Single-nucleotide polymorphisms: a perspective of cardiovascular prevention

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Summary

Introduction: several studies have evaluated the utilization of lipid biomarkers in an attempt to correlate them with clinical cardiovascular events. Nevertheless, the investigation of clinical conditions under specific plasmatic levels of lipoproteins for long periods presents limitations due to inherent difficulties that are related to the follow-up of individuals throughout their lives. Better understanding of the clinical response and occasional resistance to the action of hypolipidemic drugs in several clinic scenarios is also necessary.
Objectives: to determine the role of evaluation of single-nucleotide polymorphisms (SNPs) related to the metabolism of lipids, and its implications in different clinical scenarios.
Methods: a search of the literature in English and Spanish languages was performed in Medline, Lilacs via Bireme, IBECS via Bireme, and Cochrane databases. The expected results included information regarding plasmatic lipid profile and SNPs, cardiovascular clinical outcomes and polymorphisms related to the effectiveness of statins in the treatment of hypercholesterolemia.
Results: in order to perform this analysis, 19 studies were included from a total of 89 identified citations. The evaluation of the results suggests that low plasmatic levels of LDL-c are associated with a reduction in the risk of heart attacks, although this was not observed for the rise of plasmatic levels of HDL-c.
Conclusion: polymorphisms in different populations and clinical perspectives may bring important contributions for a better understanding and adequacy of plasmatic lipoproteins aiming at reducing cardiovascular risk.

Keywords: polymorphism, single nucleotide, dyslipidemias, hydroxymethylglutaryl-CoA reductase inhibitors.

Introduction

Hyperlipidemia is a major risk factor for developing coronary artery disease (CAD), and the leading cause of ischemic heart disease.[1,2] Despite pharmacological advances and interventional treatments, morbidity and mortality of CAD remains high.[3,2] Thus, the finding that low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions are among the most requested biomarkers in clinical practice is justified.[4] However, determining a causal role in the disease process and its pathophysiological marker cannot be done only based on observational studies.[5]

Several studies of primary and secondary prevention have shown a reduction of 25 to 35% in the risk of cardiovascular events through the use of individual statins[6] despite inter variability in plasma lipid levels. This variation may be due to environmental factors such as body weight, smoking, diet and drugs, but also due to genetic polymorphisms involved in lipoprotein metabolism.[4,7] The different responses to statins in reducing plasma lipid profile[12] also play an important role in monitoring the dyslipidemic patient.

Thus, assessment of effect for a prolonged period of exposure to concentrations of lipoproteins may have a role in the risk considerations for CAD and for defining therapy. Therefore, evaluating lipoprotein subfractions as well as single nucleotide polymorphisms (SNPs) in

genes involved in lipoprotein metabolism can clarify important aspects of the clinical monitoring of patients and correlations with cardiovascular outcomes. In this study, a systematic review of the literature aimed to evaluate the different SNPs and their correlations with the plasma lipid metabolism in various clinical settings, and populations studied was performed.

Methods

The present studies were found from the search of original articles, clinical trials, observational studies and case-control studies in the following electronic databases: Medline, Lilacs via Bireme, IBECS via Bireme and Cochrane. A search for articles of references was also performed manually.

The following MeSH terms for research in their different combinations were used: "Hypercholesterolemia", "Cholesterol, LDL", "Cholesterol, HDL", "Lipoproteins", "Dyslipidemias" and "Polymorphism, Single Nucleotide". The expected results included information related to various SNPs and their relationship with lipid profile and risk of cardiovascular events (Table 1). An independent researcher conducted the survey in the databases and then selected the relevant items, according to the inclusion and exclusion criteria.

- Inclusion criteria were: original studies from clinical trials, observational studies, cohort and case-control studies that investigated the influence of genotypic variations of SNPs and their relationship with lipid metabolism and cardiovascular risk.
- Exclusion criteria were: experimental studies, articles with polymorphisms unrelated to plasma lipid profile, studies with small sample size and study in languages other than English and Spanish.

Results

Out of 89 citations identified in the databases, 19 were eligible according to the criteria for inclusion in this systematic review (Figure 1). Of the total citations found, 16 were excluded for addressing experimental studies, two because they were written in Japanese, 4 due to the small size of samples and 48 studies for assessing polymorphism unrelated to the plasma lipid profile.

Nineteen studies were eligible and included in this review. The data from these studies are summarized in Tables 2 and 3.

