2	CYP1A2*1C_-3860G>A (Promoter)	rs2069514	0.915	0.020	0.081	ND	ND	0.313	0.242
	CYP1A2*1F_-163C>A (Promoter)	rs762551	0.699	0.320	0.279	0.395	0.337	0.434	0.312
	CYP1A2*1K_-729C>T (Promoter)	rs12720461	0.958	n.a.	0.000	0.000	0.023	0.000	0.023
	CYP1A2*1K_-739T>G (Promoter)	rs2069526	0.096	n.a.	0.004	0.041	0.09	0.128	0.093
CYP2C8	CYP2C8*2	rs11572103	n.a.	0.004	0.000	0.000	0.000	0.190	n.a..
	CYP2C8*3	rs1050968, rs11572080	n.a.	0.118	0.137	0.000	0.000	0.000	0.000
	CYP2C8*4 (C>G)	rs1058930	n.a.	0.058	0.066	0.000	0.000	0.004	0.000
	CYP2C8*8	rs72558195	n.a.	0.001	n.a.	n.a.	n.a.	n.a.	n.a.
CYP2C9	CYP2C9*11_42542C>T (R335W)	rs28371685	0.996	0.002	0.022	0.006	ND	0.024	0.000
	CYP2C9*2_3608C>T (R144C)	rs1799853	0.852	0.124	0.104	0.000	0.000	0.008	n.a.
	CYP2C9*3_42614A>C (I359L)	rs1057910	0.944	0.059	0.058	0.023	0.047	0.000	0.044
	CYP2C9*6 (-/A)	rs9332131	N.A.	0.000	0.000	N.A.	N.A.	0.008	N.A.
CYP2C18	CYP2C18_c.*31C>T (3'UTR)	rs2860840	0.269	0.384	0.384	0.224	0.233	0.004	0.233
	CYP2C18_c.*592C>A (3'UTR)	rs1326830	0.009	0.042	0.000	0.215	0.174	0.021	n.a.
	CYP2C18_c.204T>A (Y68X)	rs41291550	0.012	n.a.	0.006	0.106	0.037	0.064	n.a.
CYP2C19	CYP2C19*17_-806C>T	rs12248560	0.744	0.224	0.217	0.000	0.022	0.275	0.022
	CYP2C19*2	rs4244285	n.a.	0.145	0.155	0.284	0.256	0.144	n.a.
	CYP2C19*3	rs4986893, rs57081121	n.a.	0.000	n.a.	n.a.	n.a.	0.002	0.058
CYP2D6	CYP2D6*4	rs3892097	n.a.	0.186	n.a.	n.a.	n.a.	0.061	0.006
	CYP2D6*17	rs28371706(T); rs16947 (A)	n.a.	0.002	n.a.	n.a.	n.a.	0.218	0.000
SLCO1B1	SLCO1B1*5	rs4149056	n.a.	0.161	0.158	0.110	0.151	0.014	0.128
UGT1A1	UGT1A1*28	rs4148323, rs8175347	n.a.	0.007	0.000	0.111	0.200	0.001	0.161

Minor allele distribution of CAD-related variation among different ethnic groups. Asians, represents studies done in other (non-Japanese, non-Chinese) ethnicities; Afr, Africans, predominantly Yoruba; Arabs, ethnic Middle East Arabs; Chin, Chinese, primarily the Han population; CEU, Caucasians; EUR, Europeans; Jap, Japanese; RS ID, DBSNP ID.

Table 3. Ethnicity and anti-hypercholesterolemia therapy-related gene variants.

The CYP2Cs involved in anti-lipidemic drug metabolism consist of four isoform members, CYP2C8, CYP2C9, CYP2C18 and CYP2C19, which are also thought to metabolize approximately 20% of all clinically used drugs [81]. The CYP2C8 gene resides within a cluster of CYP450 genes on chromosome 10q23.33. In liver microsomes, it is involved in an NADPH-

dependent electron transport pathway engaged in the oxidation of structurally unrelated compounds. It exhibits at least 16 allelic forms denoted *1A, *1B, *1C and *2-*14 (<http://www.cypalleles.ki.se/>). At least five of these (*2, *3, *4, *8 and *14) encode proteins with decreased enzyme activity. The distribution of variant alleles of *CYP2C8* gene differs among ethnic populations [4]. The *CYP2C8**2, the variant most common in Africans, is related to a poor metabolizer phenotype (PM) in subjects carrying at least one copy of the defective allele [4, 9]. Poor metabolizers experience a longer drug half-life [12] and increased adverse side effects.

