Reassessing lipid metabolism and its potentialities in the prediction of cardiovascular risk

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ABSTRACT
There are numerous particles, enzymes, and mechanisms in the lipid metabolism that are involved in the genesis of cardiovascular disease (CVD). Given its prevalence in populations and its impact on mortality, it is relevant to review the lipid metabolism as it may potentially provide subsidies to better prediction. This article reviews the importance of traditional cardiovascular risk factors and comments on the potential of novel lipid biomarkers involved in the physiopathology of CVD. The Framingham cohorts proved the role of traditional risk factors (physical inactivity, smoking, blood pressure, total cholesterol, LDL-C, HDL-C, plasma glucose) in the prediction of cardiovascular events. However, a significant number of individuals that suffer from a cardiovascular event has few or none of these factors. Such finding indicates the need for new biomarkers able to identify plaques that are more susceptible to rupture. Some of bloodstream biomarkers related to lipid metabolism are modified LDL particles, apolipoprotein AI (apo AI), apolipoprotein B, lipoprotein (a) [Lp (a)], cholesteryl ester transfer protein (CETP), subtypes of LDL and HDL particles, and lipoprotein-associated phospholipase A2 (Lp-PLA2). These factors participate in the atherosclerotic process, and are abnormal in individuals at high risk, or in those who suffered from a cardiovascular event. Lp (a) determination is already employed in clinical practice and should be included as a reference parameter for CVD monitoring. Furthermore, there are expectations for wider use of apo B, non-HDL cholesterol and total cholesterol / HDL-C determination to improve cardiovascular risk assessment. Arch Endocrinol Metab. 2015;59(2):171-80

Keywords
Lipid metabolism; cardiovascular disease; risk marker

INTRODUCTION

Current epidemiological scenario
The understanding of lipid metabolism has been of constant clinical and academic interest. The abundance of terms in the study of the issue due the countless particles, mechanisms and enzymes involved, do not limit the interest of professionals in the importance of dyslipidemias in the genesis of chronic, non-communicable diseases (CNCDs). These diseases are responsible for the most important mortality rates in populations all over the world, and death rate projections due to this cause are alarming (1). The prevalence of CNCDs in emerging countries like Brazil (2) tends to worsen socioeconomic problems, making the use of healthcare resources difficult. To a great extent, this scenario is a result of population aging, associated with changes in their nutritional status. Excess weight caused by inadequate dietary habits and physical inactivity, increases the risks of CNCDs, specially atherosclerosis. Thus, preventive measures should focus on fighting obesity, as well as understanding the mechanisms by which body fat generates cardiovascular risk.

Atherosclerotic cardiovascular disease (CVD) is responsible for 30% of the deaths worldwide (1); in 2009, a similar number was reported in Brazil (2). Although a drop in mortality rates due to cardiovascular events was recorded – which was attributed to dyslipidemia and hypertension treatment and to the fight against smoking – lack of control of obesity and diabetes mellitus (DM) prevents more expressive reductions.

Dyslipidemias involved in the physiopathology of atherosclerotic disease are characterized by isolated increase in low density lipoprotein (LDL-C ≥ 130 mg/dL), triglycerides (TG ≥ 150 mg/dL), both LDL-C and TG, or by the reduction in high density lipoprotein (HDL-C < 40 mg/dL) (3). In an American study on health and nutrition from 2003-2006, dyslipidemias

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affected 53% of the adults (4). Based on data from eight countries, the World Health Organization (WHO) reported mean prevalence of dyslipidemia as 33%, ranging from 19.2 to 61.6%. The proportion of undiagnosed individuals ranged from 16% in the USA to 78% in Thailand. Among diagnosed individuals, 9% in Thailand and 53% in Japan were not in treatment. Among treated individuals, 4% of the Germans and 58% of the Mexicans showed controlled lipid profile (5).