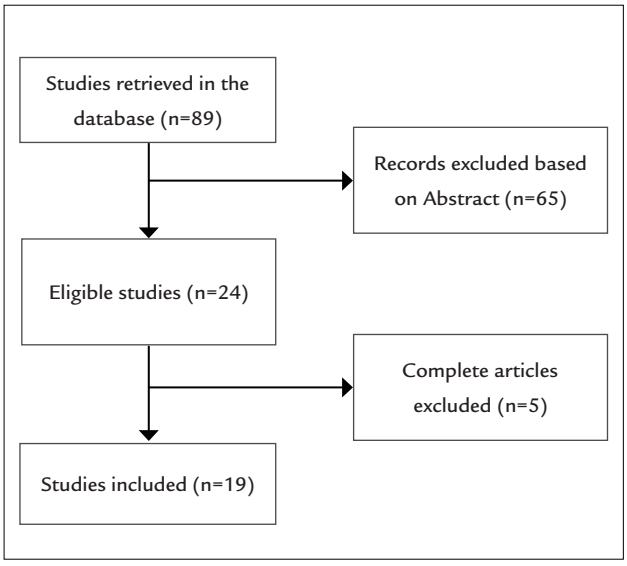

FIGURE 1 Flowchart of records retrieved and included.

TABLE 1 Search in electronic databases performed on 10/28/2013.

Base	Terms	Results	References selected	References used
Lilacs via Bireme	"Single nucleotide polymorphisms"	25	2	1
IBECS via Bireme	"Single nucleotide polymorphisms"	35	2	1
Medline via Bireme	((((("Hypercholesterolemia"[MeSH] AND "Cholesterol, LDL"[MeSH]) AND "Cholesterol, HDL"[MeSH]) AND "Lipoproteins"[MeSH]) AND "Dyslipidemias"[MeSH]) AND "Polymorphism, Single Nucleotide"[MeSH]	14	10	10
Cochrane via Bireme	"Single nucleotide polymorphisms"	13	7	4
Manual search	"Single nucleotide polymorphisms"	2	2	2
Total	–	89	23	19

TABLE 2 Summary and evaluation of the quality of the selected studies on SNPs – matter of study, study design, population and number of participants.

Study	Objective	Study design	Population
Voight et al. 2012 (5)	Use of SNPs to test the hypothesis that genetic increases in plasma HDL-c can protect from MI	30 case-control studies 6 cohort studies Meta-analysis with Mendelian randomization	20,913 cases 95,407 controls
Ference et al. 2012 (8)	Exposure for extended periods to low LDL-c mediated by different polymorphisms decreases cardiovascular risk	Meta-analysis of the risk of CAD mediated by 9 polymorphisms in 6 different genes 26 randomized clinical trials on the use of statins	312,321 participants with polymorphisms 169,138 participants treated with statins
Rosa et al. 2012 (17)	Analyze if the *LRP1* gene modulates the genetic risk of premature cardiovascular disease onset in patients with familial hypercholesterolemia upon association of polymorphisms	Case-control study with patients from the SAFEHEART study	339 patients (77 with cardiovascular disease and 262 controls). Genotyping of 10 single nucleotide polymorphisms of the LRP1 gene
Taegtmeyer et al. 2011 (1)	Evaluate the *ABCB1* genotype and its association with lipid levels and response to statin in patients with advanced HF who underwent transplant	Retrospective cohort study	Retrospective analysis of biochemical data of 268 adult transplant recipients, and one year after transplantation (176 patients)
Cerda et al. 2010 (20)	Test the relation of 3 SNPs of the *SCARB1* gene to hypercholesterolemia in a Brazilian population, and if variants can affect the response to treatment with atorvastatin	Cohort study	147 hypercholesterolemic patients and 185 controls
Lamon et al. 2010 (9)	Evaluate variations in the ESR1 receptor and genes involved in lipid metabolism to explain some of the variability in response to hormone replacement therapy	Randomized clinical trial	208 postmenopausal Caucasian women with 3.2 years of use of hormone therapy, 73 randomized to placebo, and 135 to other hormonal treatment Patients from the Estrogen Replacement and Atherosclerosis (ERA) trial All participants with established CAD assessed by angiography
Salazar et al. 2010 (16)	To evaluate the frequency of 45TMJ (rs2241766) polymorphism in the gene encoding adiponectin (*ADIPOQ*) and its possible contribution to the emergence of coronary heart disease in individuals of southern Chile	Case-control study	416 adult participants 200 cases (confirmed by angiography) 216 controls
Zintzaras et al. 2009 (21)	To estimate the lipid response to statin treatment between genetic variants of the *APOE* gene (e2 carriers, e3e3 homozygotes, and e4 carriers)	Meta-analysis of 24 studies	Patients using statins from 24 studies
Smart et al. 2009 (22)	To evaluate the influence of 10 common variants in genes for lipoprotein lipase, *CETP-Taq1B*, *APO E*, *APOA5*, *APOA4* and *APOC3* on lipoprotein levels of children from the Gendai study	Cohort study	882 children (418 female) aged 11.2 /- 0.7 years on average.
Lindi et al. 2008 (23)	To study the effects of G-250A polymorphism in the activity of the hepatic lipase, serum lipid profile, and insulin sensitivity	Randomized clinical trial	151 healthy participants

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TABLE 2 Summary and evaluation of the quality of the selected studies on SNPs – matter of study, study design, population and number of participants.