The *CYP2C9*, which constitutes the main enzyme for rate-limiting metabolism of fluvastatin, pravastatin and rosuvastatin, appears to have the largest impact on the dose requirements, and is thought to hydroxylate about 16% of therapeutically used drugs. The gene resides on chromosome 10q23.33. It exists in at least 66 allelic forms (*1A-D, *2A-C, *3A, B, *4-*60) (<http://www.cypalleles.ki.se/>), whereby the vast majority encode proteins with decreased activity. Hence, the impact of its variants on anti-lipidemic drug therapy is of significant consequence. Of special interest are those with a narrow therapeutic index, where impairment in *CYP2C9* metabolic activity might cause difficulties in dose adjustment as well as toxicity [82]. *In vitro* data have demonstrated an association of the *CYP2C9**2 and *3 alleles with significant reduction in intrinsic clearance of a variety of *CYP2C9* substrates compared with the wild-type *CYP2C9**1. However, the extent of these reductions appears to be highly substrate-dependent [83]. In addition, multiple *in vivo* investigations and clinical case reports have associated genotypes expressing the *CYP2C9**2 and *3 alleles with significant reductions in both the metabolism and daily dose requirements of selected *CYP2C9* substrates [83]. For example, an allelic variant causing a Leu359 to Ile359 substitution has been implicated in the decreased metabolic clearance of various therapeutic agents [81, 83]. Similarly, the variants coding for R144C (*2) and I359L (*3) amino acid substitutions have been suggested to exert significant functional effects and exhibit appreciably high population frequencies. Accordingly, individuals expressing these variant genotypes also appear to be significantly more susceptible to adverse events with the narrow therapeutic index agents, especially during the initiation of therapy [84]. The pharmacokinetics of fluvastatin enantiomers were found to depend on the *CYP2C9* genotypes [85], leading to the proposition for potential clinical utilization of the later in adjustment of drug dose of the former [85].

Probably the most familiar of the *CYP2C* subfamilies with respect to their impact on drug efficacy is the *CYP2C19* [86, 87]. The encoding *CYP2C19* gene is located on chromosome 10q23.33. At least 49 allelic forms (*1A-C, 2A-H, *2J, *3A-C, *4A, B, *5A, B *6-*35) have been reported for this gene. The important phenotypes for its anti-lipidemic therapy include the ultra-rapid (URM; *17), extensive (EM), intermediate (IM) and poor (*2 or *3) metabolizers as well as loss-of-function (*4). Its PM phenotype is important in statin therapy, whereby these individuals quite frequently experience exaggerated drug response and side effects at standard doses.

The *CYP2D6* (debrisoquine/sparteine hydroxylase) acts on about 25% of all prescription medications, including the drugs that are employed in management of dyslipidemic disorders. The encoding *CYP2D6* gene itself, located on chr22q13.2, is highly polymorphic, and several

mutations leading to the absence of a functional enzyme have been identified [80]. Currently, there are more than 77 alleles (including *1A-E, *1XN, *2A-H, *2J-M, *2XN, *3A, B, *4A-H, *4J-P, *5, *6A-D, *7-9, *9X2, *10A-D, *10X2K, *11-13, *14A, B, *15-17, *17XN, *18-35) described for this locus. Although the gene appears in several polymorphic forms, probably only the six most common defective alleles will predict its phenotype with almost absolute certainty [88]. The PMs include *2 - *6, *10, *17, *29 *35 and *41, whereby the null alleles do not encode a functional protein with detectable residual enzyme activity. Combinations of altered alleles have been described resulting from substitutions, deletions or copy number changes, such as duplications of the entire gene leading to variant metabolizer phenotypes ranging from PM to URM. The CYP2D6 PM phenotypes are important for patients taking anti-lipidemic agents, as they may exhibit poor tolerance to these drugs [89]. Like the CYP2C19, PMs of drugs metabolized through the CYP2D6 often experience exaggerated drug response and side effects at standard statin doses. Clinical consequences of the CYP2D6 polymorphism may manifest either in form of adverse drug reactions or altered drug response. It has been demonstrated, for example, that the pharmacokinetics of fluvastatin enantiomers depend on the CYP2C9 genotypes, leading to potentially toxic bioactivation reactions [85].

The *CYP3A4* and *CYP3A5* form part of a CYP450 gene cluster constituting a group of heme-thiole mono-oxygenases on chr7q21.1. The CYP3A4 protein localizes to the endoplasmic reticulum and its expression is induced by glucocorticoids and some pharmacological agents. The enzyme is apparently involved in the metabolism of about 50% of the drugs in use today, including several HMGCR inhibitors, through the hydroxylation process. This process is often followed by dehydrogenation leading to more complex metabolites [90]. However, most of the drugs undergo deactivation by CYP3A4 either directly or by facilitated excretion from the body. Alternative splicing of the gene results in many transcript variants. Thus far, about 45 alleles (*1A-H, *1J-T, *2-14, *15A-B, *17, *18A-B *19-26) have been described, majority of which result in decreased function of the enzyme. The other member, CYP3A5, is localized to the endoplasmic reticulum in liver tissue. In liver microsomes, the CYP3A5 is involved in NADPH-dependent electron transport pathways. At least two pseudo-genes of the CYP3A5 gene have been identified at this locus. It exists in about 25 allelic forms (*1A-E, *2, *3A-L, *4*10), the majority of which encode proteins with severely attenuated enzyme activity. Furthermore, the CYP1A1 resides on chromosome 15q24.1. To date, 16 alleles, *1, *2A-C, 3-*13, have been described, but their characteristics have not been fully elucidated yet.