In Brazil, a study conducted in Campinas involving 227,359 individuals showed the prevalence of hypercholesterolemia ranging from 36% to 44% (6). These researchers found a seasonal variation in dyslipidemia frequency. Hypertriglyceridemia ranged from 37% (in the summer) to 82% (in the winter), and low HDL-C from 21% (in the winter) to 30% (in the summer). In Ribeirão Preto, prevalence of dyslipidemia was even greater, 61.9% (7). These rates call attention to the need for intervention related to this important cardiovascular risk. In fact, the Cholesterol Treatment Trialists estimated that every 18 mg/dL reduction in LDL-C decreases the risk of cardiovascular events in 21% (8).

Several prospective studies that employed inhibitors of HMG-CoA reductase (statins) proved that reduction in LDL-C and increase in HDL-C are associated with fewer non-fatal and fatal cardiovascular events (9,10). In spite of the efficacy of this drug class, some individuals do not reach the lipid control target with monotherapy, whereas others present adverse effects that limit the use of this therapy. Drug associations have been recommend, but their number is limited. The complexity of lipid metabolism opens a window of opportunity for new alternatives in the treatment of dyslipidemias. Morbidity and mortality due to CVD show that much has to be done to improve prediction and prevention of possible events. In this context, understanding the lipid metabolism and potential intervention targets are highly relevant to the current epidemiological scenario.

**RELEVANT PHYSIOLOGICAL ASPECTS OF THE LIPID METABOLISM**

Lipids are transported in the bloodstream inside lipoproteins, which are essentially made up by proteins (apolipoproteins), cholesteryl esters, cholesterol, TG, and phospholipids. An important aspect related to the knowledge on the composition of lipid particles is estimating cardiovascular risk by determining apolipoproteins that make up LDL and HDL. Some apolipoproteins, either alone or in combination, may become part of scientific guidelines very soon (11). The difference between the five most important lipoproteins is their composition: a) chylomicrons (CM): Rich in TG, made up of apolipoprotein C-I (apo C-I), C-II (apo C-II), C-III (apo C-III), B-48 (apo B-48), and E (apo E); b) very low density lipoprotein (VLDL): Rich in TG, made up of apolipoprotein B-100 (apo B-100), apo E, apo C-I, apo C-II, and apo C-III; c) intermediate density lipoprotein (IDL): Rich in TG, made up of apo B-100; d) low density lipoprotein (LDL): Rich in TG, made up of apo B-100, apo C-I, and apo E; e) high density lipoprotein (HDL): Rich in cholesteryl, made up of apolipoprotein A-I (apo A-I), A-II (apo A-II), apo C-I, apo C-II, apo C-III, and apo E.

Lipids that are absorbed in the intestines go from the lymphatic vessels to the bloodstream. In the enterocyte, lipids bind to lipoproteins, specifically apo B-48, A-I, A-II, and A-IV, which are synthetized there. This resulting particle, called CM, is full of TG and food cholesterol and interacts with HDL, which donates apo C-II and apo E, and receives apo A-I and apo A-IV. Besides apolipoproteins, there is an exchange in lipid contents; HDL donates cholesterol to CM, which donates TG in its turn. The contribution of apo C-II is essential, as this apolipoprotein activates lipoprotein lipase (LPL), which hydrolyzes TG found in CM. Free fatty acids are deposited in adipocytes. After this process, CM particle becomes smaller, and is called remaining CM. It is then captured by hepatocytes, broken down, and shed in the bile together with biliary acids.