Study	Objective	Study design	Population
Caamaño et al. 2008 (17)	To evaluate the possible association between ABCG5 and ABCG8 polymorphisms and the presence of hypercholesterolemia in Chilean individuals	Case-control study	118 hypercholesterolemic patients and 104 controls
Unno et al. 2006 (14)	Evaluate the joint effect of polymorphisms and hypercholesterolemia on the risk of atherosclerosis	Case-control study	150 patients undergoing surgery for peripheral arterial occlusive disease and 158 controls matched for age and sex
Fiengenbaum et al. 2005 (11)	To investigate the effect of SNPs in sterol regulatory element-binding proteins SREBF-1a, SREBF-2 and SREBF (SCAP) on lipid reducing response mediated by the use of simvastatin	Nonrandomized clinical trial	146 hypercholesterolemic patients
Fjuita et al. 2005 (18)	Evaluate predisposing factors for phenotypic characteristics of high total cholesterol (T-Cho) and their association with two variants of *APOB48R*	Longitudinal study	352 adult Japanese individuals
Fan et al. 2005 (10)	To investigate the effect of hormone replacement therapy on the progression of atherosclerosis over a follow-up period of 5 years	Cohort study	88 post-menopausal women
Poliseckil et al. 2005 (12)	Investigate whether the five variants (-133A>6, 118A>C, L272L, V1296V e U3_28650A>G) of the *NPC1L1* gene have effects on lipid levels and prevalence/incidence of CAD, as well as response to pravastatin in reducing plasma lipid profile	Randomized clinical trial	5,804 elderly participants from the PROSPER study followed up for 3.2 years
Chasman et al. 2004 (13)	To evaluate the influence of 148 SNPs in 10 genes involved in lipid metabolism on the response to treatment with pravastatin	Randomized clinical study and cohort study derived from the PRINCE study	1,536 patients treated with pravastatin
Ono et al. 2003 (19)	To evaluate the association between SNP of the *GSBS* gene and plasma lipid levels	Case-control study	368 adult Japanese individuals
Stanislovaitiene et al. 2013 (24)	Assess the impact of SCARB1 rs5888 SNP on lipid profile and its association with CAD in a Lithuanian population	Cohort study	3,442 adult Lithuanian individuals

SNP: single-nucleotide polymorphism; CV: cardiovascular; TC: total cholesterol; CAD: coronary artery disease; IM: myocardial infarct; HF: heart failure.

TABLE 3 Main results of selected studies.