Several protein families, other than the CYPs, such as the uridine 5'diphosphate-glucuronosyltransferase (UGTs) and solute carrier organic anion transporters (OATPs, SLCs), also contribute to the ADME processes of anti-lipidemic agents. The UGT family is responsible for catalysing the glucuronidation and transfer of a wide range of drugs including statins, environmental chemicals and endogenous substances. The major UGTs include the UGT1A1, UGT2B7 and UGT2B15. Several non-functional alleles have been described for the UGT1A1 including UGT1A1*6, UGT1A1*60 and UGT1A1*93. However, polymorphisms of this gene have been primarily associated with disease manifestation, rather than drug response. The SLCs are key determinants of ADME of various drugs, including statins, as a result of their broad substrate specificity and tissue distribution. Several alleles have also been described,

which form haplotypes leading to altered transport activity. Thereby, the *SLCO1A2* mediates the sodium-independent transport of organic anions and conjugated and unconjugated bile acids.

3.3. Impact of ethnicity on the role of genetic variations in anti-lipidemic drug metabolizing enzymes

Apart from changes in the metabolic enzymes themselves, variations also exist in the impact of these changes on anti-lipidemic therapy among different ethnicities [91–97]. These variations can be manifested in various ways, including changes in drug potency or metabolism and the pharmacokinetics of the drug may in turn be attributable to alterations in polymorphic traits of metabolic pathways. The impact of ethnicity becomes particularly apparent in the way individuals respond to drug therapy of dyslipidemia, in which multiple researchers have demonstrated great variability in the distribution of these genetic variants by ethnicity. For example, in a number of studies in the USA, differences have been described in variants both among indigenous populations as well as in comparison with African, Asian and European populations. Such differences were documented, for example, between Oriental, Caucasians, Saudis and American black populations, in the prevalence of defective *CYP2C19* alleles [98]. Thereby, PMs represented approximately 3–5% of Caucasians and African-Americans, but 12–100% of Asian groups [81]. Similar variations have also been reported among Caucasians, Africans and East Asians [99], whereby higher *CYP2C19*2* and **3* (PMs) were observed in Mexicans than in African-Americans, whites, East Asians and Southeast Asians [100], among the Chinese ethnic populations [101–103], between Sri Lankan and European populations [104], between Hungarian and Roman populations [105] in a US pan-ethnic groups of whites, African American, Hispanics and Ashkenazi Jewish populations [106] as well as Pacific individuals and New Zealand Europeans [103], among others. The *CYP2C19*2* also appears to be more common in Finland and Spain, respectively, than in the UK, while Asians appear to exhibit low *CYP2C19*2* and *CYP2C19*12*, but higher *CYP2C19*2* frequencies compared to the UK residents of European ethnicity [107]. Both variants have been found to be also more frequent in East Asians and even higher in native populations from Oceania compared to Mediterranean, South European and Middle Eastern ethnicities. The observation of an increase in the Oceanians has been explained by genetic drift in the Pacific Islands [108]. Similar differences have also been reported between the Malaysian Chinese and Caucasians and in Israeli individuals of different ethnic backgrounds [109, 110]. Like the **2* and **3*, significant ethnic difference have also been observed in the frequency of the **17* (UM) variant that leads to very rapid metabolism of its substrates among various groups in a pan-ethnic study including Mediterranean, South European and Middle Eastern than in East Asians [108]. Furthermore, although the role of *CYP2C18* in drug metabolism remains obscure, it was recently suggested that defective *CYP2C19*3* and *CYP2C18*1* alleles are completely linked, implying that a *CYP2C19*3* PM is a *CYP2C18* PM and vice versa [111]. A gender-dependent activity of the *CYP2C19* and higher incidence of PMs was also described in Koreans as compared to Swedish [112].

The gene encoding the *CYP2C9* also harbours numerous variations which have increasingly been acknowledged as determinants of the metabolic phenotype underlying inter-individual and inter-ethnic differences in response to drug therapy [91, 92]. Existing data suggests that the *CYP2C9**2 and *3 alleles are present in approximately 35% of Caucasian individuals, but significantly less so in African-American and Asian populations [83]. Similar differences have been observed between Amerindians and Admixed or European populations [113] as well as Swedes and Koreans [114]. Thus, for example, *CYP2C9**2 and *3 variants were more frequent among white populations than in Africans and Asians, while *CYP2C9**2 was detected only in Asians [115]. The *CYP2C9**2 frequency also appears to be lower in South Asians compared to the UK residents of European ethnicity [107], but more common in Finland and Spain than in the UK [107], comparatively lower among Mexican-Americans compared to Spaniards [116]. Its distribution also varies between Beninese and Belgian populations [117], Ethiopians and Italian Caucasians [118], Amerindians and European admixtures [119], Iranians, African and Eastern Asian populations [120], Hungarian and Roma populations [121], as well as among the Chinese minority ethnicities [101], ethnic Jewish groups [122] and Mexican ethnicities [123, 124]. Interestingly, to date, the *CYP2C9**4 appears to have been exclusively identified in Japanese patients, while the *CYP2C9**5 and *6 were only found with a low allelic frequency among African-Americans, respectively [115].