TG and cholesterol are also endogenously produced. Lipid particles synthesized by the liver and released in the bloodstream are called VLDL. Similar to CM, VLDL interacts with HDL and receives apo C-II and apo E. Apo C-II activates LPL, which hydrolyses its TG. Gradually, this particle increases its cholesterol portion, reaching an intermediate density, that is, becoming IDL, which may follow one of two paths: it may be either captured by hepatocytes and shed in the bile, or continue to lose TG by the action of LPL and hepatic lipase (HL), transferring apo C-II and E to HDL and becoming LDL, with about 50% cholesterol. Besides this apolipoprotein exchange, lipid contents are exchanged between HDL and particles rich in TG (VLDL, IDL and LDL): HDL donates cholesterol, and the other particles donate TG. This exchange is catalyzed by cholesteryl ester transfer proteins (CETP).
Atherosclerotic CVD has an inflammatory character, involving multiple determining factors. Among them, excess body fat, abnormal blood pressure, and glycemic metabolism. Atherosclerosis begins with endothelial dysfunction, which may be observed by the increase in the expression of endothelial adhesion molecules (14). The adhesion molecules favor the subendothelial penetration of LDL, specially its dense and small fractions, which are more easily oxidized, stimulating inflammatory cytokines. Among these cytokines, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), interleukin 2 (IL-2), and interferon gamma (INF-γ) are molecules responsible for a low-grade, chronic inflammatory status that negatively affects insulin signaling and glucose capture by cells (insulin resistance). In parallel to these actions, mononuclear cells enter the tunica intima, potentializing the pro-inflammatory state. Macrophages are strongly activated, and phagocytize oxidized LDL particles (LDLox) by means of scavenger receptors, becoming full of lipids (foam cells). Their activation, besides increasing the production of pro-inflammatory cytokines, stimulates muscle cells migration to the endothelium. These muscle cells also become full of lipids, which determine their apoptosis. The atheroma is formed by gradual deposition of fat on the arterial wall. Muscle cells produce collagen, elastin and elastase, which stabilize the atheromatous plaque (15,16), and its rupture leads to thromboembolic events.

Frequently, dyslipidemic individuals also show arterial hypertension and DM, aspects that make up the metabolic syndrome, which is associated with high cardiovascular risk. DM favors atherosclerosis by several mechanisms. Hyperglycemia induces endothelial dysfunction, expression of adhesion molecules, greater vascular permeability, and oxidative stress; besides, it favors the modification of LDL particles (17). These disorders, frequently found together with visceral obesity, show insulin resistance as a common feature. Hypertrophic fatty tissue produces MCP-1, which stimulates the infiltration of M1 macrophages. These cells, together with adipocytes, produce inflammatory cytokines that compromise insulin signaling, such as TNF-α, IL-6, IL-2 and INF-γ, whereas the production of anti-inflammatory compounds (IL-4 and IL-10) is reduced, determining a metabolic condition that is adequate for atherosclerosis development.

There is clear evidence that circulating lipids are essential for the atherosclerotic process to develop. If these classic and new lipid biomarkers are investigated, the predictive ability for cardiovascular events may be improved. Knowledge on the mechanisms may provide support not only for risk prediction, but also for the development of new therapeutic strategies.

TRADITIONAL CARDIOVASCULAR RISK FACTORS

Major, classic or traditional risk factors are those defined from the Framingham studies, which are proven to predict the occurrence of cardiovascular events, specially coronary and cerebral ones. More recently, new risk biomarkers have been proposed, part of them lipids that are also involved in the physiopathology of atherosclerotic disease.

The Framingham cohorts began in 1948, and are relevant milestones in the identification of cardiovascular factors. These cohorts identified the role of age; sex; total cholesterol, LDL-C and HDL-C levels; systolic pressure; smoking; high blood glucose; body weight; certain dietary habits; and physical inactivity. Based on these findings, cardiovascular risk scales were develop-
The Framingham cardiovascular risk score is widely used, but there are other proposals, such as the HEARTSCORE (18), the Adult Treatment Panel III (3), and the Prospective Cardiovascular Munster (PROCAM, which predicts only the risk of myocardial infarction) (19). Each of them was determined in a specific population, and none of them include all the known risk factors. The Framingham score, for example, does not include weight, physical activity, and diet. Based on the recommendation of the international scientific society, all proposals use a group of variables to better estimate cardiovascular risk.

To a large extent, the need for the identification of additional risk markers is due to the observation that a considerable proportion of the individuals that suffer from cardiovascular events show either few or none of the traditional risk factors (20,21).