Study (year and reference)	Outcomes	Results	Conclusions
Ference et al. 2012 (8)	Combination studies with Mendelian randomization in meta-analysis (association of 9 SNPs in six different genes) to obtain the most accurate estimate of long-term effect of exposure to low concentrations of LDL-c, and its relationship with risk of CAD and the comparison with effect of lowered LDL-c by use of statins	CAD risk reduction between 6-28% was observed in 9 SNPs evaluated. The variation of significance for LDL-c values were from - 16.68 to - 2.63 mg/dL. A log-linear variation between exposure to reduced LDL-c and the risk of CAD was verified. Among the 312,321 participants with different SNPs, a risk reduction of 54.5% (OR: 0.45) was found for each mmol/L or 38.7 mg/dL reduction in LDL-c. For 83,873 participants - score LDL-c in 6 SNPs, risk reduction was 53.2% for CAD. On the other hand, in 26 trials that included 169,138 participants treated with statins, risk reduction for CAD was 24% (OR: 0.44) for each 3 mmol/L or 116 mg/dL reduction in LDL-c	9 polymorphisms were consistently associated with reduced risk of CAD as measured per unit of LDL-c reduction Protective effect is independent of the mechanism of LDL-c reduction What matters is not the reduction method, but the magnitude and duration of exposure to low concentrations of LDL-c A weighted LDL-c genetic score including 13 polymorphisms was associated with 2.13-fold increased risk of MI for each SD (34.1 mg/dL) increase in LDL-c
Voight et al. 2012 (5)	Assessment of cardiovascular outcomes such as myocardial infarction in populations with genetically high HDL, through Mendelian randomization of SNPs	Meta-analysis data of 7 cohorts with 19,840 patients of 15 *loci* related to high HDL-c plasma levels, 6 associated with reduction of MI but presenting pleiotropic effects of reduction in triglycerides and LDL-c. The remaining SNPs have no association with reduction in MI, and SNP rs16988929 on chromosome 20q13 showed increased risk of MI. In the 20 studies (13 case-control and six cohort studies) with a total of 116,320,000 participants, there was no association between LIPG Asn396Ser and IM risk reduction	The genetic variant LIPG Asn 396Ser, which raises HDL, did not reduce MI The Score which combined 14 variants related to HDL were not associated with AMI only The data challenge the relation between the increase in HDL and lower risk of AMI The AIM-HIGH trial, which added niacin on statin therapy, showed no lower risk of cardiovascular events, either
Lamon et al. 2010 (9)	Information about metabolic effects derived from the response of the gene involved with different subclasses of lipoproteins of hepatic lipase	Carriers of the ESR1 PvuII or IVS1-1505 variants had lower plasma TG concentrations and higher plasma HDL-c, alfa1 and pre alfa-1 HDL, apo A-I and alfa-1 levels after hormone therapy than wild-type carriers. Carriers of the N291S and D9N variants in the lipoprotein lipase gene had higher levels of lipoproteins and lower levels of alfa-2 HDL	Variations in gene *loci* are involved in the lipid metabolism, as well as subpopulations of TG-rich and HDL lipoproteins. SNPs in ESR1, CETP and LPL had significant effects on baseline plasma levels of these populations. Polymorphisms in genes involved in lipid metabolism do not explain much of the lipid variability and lipoproteic subfractions response to hormone therapy
Rosa et al. 2012 (15)	Presence of early cardiovascular disease in patients with familial hypercholesterolemia and association with polymorphisms	Significant association with polymorphism c.677c>T (rs 1799986) and early CAD, and effect on mutation of low density lipoprotein receptor in the dominant model (CT TT *versus* CC: OR=1.95; 95CI 1.08 - 3.48; p=0.029)	Polymorphism c.677C>T is associated with increased chance of early cardiovascular disease in patients with familial hypercholesterolemia
Taegtmeyer et al. 2011 (1)	Association of genetic variation of *ABCB1* and plasma levels of LDL-c in patients with advanced heart failure	Association between LDL-C in patients before transplant with the C345T genotype and G2677T/A-C3435T, C1236T-G2677T/A-C3435T haplotypes. Carriers of the T allele at all *loci* (n=77) had higher levels of LDL-C compared to non-carriers of the allele (n=24, p=0.025)	The ABCB1 haplotype is associated with fasting LDL-c plasma levels in patients with advanced heart failure. However, this finding was not observed after 1 year of cardiac transplantation

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TABLE 3 Main results of selected studies.