Another genetically polymorphic CYP2C of potential clinical relevance with respect to anti-lipidemia therapy is the *CYP2C8*. Differences in the prevalence of the *CYP2C8**2 allele have been described between the Bantu and San populations in Botswana [125], between Caucasian Europeans and South Asians [126], among the Chinese minority populations [127], South Indian populations, African, European Chinese and Japanese [128], Ghanaian, Caucasians and Asians [129], as well as among African-American, European-Americans, Japanese, Han Chinese and Koreans [130]. Interestingly, Caucasian Americans also display large variability in *CYP2C8* and *CYP2C9* suspected to be along ethnic ancestry, and a higher frequency is thought to exist among Caucasian Americans with South European ancestry than with North European ancestry. Notably, differences in the prevalence of *CYP2C8**3, *CYP2C9**2 and *CYP2C9**3 alleles have also been reported between Chinese and Japanese individuals, East and South Asians as well as among Caucasian Europeans [126]. Furthermore, apart from inter-ethnic differences, there appears to be also intra-ethnic variability in the *CYP2C8* and *CYP2C9* allele frequencies [126]. This implies therefore that, for example, Asians or Caucasians cannot be conceived as homogeneous populations with respect to these enzyme families.

The *CYP2D6* can convert statins to a metabolizer that has a greater effect. It also exhibits multiple non-functional variants. In contrast to *CYP2C19* distribution, *CYP2D6* PMs are reportedly more frequent among Europeans than in Asians, while differences were also observed between Chinese and Caucasians in *CYP2D6* PMs and IMs [109]. It has been suggested that about 10% of Caucasians lack any *CYP2D6* activity due to deletions and frameshift or splice site mutations in the gene. The *CYP2D6**4 appears to be the most common PM among Europeans and to be more frequent in the UK than in Spain and Finland [107]. Furthermore, approximately 3% of Middle-Europeans and 29% of Ethiopians display gene duplication, leading to elevated URM phenotype. Distribution of *CYP2D6* PM has also been

reported to differ between the Russian, Yemente and Israeli Arab ethnic groups [131], Tibetan and Han populations [132], the Amerindians and Asians in Venezuela [133] and among some Chinese ethnic minorities [101, 103, 134]. In Mexico, differences have been observed in CYP2D6*4 between Caucasians and Mexican Americans [135], while in Israel such variation in CYP2D6*4, *10 and *17 alleles and CYP2D6 duplications have been described between the Ethiopian, Sephardic Beduoin and Yemente Jews [136]. Prevalence of CYP2D6 UM in the Mediterranean population was higher than those from North Europe [137], in the Mestizo than in Amerindian and Afro-Caribbean population in a Costa Rican study [138] and in the Mediterranean compared to Northern Europe in an Italian study [139]. Similarly, differences exist in the prevalence of defective alleles between Africans and South-East Asians [140] and Hispanics, North American Caucasians and African Americans [141] and between African Americans and Caucasians [142].

The other enzyme sub-families engaged in anti-lipidemic therapy exhibiting significant inter-ethnic variation in defective alleles are the CYP3A4/5 gene cluster [143, 144]. The CYP3A4*19 appears to be frequent in Hispanics, while differences have been described in CYP3A4*18 among the different ethnic Chinese minorities [101, 145]. Also variations have been observed in CYP3A4*1B and CYP3A5*3 between Brazilians of African and European descents [146, 147], between African-Americans and Caucasians [148, 149] and between Indian, Malay, Chinese and Caucasians in Singapore [150, 151]. In contrast, in Indo-Pakistanis, for example, it has been reported that, with the exception of the CYP3A4*1B, the proportion of patients without a CYP3A4 polymorphism appears low.

The CYP1A constitutes a gene family that has been implicated in both drug metabolism and disease. Thus, the gene contains at least four major polymorphisms that exhibit population distribution that is dependent on ethnicity. Among the Chinese, variations have been observed in the CYP1A2 distribution among a number of ethnicities [152]. In European studies, Hungarians showed elevated rapid metabolizing tendencies compared with the Romans [153]. The CYP1F2*1F was found to be more frequent in Mexican Amerindians than Mestizos in a Mexican study [154], while differences in frequency were also reported among ethnic groups in Singapore [155], between Taiwanese, Caucasians and African Americans [156], while Ethiopians appeared to display at least twice the variations found in all other populations combined. A significant association between CYP1A*2c and triglyceride level has been described in Mexican Amerindian Tarahumaras compared to the Tepehuanos [157, 158]. It has also been suggested that CYP1A1*3 may be specific for individuals of African descent, while the CYP1A1*2 is closely linked to Asian ethnicity but less so to Caucasian [159].

Inter-ethnic variation in the distribution of genetic alleles is not limited to the CYP450s only, but is rather a general phenomenon for the majority of proteins involved in the bio-distribution, transport, metabolism and excretion of all drugs and pharmaceutical agents. One of such protein families important for anti-lipidemic drugs is the UGT. Polymorphisms of this gene have been primarily associated with disease manifestation, and only scanty ethnicity-based studies are currently available. One such study in the Chinese has shown heterogeneity among different ethnic groups [160]. Furthermore, differences have also been reported in the prevalence of the UGT1A1*28 between Caucasians and Asians [161]. Besides, some sex-dependent

differences have also been discussed with regard to UGT functionality. They are also believed to be involved in drug-drug interactions. Several cell membrane transporters, such as the anion transport polypeptide (OATP) 1B1, encoded by the *SLCO1B1* gene, can influence the disposition of statins. They are key determinants of ADME of various drugs as a result of their broad substrate specificity and tissue distribution.

3.3.1. *Gene polymorphism, ethnicity and adverse anti-lipidemic drug response*

Many of the anti-lipidemic agents frequently exhibit very serious side effects, often leading to discontinuation of the therapeutic regimen. For example, it is thought that statin discontinuation rate due to side effects ranges between 1% and 5%. This is, in the majority of cases, due to the sharing of metabolic pathways by other concomitantly employed drugs, but may also be caused by mutations in the metabolic genes. Adverse effects of anti-lipidemic drugs also include drug resistance and intolerance, which have been linked to genetic polymorphisms in several genes including *LDLR*, *HMGCR*, *PCSK9*, *CETP*, *APOE*, P-glycoprotein and *OATP*, just to name a few. Furthermore, drug dosage requirements are often dependent on ethnic differences as explained, at least in part, by genetic and dietary factors. Such adverse effect would be exacerbated in the presence of defective metabolizing alleles. Several factors, including modes of action, biotransformation routes or concomitant food ingestion, may contribute to these phenomena. Of particular importance in this regard are the CYP450s, which are thought to mediate the majority of unwanted drug effects, as drugs interact with members of this protein family in many different ways, whereby a drug may be metabolized by one or multiple of these enzymes. Thereby, drugs that cause CYP450 metabolic interactions are referred to as either inhibitors or inducers. Such drugs block the metabolic activity of one or more enzymes, whereby the extent of its influence will depend on factors such as dose and the capability of the drug to bind to the enzyme. On the other hand, a drug may induce its metabolizing enzyme. Such enzyme inducers increase the CYP450 activity by increasing its synthesis, often dependent on the half-life of the drug. These factors render the therapy with drugs undergoing metabolism through the CYP450 system complex. Notably, a drug may inhibit the function of an enzyme that metabolizes it, with each cytochrome isozyme responding differently to exogenous chemicals in terms of its induction and inhibition. Typically, individuals with an aberrant CYP450 gene may experience diminished efficacy or increased toxicity in response to particular drugs as a result of the difference in activity levels associated with the variant genotypes. One example is myositis, the most important adverse effect of statins, which may be greatly influenced by the presence of the defective enzymes, such as the *CYP2C9*, *CYP2C19* and *CYP3A4* variants. Inhibition of these enzymes often adversely affects the function of the *HMGCR* inhibitors in different fashions. For example, the *CYP3A* inhibitors significantly enhance simvastatin plasma concentrations and its active forms. It has also been shown that peak serum levels of simvastatin, which is metabolized solely by *CYP3A4*, can increase by many times in PMs or with the addition of a potent inhibitor, leading to an increase in the risk of myopathy and rhabdomyolysis at usual doses. The effect of *CYP3A4**22 allele is thought to lead to reduced enzyme expression. Combination of non-functional *CYP3A5**3 and putative, functionally reduced *CYP3A4**1G alleles may predict diminished clearance of *CYP3A4* substrates [162]. Carriers of one or more *CYP2C* variant alleles may be at risk for

adverse drug reactions when prescribed together with drugs extensively metabolized by CYP2C9 [115]. Atorvastatin-related rhabdomyolysis and acute renal failure has also been linked OATP1B1 polymorphism and CYP2C19 PMs [163].

The other important enzyme family in anti-lipidemic drug metabolism is the UGT, which may invariably influence drug metabolism through the CYP450 pathways, as demonstrated by the observations that, for example, gemfibrozil exhibits glucuronidation- and reduction-dependent activation to metabolites that inhibit CYP2C8, whereas ezetimibe shows glucuronidation-dependent protection against metabolism-dependent inhibition of CYP3A4. Its polymorphism has also been linked to atorvastatin adverse effects by increasing its lactonization in the liver through UGT1A3*2 [164, 165]. While atorvastatin lactone is pharmacologically inactive, it is suspected to be a muscle toxic and to cause statin-induced myopathy. Furthermore, UGT1A1*28 has been associated with decreased exposure of atorvastatin lactone [166], and also linked to changes in the pharmacokinetics of ezetimibe [167].

Other important gene variants influencing the actions of anti-lipidemic drugs include the CETP-Taq1B and adenosine triphosphate binding cassette transport A1 (ABCA1)-R219K gene polymorphism, which seem to modify the response to lipid lowering therapy with simvastatin or atorvastatin treatment [168, 169]. The frequency of the variant alleles for these drug metabolizing enzymes often differ among ethnic populations. For example, inter-individual variability in statin exposure has been associated with changes in the uptake and efflux of transporter genes. Hence, for each individual, it is important to establish the impact on drug ADME characteristics in order to achieve maximal therapeutic outcomes. Mutations in the solute carrier organic anion transport 1B1 (SLCO1B1) are also known to increase plasma concentrations of simvastatin (and simvastatin-induced myopathy) as well as moderately increase those of pravastatin. In some studies, atorvastatin concentrations have been associated with changes in the SLCO1B1 [170], although some other investigators failed to report similar effects [171]. SLCO1B1 polymorphism, particularly the SNP rs4149056 (c.521T>C), has also been linked to statin-induced myopathy, while the SLCO1B1*5 allele and female sex have been associated with mild statin-induced side effects [172]. Other anti-lipidemic drugs influenced by the OATP1B1 include ezetimibe [173].