Study (year and reference)	Outcomes	Results	Conclusions
Cerda et al. 2010 (20)	Relation between 3 SNPs SCARB1 with hypercholesterolemia in a Brazilian population, and the influence of their variations on response to treatment with atorvastatin	The c.726 54C>T allele was associated with higher levels of LDL-c in normolipidemic (NL) patients, with increased levels of *APO B* and *APOB/APOAL* in hypercholesterolemics (HC) ($p<0.05$). Carriers of the CETP TaqIB B2 allele had much higher levels of HDL-c ($p<0.0001$)	The studied polymorphisms are associated with serum lipid levels in healthy pediatric patients. It highlights the potential of early prediction of an adverse lipid profile
Salazar et al. 2010 (16)	CAD risk in a Chilean population, associated with 45 TMJ polymorphism (rs2241766) in the gene encoding adiponectin (*ADIPOQ*)	The results showed that the presence of the G allele in the 45T>G polymorphism of *ADIPOQ* gene doubled the risk of CAD in the Chilean study population (OR=2.06; 95CI 1.36-3.14)	First finding of relationship between 45T>G polymorphism of *ADIPOQ* gene and CAD in a Chilean population
Zintzaras et al. 2009 (21)	Response of plasma lipid values to treatment with statins between genetic variants of the *APOE* gene (e2 carriers, homozygotes e3e3 and e4 carriers)	The mean reduction of total cholesterol was significant for all variants - e2 carriers: Delta mu=-27.7% (-32.5 to -22.8%), e3e3: Delta mu=-25.3% (-28 to -22.6%) and e4 carriers: Delta mu=-25.1 (-29.3 to -21%)	Non-significant results of *APOE* genotypic variation regarding lipid plasma levels. Its suggests that there is little reason to consider the use of *APOE* genetic testing for guiding treatment with statins
Smart et al. 2009 (22)	Children evaluation by the Gendai study on variants in the genes for lipoprotein lipase, *CETP-Taq1B*, *APO E*, *APOA5*, *APOA4* and *APOC3* regarding plasma levels of lipoproteins	Carriers of the epsilon4 *APOE* variant, compared to epsilon3/epsilon3 homozygotes and epsilon carriers, have higher levels of total cholesterol ($p=0.0001$) and LDL-c ($p=0.0001$). Carriers of the TAqIB B2 CETP allele have higher levels of HDL-c ($P=0.0001$) and TC	These common variants are associated with plasma levels of healthy pediatric patients
Lindi et al. 2008 (23)	The effects of G-250A polymorphism in the activity of the hepatic lipase, serum lipid profile, and insulin sensitivity	The A-250A genotype was associated with high levels of LDL-c ($p=0.03$ for the 3 genotypes). In the group with monounsaturated fatty acids diet, patients with A-250A genotype showed strong decrease in LDL-c compared to other genotypes ($p = 0.007$). The -250A allele was associated with low activity of hepatic lipase ($p<0.001$). The diet did not affect the activity levels of hepatic lipase among the 3 groups	The A-250A genotype of the hepatic lipase gene was associated with high plasma levels of LDL-c. Nonetheless, those patients who used diets rich in monounsaturated fatty acids showed reductions in serum levels of LDL-c especially in patients with genotype A-250A
Caamaño et al. 2008 (17)	Association between ABCG5 and ABCG8 polymorphisms and the presence of hypercholesterolemia in Chilean individuals	The frequency of homozygous genotypes for the ABCG5 1950>G polymorphism was higher for patients with hypercholesterolemia compared to controls (42 *versus* 10%, $p<0.001$). Hypercholesterolemic individuals carrying the GG genotype for 251A > G had higher levels of HDL-c compared to all other genotypes ($p=0.02$)	The data show an association between ABCG5 1950 > G polymorphism and hypercholesterolemia. The small size of the sample was a limitation
Unno et al. 2006 (14)	Presence of PAF acetylhydrolase (PAF-AH) in genetic polymorphism G994 - T, exon 9, in patients with peripheral arterial occlusive disease and the association between polymorphism and hypercholesterolemia in the risk of atherosclerosis	Plasma activity of *PAF-AH* was associated with plasma levels of total cholesterol and LDL, and inversely related to plasma HDL in patients with normal genotype (GG) and peripheral arterial occlusive disease	The association between plasma polymorphism of the *PAF-AH* gene and hypercholesterolemia may increase the risk of atherosclerotic disease

(Continue)

TABLE 3 Main results of selected studies.

Study (year and reference)	Outcomes	Results	Conclusions
Fiengenbaum et al. 2005 (11)	The effect of SNPs in sterol regulatory element-binding proteins SREBF-1a, SREBF-2 and SREBF (SCAP) on lipid reducing response mediated by the use of simvastatin	Carriers of the SCAP 2386G allele have greater decrease in plasma total cholesterol compared to 2386 allele homozygotes	The results suggest that polymorphism in the gene SCAP 2386A>G was a significant predictor of response to treatment with statin for levels of total cholesterol and triglycerides
Fjuita et al. 2005 (18)	Predisposing factors for phenotypic characteristics of high total cholesterol (T-Cho) and their association with two variants of *APOB48R*	Significant correlation between genotypic variations of A419P and total cholesterol levels was observed. Among the homozygous carriers of the G allele (n=265), heterozygous carriers of the G allele (n=78), and homozygous carriers of the C allele (n=9), total cholesterol levels indicated a co-dominant effect of the C allele of increase in total cholesterol (r=0.15, p=0.007). A similar effect was observed for c.934-960/Del (r=0.13, p=0.015)	Variations in *APOB48R* and other genes located closely are among the many factors involved in hypercholesterolemia
Fan et al. 2005 (10)	Hormone replacement therapy and the progression of atherosclerosis over a follow-up period of 5 years	A significant association between HRT and genotypes of hepatic lipase was found for increased atherosclerosis severity score (ASC) (p=0.046). In patients with T allele, ASC progression was significantly faster in the control group compared with the HRT (p=0.0006) group, while the CC genotype showed no significant differences	The results suggest that the beneficial effect of HRT on the progression of atherosclerosis was restricted to women carriers of the T allele
Poliseckil et al. 2005 (12)	Effects on lipid levels and prevalence/incidence of CAD as well as response to pravastatin in reducing plasma lipid profile, and the five variants of the *NPC1L1* gene	Homozygotes for alleles of four *NPC1L1s* (*-18 A>C*, *L272L*, *V1296V* and *U3_28650 A > G*) had 2-8% higher levels of LDL-c than homozygotes carrying common alleles (p<0.05). Homozygotes for rare alleles also had a significant increase in risk of CV events (OR 1.5-167; p<0.02)	Variations in the Niemann-Pick C1-lie 1 protein (*NPC1L1*) gene are associated with the levels of LDL-c and risk of cardiovascular disease
Chasman et al. 2004 (13)	Lipid metabolism and response to therapy with pravastatin and its relationship to genetic variations of 148 SNPs in 10 genes	When compared to homozygotes for the major allele of one of the SNPs, those with a single copy of the minor allele had 22% less reduction in total cholesterol (p =0.01), with an absolute difference of 9.2 mg/dL (95CI 3.8 - 14.6 mg/dL), and 19% less reduction in LDL-c (p=0,005), with an absolute difference of 6.4 mg/dL (95CI 2.2-10.6 g/dL)	Heterozygotes for the genetic variant of the *HMG-CoA* reductase gene may have smaller reductions in cholesterol when treated with pravastatin
Ono et al. 2003 (19)	Association between SNP (-1323T>C) promoter/*GSBS* gene and plasma levels of total cholesterol	Of the 341 carriers of the T allele, approximately 80% had hypercholesterolemia *versus* 44% of the 27 individuals who did not carry this allele (p=0.0001)	Significant increases in total cholesterol were associated with the SNP promoter (-1323T>C) and with the *GSBS* gene, which may play a role in plasma lipoprotein levels
Stanislovaitiene et al. 2013 (24)	Impact of SCARB1 rs5888 SNP on lipid profile and its association with CAD in a Lithuanian population	Men with TT genotype had higher levels of TC and TGC than older men who had higher HDL-c levels. Younger women with TT genotype had lower levels of LDL compared to the CC genotype. The frequency of the SCARB1 TT genotype among older individuals in the MI group was lower than that of the control group	SCARB1 polymorphism is associated with age and gender regarding risk of atheromatous disease and heart failure

SNP: single-nucleotide polymorphism; CV: cardiovascular; TC: total cholesterol; CAD: coronary artery disease; HRT: hormone replacement therapy; TGC: triglycerides; SD: standard deviation.

Discussion

Of the 89 studies identified for analysis, 19 were eligible for including relevant data to the plasma lipid profile and their relationship with several polymorphisms, thus allowing the analysis of data and results of interest. Among the selected studies, one used SNPs to test the hypothesis that genetic increases in HDL-cholesterol were associated with reduced risk of myocardial infarction (MI). Another study examined the exposure to LDL cholesterol in low plasma concentrations for extended periods of time against different polymorphisms and risk of cardiovascular disease (CVD). Nine studies tried to correlate premature CVD and hypercholesterolemia and their corresponding polymorphisms. Six studies assessed polymorphisms related to the therapeutic response to statins, and two studies were designed to correlate hormone replacement therapy (HRT) with polymorphisms and their lipid phenotype.

Two authors, Voight et al. [5] and Ference et al,[8] conducted meta-analyzes using Mendelian randomization to assess prolonged action of high levels of HDL-c and low levels of LDL-c, respectively, and their association with the risk of cardiovascular outcomes. The study by Voight et al.[5] aimed to evaluate high plasma levels of HDL--c through meta-analysis of 7 cohort studies with 19,840 patients. None of the 15 SNPs assessed correlated with risk of MI and, surprisingly, SNP rs16988929 was associated with increased risk of MI despite high levels of HDL-c. When this study assessed the genetic variant LIPG Asn 396Ser using meta-analysis of 20 studies with 116,320,000 patients, the same result of no correlation was found for MI. These findings are relevant, because they cast doubt on interventions proposed until recently, from a clinical point of view, which are to increase HDL-c and use this biochemical marker as a substitute outcome in future studies. Similarly, a study by Ference et al.[8] analyzed SNPs associated with lower plasma levels of LDL-c and their relation with cardiovascular outcomes through Mendelian randomization analysis, compared to the LDL-c reduction effects of statins. The main finding of this study was that all SNPs related with lower LDL-c levels were also linked to lower risk of CAD. In this study, with a large number of participants, a relation between polymorphism profile and significant risk reduction for cardiovascular events was observed, with a reduction in risk between 54.5 and 53.2% for each mmol/L decrease in LDL-c. However, in the analysis of 26 trials of studies using statins, there was a need to reduce the levels of LDL-c three times more to achieve the same magnitude of CAD risk reduction. The study suggests that the effect of independent protection of the LDL-c reduction mechanism and the method of reduction become less significant than the magnitude and time of exposure to low concentrations of LDL-c.