Besides, genes such the *CETP* and multi-drug resistant protein 1 appear to harbour variants that may either enhance LDL-cholesterol or decrease triglyceride and HDL-response to pravastatin treatment [174], while certain *LDLR* and *APOB* mutations and haplotypes reportedly influence the lipid lowering effect of atorvastatin on LDL-cholesterol and apoB levels [175]. Treatment with pravastatin may lead to reduction of cholesterol in individuals harbouring heterozygous variants of the *HMGCR* [176]. These variants have also been implicated in the variations in response to therapy with different anti-lipidemic drugs. An example is that of the *APOE* genotypes associated with response to treatment with fenofibrate [75]. Many drugs are known to inhibit OATP1B1 function, *in vitro* at least, possibly resulting in, for example, an increase in plasma concentrations of statins. Gemfibrozil has also been shown to increase concentrations of several OATP1B1 substrates.

The sterol regulatory binding proteins 1 and 2 (SREBPs) are transcription factors that regulate lipid metabolism. A recent report also showed that the SREBP-1c polymorphism (G952G) is

associated with elevated cholesterol synthesis, and increased response to the effects of ezetimibe on cholesterol absorption [177]. It is thought that inhibition of mevalonate synthesis by statins reduces not only the biosynthesis of cholesterol, but also the production of ubiquinone (CoQ10), which is synthesized in all cells. Reduction of CoQ10 levels causes statin-induced myotoxicity.

3.4. Confounders for the role of ethnicity in hyperlipidemia drug therapy

Since alterations in the metabolizing proteins will affect the pharmacokinetics of a drug, it is also understandable that such changes are likely to play a major role in drug adverse effects. In particular, the effects of anti-lipidemic drugs are influenced in many different directions in the presence of variations in their metabolizing enzymes, which may in turn be also influenced by both modifiable and non-modifiable confounders, including gender and age, as well as concomitant therapies with different families of drugs. For example, one proposed mechanism responsible for a differential effect of statins could be sex-dependent drug clearance, given that the clearance of lipid-soluble statins involves CYP450s and the protein expression can vary by sex. In some animal studies, the metabolic rate of simvastatin was found to be considerably higher in males than in females. The statins might therefore be expected to have a greater clinical effect on males. In contrast, human volunteers showed a lower degree of metabolism of simvastatin and lovastatin in men than in women. Moreover, several epidemiological studies have reported greater reductions in both LDL and total cholesterol in response to statins in women than in men, which presumably could lead to between-sex differences in clearance rates, bioavailability and, consequently, the clinical effects achieved with the same dose of the drug. One study has, for example, indicated that the variability in CYP1A2 activity could be explained by the diet, lifestyle and genetic factors [178]. Some studies even suggest that statin therapy leads to a greater reduction in the risk of cardiovascular events in men than in women with cardiovascular disease. Several of the CYP450s are also implicated in diseases, which may influence the therapeutic outcome with drugs that are metabolized through these enzymes. Besides, diseases such as HIV/AIDS are also known to trigger lipid disorders and need to be considered seriously in their management. It has been shown, for example, that a combination of anti-retroviral therapy is likely to trigger the incidence of metabolic risk factors such as insulin resistance, dyslipidemia, lipodystrophy and abnormal fat distribution. As such, HIV-dyslipidemia is regarded as a common problem linked to an increase in the incidence of cardiovascular disease.

Other confounders include awareness, availability of resources and adequate health service products. Such disparities contribute to inequality in health product supply of any societal community, and to the way management of disease may be accomplished within a society. Some disparities by ethnicity have also been established in the use of pharmacotherapy for hyperlipidemia, orders by physicians, counselling of individual on food intake and exercise [179]. Besides, drug responses are influenced by clinical variables such as age, gender, body weight, general medical condition and liver function. All these factors contribute negatively to attaining national therapeutic goals.

3.5. Ethnicity-gene interactions and future management of hypercholesterolemia

The preceding paragraphs have summarized the causative genes for hyperlipidemia, the diversity in gene variants encoding metabolizing proteins and their distributions in different populations by ethnicity. The summarized data demonstrates that the interactions of these variables do not only influence the expected drug actions, but, more importantly so, also the untoward effects of the therapeutic agents for hypercholesterolemia. It is also evident that, in addition to the complexity of the ethnicity-gene environment interactions, intra-ethnic population admixtures of many modern societies may introduce an element of uncertainty with regards to the interpretation of observations in such population structures. As a result, this may lead to spurious genotype-phenotype associations, which presents a challenge in thriving to unequivocally isolate the ethnic-specific disease-related alleles from those pertaining to multiple population groups. However, the importance of ethnicity in complex disease manifestation such as hyperlipidemia and its pharmacogenetics is now generally acknowledged and cannot be ignored. Rather, it should constitute a central focus of research as a basis for establishing therapeutic goals for targeted disease management. To begin with, existing data reveals that, for example, the disease-causing gene variants and ADME-related alleles are not uniformly distributed among Caucasian, European or individuals from East Asia or Africa. This asymmetric distribution of genotypes implies that we need to decipher their prevalence by ethnicity for us to determine their relevance for any given ethnic group. Hence, knowledge of the extent to which a particular variant may be present within an ethnic population is therefore mandatory in order to establish the chances of success for a personalized therapeutic regimen for anti-hyperlipidemia therapy. The implication for this variability is also that therapeutic modalities have to be predetermined for each individual ethnic population for optimal disease management in any given society. In this regard, the WHO has recommended establishing health action points that may be specific for each nation. On the other hand, there might be some geographic similarities in the prevalence of some variants as shown by some Asian populations sharing unique traits compared to Caucasians, for example. Therefore, it also appears that the distribution of some of these genotypes is heavily influenced by geographic origin. This scenario implies that, while the individuals belonging to these different populations cannot be treated as homogeneous groups, they may nonetheless inherently share some genetic traits that are regulated by geographic demarcations. Hence, the identification and discerning of ethnic-specific variants from such common regional traits should enhance our understanding of the human diversities in genetic traits, and can therefore be exploited more appropriately for therapeutic purposes in the future.