The study by Lamon et al.[9] covers the effects of hormone replacement in women and their consequent lipid metabolic effects. In this study, SNPs in estrogen receptor alpha (ESR1), cholesterol ester transfer protein (CETP) and lipoprotein lipase (LPL) show significant baseline plasma effects of subpopulation with high levels of triglycerides (TGC) and HDL-c. However, polymorphisms of genes involved in lipid metabolism, with the exception of ESR1 SNPs, showed very modest effect on the lipoprotein variability in patients treated with hormone replacement. Hormone replacement therapy (HRT) and progression of atherosclerosis was also evaluated in a study by Fan et al.[10] that evaluated 88 postmenopausal women with different genotypes of hepatic lipase. A significant association between HRT and genotypes of hepatic lipase was found for increased atherosclerosis severity score (ASC) measured by abdominal aorta and carotids ultrasound (p=0.046). In patients with T allele, ASC progression was significantly faster in the control group compared with the HRT (p=0.0006) group, while the CC genotype showed no significant differences in ASC progression between controls and patients treated with HRT. Thus, the results suggest that the beneficial effect of HRT on atherosclerotic progression was restricted to women carriers of the T allele and not general, which contributes to the understanding of the role of HRT and its possible association with risk of atherosclerotic disease.

In a study to evaluate response to statin, Fiegenbaum et al.[11] evaluated the effect of SNPs in sterol regulatory element-binding factors-1a (SREBF), SREBF-2 and SREBF cleavage activating protein (SCAP) on lipid reducing response mediated by the use of simvastatin. The results suggest that polymorphism in the gene *SCAP 2386A>G* was a significant predictor of response to treatment with statin for levels of total cholesterol and TGC. In the same line of study, Poliseckil et al.[12] evaluated the effects on lipid levels and prevalence/incidence of CAD as well as response to pravastatin in reducing plasma lipid profile, and the five variants of the Niemann-Pick C1-lie 1 (*NPC1L1*) gene. The findings of the study indicate that variations in the *NPC1L1* protein gene are associated with the levels of LDL-c and risk of cardiovascular disease. Also assessing efficacy reduction with the use of pravastatin in hypercholesterolemia, Chasman et al.[13] examined the lipid profile and response to therapy with pravastatin, and its relation to genetic variations of 148 SNPs in 10

genes. Knowing that 3-hydroxy-3-methylglutaryl (*HMG*)-*CoA* reductase is the target enzyme that is inhibited by pravastatin, they observed that, compared to homozygotes for the larger allele of one of the SNPs, the ones that had a single copy of the minor allele had 22% less reduction in total cholesterol (p=0.01). Thus, heterozygotes for the genetic variant of the *HMG-CoA* reductase gene may have smaller reductions in cholesterol when treated with pravastatin. In another study,[14] a significant association between hypercholesterolemia/risk of atherosclerosis and plasma *PAF-AH* gene polymorphism in patients with peripheral arterial occlusive disease was observed.

In a study by Aledo et al.,[15] the development of early cardiovascular disease and mortality especially by CAD were assessed in patients heterozygotes for familial hypercholesterolemia (HFh). Genotyping for 10 polymorphisms of single nucleotide in the lipoprotein receptor-related protein 1 (LRP1) gene was performed. The results showed an association between the c.677C>T polymorphism and increased risk of premature cardiovascular disease in this population with familial hypercholesterolemia. Similarly, a study by Salazar et al.[16] found correlation between *45 TMJ* polymorphism in the adiponectin (*ADIPOQ*) gene and CAD in a Chilean population. Another Chilean study conducted by Caamaño et al.[17] found an association between *ABCG5 1950 > G* polymorphism and hypercholesterolemia in that specific population. Likewise, Fujita et al.[18] found a significant correlation between the genotypes of A419P variants and the levels of total cholesterol. Their findings also indicate that variations in *APOB48R* and other genes located closely are among the many factors involved in hypercholesterolemia. In a study by Ono et al.,[19] significant increases in total cholesterol were associated with the SNP promoter (*-1323T>C*) and with the G-substrate (*GSBS*) gene, which may play a role in plasma lipoprotein levels.