Importantly, the gene-ethnicity relationships are also commonly influenced by confounders, such as age and gender. These two variables are, however, not ethnic-specific, and would independently exert a similar impact on disease or therapy across ethnic groups. On the other hand, however, modifiable traits such as obesity or BMI would be identifiable ethnic-specific traits. Therefore, combinations of these various confounders will impact the relationship of the genotype, ethnicity and disease or therapy in different fashions that cannot be easily transposed from one ethnicity to another. Accordingly, consideration of specific underlying environmental factors is a prerequisite in the management of complex disorders such hyper-

lipidemia for any given population. With regard to hyperlipidemia specifically, the issue is not made easier by the fact that drugs, such as statins, are invariably metabolized through several CYP450s, and vice versa. Thus, the rate of defects in ADME genes may occupy a unique position in mediating these interactions. Therefore, specific knowledge of the metabolic pathway of these ADME enzyme variants is also key to establishing the success of individual therapy in any ethnic group within societies. Furthermore, understanding of the causal relationship of these polygenic influences on drug dose requirements is vital in reducing inter-patient variability and optimizing anti-lipidemic therapy. Detecting such genetic variations in drug metabolizing enzymes is also particularly important for identifying individuals who may experience adverse drug reactions or lack of drug response. In turn, it should help in the prediction of more individualized loading and maintenance doses for safer drug therapy. In fact, the different isoforms of the ADME enzymes probably present greater challenges with respect to their possible adverse effects and the safety issues than the activity level, not only due to intra-individual, but more so inter-ethnic differences in their prevalence across societies. Ethnic diversity in some of these variants and complex interplay among them will therefore dictate the success of anti-lipidemic therapy in any given population. Thus, for example, dosing for poor metabolizers may have to be significantly modified to meet the ethnic-specific requirements for adequate therapy, which may not necessarily be the case in some societies. On the same note, ethnic-based genetic tests can be used to screen for individuals with poor metabolizer phenotypes, for example, with the ultimate goal of predicting the clinical effects of drugs. Furthermore, apart from drug efficacy, inter-ethnic variations in the prevalence of metabolic genes will naturally also influence drug toxicity. In addition to ethnic-delineable variants, common multi-ethnic variants in important drug metabolizing genes have also been described across ethnicities. This is exacerbated by the fact that some ethnic populations also display a wide range of variations in the frequencies of these polymorphisms, possibly due to population migrations. Put together, the overall clinical merits of a genotype-adapted anti-lipidemic treatment regimen in a patient population can best benefit only if the actual prevalent variants are known for that particular ethnic population. Thus, identification of such ethnic-specific allele frequencies and their phenotypic designation will provide the basis for better clinical management.

Apart from traits directly related to societal structure, gene polymorphism and the reigning classical modifiable risk traits, there are many other events that will determine the outcome of therapeutic management hyperlipidemia. These features include public awareness as well as availability of and access to information or national resources. To begin with, it has been shown that the difference in the availability of health insurance may influence the way patients of different ethnic groups respond to treatment. Furthermore, in many communities there is a suffocating lack of data on the prevalence of the important disease-causing or therapy-related genotypes. Unfortunately, thus far, the phenotypic expression has been studied primarily in Caucasians and a few other ethnicities, but only poorly so in developing or semi-developed countries, such as Africa of the Arab world. Yet by virtue of consanguinity and inbreeding in some of these societies, for example, the distribution pattern of clinically important variants may differ considerably in such communities compared to others, as a result of disparity in Hardy-Weinberg distribution principal. Hence, there is acute need to characterize the preva-

lence of such variants in such ethnic populations, as they will almost certainly always be unique in a particular society. For dyslipidemia specifically, this complexity is compounded by the lack of community awareness reigning in developing countries. Besides, often there are many inconsistencies in the data pertaining to different ethnic groups within the same geographical regions. This naturally leads to disparity in the effectiveness of therapy in such societies. One study suggested, for example, that the disparities in the use of pharmacotherapy for hyperlipidemia, physician-ordered or provided cholesterol screening, diet and exercise counselling by specialists may be partly a result of lack of information [179]. Awareness influences compliance, and compliance is a key determinant of successful drug therapy. Furthermore, compliance to drug therapy is influenced by a number of other factors, including volume of drugs to be consumed and rate of daily drug intake, and possibly even gender. Recently, a gender difference in lipid control due to non-adherence has been described [180]. Moreover, apart from the cited studies pointing to differences among ethnic groups, there is also a large amount of data failing to replicate the reports of such genotype-related effects in the same ethnic populations. This may be attributable to several factors, including admixture and lack of information. These will in turn contribute to intra-ethnic variations in the management of drug treatment in a given community.

Availability or lack of resources and adequate health service products also play a central role in the outcome of dyslipidemia therapy. For example, it has been shown that the difference in the availability of health insurance may influence the way patients of different ethnic groups may respond to treatment. In the USA, for example, variations across states in health insurance and racial/ethnicity mixture have been associated with variations in the management of hyperlipidemia. Thus, less-insured states may be less effective, whereas those with more private, Medicare or Medicaid coverage may be more effective. In states with proportionately more African-Americans versus Hispanics, lipid medications have also been found to be prescribed differently [181]. Such disparities contribute to inequality in health product supply of any societal community and therefore to the way management of dyslipidemic disorders may be accomplished within that society. Indeed, such environmental factors will have an impact on disease management that often goes unnoticed. Other environmental factors include access to education, information or resources within the different ethnic populations, whose importance can hardly be overstated. For example, in the USA the native Hawaiians are regarded as the least educated proportionally and the lowest portion of the ladder of socio-economic strata relative to most ethnic groups in the USA, which may explain some of the remarkable differences compared to other groups. One problem is the issue of availability of basic information on disease risk factors and involvement in decision making for therapy regimens, as shown by a study indicating that minorities considering hyperlipidemia therapy may be less informed and less involved in the final decision-making process therefore contributing to racial disparity in health management of a nation [182].

Furthermore, while some developed societies may be made more conscious of risk factors for a given disease, heterogeneity through population migration and levels of consciousness among the different ethnic groups within a society may always change the dynamics of the situation. This indeed plays a central role in the unequal distribution of the resources contri-

buting to disparities in the availability of health services. Most of it can be explained by the prevalence of confounders, such as lack of awareness, in which disproportionate rates seem to rank highly even in developed countries. Given the likelihood of ethnic differences in lipid profiles and the prevalence of hyperlipidemia together with the lack of research in ethnic minorities, it becomes clear that therapy of dyslipidemia remains a major concern worldwide. Being a recognizable risk factor for cardiovascular diseases, it is also questionable whether anti-lipidemic therapy attains the same effect of cardiovascular risk prevention globally under these conditions. Most importantly, profiling the gene variants in disease and drug response to anti-lipidemic therapy is the inevitable pathway towards establishing personalized treatment for this disorder. Pharmacogenetics has slowly found its rightful place in disease management. It is now well acknowledged that polymorphisms in drug-metabolizing enzymes and transporters of anti-lipidemic agents contribute to a wide variability in the pharmacokinetic response and toxicity of these drugs. In this regard, ethnicity plays an important role in defining the relevance of the genetic changes in achieving the ultimate goal of personalized drug therapy. However, as demonstrated in the preceding paragraphs, further studies are needed to explore deeper the gene-dose, gene-concentration and gene-response relationships especially for the drug metabolizing CYP450s. The more we make progress in identifying the genetic variations of dyslipidemia or drug response to therapy, the greater the likelihood that personalized medicine becomes a reality rather than remaining a myth in the foreseeable future.

Because of the uncertainties summarized above, for the time being targeted drug therapy of hyperlipidemia remains a dream of the future. Nonetheless, profiles of rare variants reflecting on the inter-individual variability in drug response are becoming more and more evident. Hence, the knowledge we have already acquired of the differential distribution of the important gene variants should provide valuable information in guiding clinicians in determining which gene variants may be relevant in screening patients for personalized therapy in clinical settings in a given society. The validity and usefulness of such an undertaking for routine procedures will depend foremost on the prevalence of such entities. Hence, recommendations for genotype-adjusted therapy will soon be of time.

4. Summary

Hypercholesterolemia is a complex disorder which presents in different forms, including the familial form, with varying underlying aetiology, and contributes substantially to CAD manifestation. Predisposing variables for the disease include modifiable risk traits, such as diet, overweight and obesity, that are controllable by adopting healthy eating habits and exercise, for example. However, diet alone is often not adequate to achieve the desired lipid lowering effect in individuals harbouring very high cholesterol levels, such as in familial hypercholesterolemia. This necessitates the use of lipid lowering medication to reduce its production or absorption or other forms of therapy including LDL apheresis or surgery. It is now well established that the response to anti-lipidemic therapy depends on genetic changes in the disease-causing as well as ADME-related genes, and the impact of these gene-drug

response relationships will depend on ethnicity. Inter-ethnic variability in pharmacokinetics of anti-lipidemic agents may trigger unexpected outcomes such as therapeutic failure, adverse effects and toxicity in individuals of different ethnic origin undergoing therapy. Hence, in-depth studies on these relationships have the huge potential of achieving optimal quality use of drugs as well as improving the efficacy and safety of both prospective and currently available anti-lipidemic therapeutic agents.

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