The interaction between Apo A-l with the ATP binding receptors is part of the process of acquisition of free cholesterol in peripheral tissue.[9] Variations in the *ABCB1* gene encoding P-glycoprotein (P-gp) are associated with lipid levels and response to statins.[1] In cardiac transplant patients, the use of a triple immunosuppressive therapy ranges between 60-80%, and hyperlipidemia is an important cardiovascular risk factor in these patients.[1] In order to assess this relationship in patients with advanced heart failure, Taegtmeyer et al.[1] confronted results of the genetic variation of *ABCB1* with plasma LDL-c levels in patients before and after cardiac transplantation. The authors observed an association between *ABCB1* haplotype and plasma levels of LDL-c prior to transplantation; however, this correlation was not maintained when patients were reassessed one year after the completion of the transplant.

Assessing polymorphisms in a pediatric Brazilian population, evaluating three SNPs of *SCARB1* gene and their relationship with hypercholesterolemia, as well as influence in response to treatment with atorvastatin was the objective of a study by Cerda et al.[20] The study demonstrated the relationship between these polymorphisms and plasma lipid levels in healthy patients of this cohort and the importance of early assessment in order to identify unfavorable lipid profiles. Also, in a study by Zintzaras et al.,[21] the results were not significant regarding the relationship between the genetic variants of APOE and plasma lipid levels. However, in a study by Smart et al.,[22] variants of genes of lipoprotein lipase, namely *CETP-Taq1B*, *APO E*, *APOA5*, *APOA4* and *APOC3*, were associated with plasma levels of healthy pediatric populations.

In an interesting randomized clinical trial conducted by Lindi et al.,[23] the relationship between the effect of G-250A polymorphism and activity of the hepatic lipase, serum lipid profile, and insulin sensitivity was evaluated. A-250A genotype of the hepatic lipase gene was correlated with high levels of plasma LDL-c. Nonetheless, those patients who used diets rich in monounsaturated fatty acids showed reductions in serum levels of LDL-c especially in patients with genotype A-250A.

The evaluation of lipid phenotype regarding differences in the expression of *SCARB1* rs5888 polymorphism, as conducted by Stanislovaitiene et al.,[24] showed differences in gender and age. Older men showed higher HDL levels while young women carriers of the TT genotype had lower LDL levels when compared to carriers of the C allele. The *SACRB1* TT genotype was associated with less chance of coronary heart disease in men aged between 65 and 75 years.

Conclusion

Polymorphisms correlated with serum lipid metabolism, especially those associated with low plasma levels of LDL-c are associated with reduced risk of myocardial infarction. These findings do not extend to the increase in HDL-c and its relationship to reduced risk of coronary artery disease. The evaluation of polymorphisms in different populations and clinical settings has a role in the future prospect of customized strategies for primary prevention of CAD, according to the genetic inheritance of different polymorphisms that can increase the vulnerability of the patient.

Resumo

Polimorfismos de nucleotídeo único: uma perspectiva de prevenção cardiovascular

Introdução: muitos estudos tem avaliado a utilização de biomarcadores lipídicos na tentativa de correlacioná-los com eventos clínicos cardiovasculares. Contudo, a investigação de condições clínicas sob níveis plasmáticos específicos de lipoproteínas por longos períodos, apresenta limitações devido às dificuldades inerentes relacionadas ao acompanhamento de indivíduos ao longo de suas vidas. Adicionalmente, há a necessidade de melhor compreensão da resposta clínica e eventual resistência da ação de drogas hipolipemiantes em diversos cenários clínicos.
Objetivos: determinar o papel da avaliação de polimorfismos de nucleotídeo único (SNPs) relacionadas com o metabolismo lipídico e suas implicações em diferentes cenários clínicos.
Métodos: foi realizada uma pesquisa na literatura de língua inglesa e espanhola nas bases de dados Medline, Lilacas via Bireme, IBECS via Bireme e Cochrane. Os resultados esperados incluíam informações sobre o perfil lipídico plasmático e SNPs, desfechos clínicos cardiovasculares e polimorfismos relacionadas à efetividade de estatinas quanto ao tratamento da hipercolesterolemia.
Resultados: para esta análise foram incluídos 19 estudos de um total de 89 citações identificadas. Os dados resultantes e avaliados sugerem que baixos níveis plasmáticos de LDL-c estão associados com redução do risco de infarto do miocárdio o que não foi observado para o aumento nos níveis plasmáticos de HDL-c.
Conclusões: os polimorfismos em diferentes populações e perspectivas clínicas podem trazer importantes contribuições para a melhor compreensão e adequação de metas de lipoproteínas plasmáticas que visem a redução de risco cardiovascular.

Palavras-chave: polimorfismo de nucleotídeo único, dislipidemias, inibidores de hidroximetilglutaril-CoA redutases.

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