A biomarker (any molecular, cellular, or blood measurement or image of physiological, pathological or therapeutic response) should be accurate to identify individuals at risk, have reproducible and stable results and, when used early, should have a preventive/therapeutic impact. Considering these characteristics, the quantification of coronary calcium by computer tomography may be an imaging biomarker (22). New soluble cardiovascular biomarkers in the bloodstream do not have, in general, an established role in CVD prediction (22). Among inflammatory biomarkers, ultrasensitive C-reactive protein has shown to be able to improve the predictive ability of LDL (23) for cardiovascular events.

The use of a new cardiovascular risk biomarkers should be based in improved discrimination and calibration of existing risk models (22). It is estimated that about 10 to 20% of the individuals that suffer from an event do not present traditional risk factors, and that 60% of them present two or less factors (22). These findings emphasize the importance of searching for evidence that emerging biomarkers may better identify plaques that are more vulnerable to rupture.

Biomarkers related to lipid metabolism are highlighted in this review due to their important role in the physiopathology of atherosclerosis (Table 1). It is expected that longitudinal studies may, in the medium range, provide subsides to their usefulness in clinical practice. Besides, cost-benefit studies will also be necessary to support their use.

**EMERGING CARDIOVASCULAR RISK MARKERS ASSOCIATED TO LIPID METABOLISM**

**LDL modified particles**

After the role of hypercholesterolemia was recognized as a risk factor and as the main prognostic measure of coronary events, knowledge on the consequences of modified LDL (oxidized LDL, electronegative LDL and glycosylated LDL) was deepened. These molecules are pro-inflammatory and highly atherogenic (24). Their structural modifications are recognized by mononuclear cells that produce inflammatory cytokines, maintaining a low-grade, chronic inflammatory status characteristic of atherosclerosis. Oxidative modifications are highlighted, whose final product is oxidized LDL, a result of the action of countless oxidizing substances, such as the superoxide anion, hydrogen peroxide, and enzymes such as lipoxygenases and myeloperoxidases.

Another target of this investigation has been the electronegative LDL (LDL(-) or minimally modified LDL), produced by oxidation and other processes, such as non-enzymatic glycosylation, hyperactivity of lipoprotein-associated phospholipase A₂ (Lp-PLA₂), enrichment by non-esterified fatty acids, cross-binding with hemoglobin and apo B-100, and increase in apo C-III and apo E content (17,25). Modified LDL particles have lower affinity by B/E receptors, which affects liver catabolism, increases the content of cholesteryl esters in macrophages, and alters endothelial function (26).

In the bloodstream, the presence of modified lipoproteins stimulates the immunological system favoring chronic diseases, such as atherosclerosis. This stimulation may be detected by the increased number of mononuclear cells, as well as other markers, such as antibodies targeting modified lipoproteins, MCP-1, interleukins, IFN-γ, TNF-α, and platelet-derived growth factor (25).

In the chronic inflammatory process related to atherosclerosis, the adherence of monocytes to the endothelium is a key event for plaque development, and the accumulation of modified LDL is an important trigger to the initial damage to the artery. The association of these particles with cardiovascular risk has been reported, frequently in relation to the severity of the disease (27,28). A study conducted in a high risk local population found an association between CVD and native...
antibodies anti-LDL and anti-LDL(-) (29). Controversial findings make it uncertain if antibodies are directly expressed in a deleterious environment, or if they are a protective response of the organisms against the atherogenic particles. Some studies indicate an association between high levels of antibodies anti-LDL(-) or anti-LDLox, and CVD (30,31), whereas other found an opposite relationship (32,33). Part of the controversy has been explained by the formation of immunocomplexes and/or other factors that interfere in the laboratory measurement of the antibodies (34).

Laboratory analysis of modified LDL or antibodies requires careful work, besides being expensive. Therefore, it is not recommended in clinical practice, for it still requires standardization and determination of reference values.

**Lipoprotein-associated phospholipase A2 – Lp-PLA2**

Among the pro-inflammatory substances stimulated by the presence of oxidized LDL in the bloodstream is lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme that is responsible for the hydrolysis of the sn-2 bond of oxidized lipids found in LDL particles. The production of Lp-PLA2 is stimulated by oxidized LDL (35). This action in initially considered to be protective, because it minimizes oxidative components associated with the particle (36). However, as a result of this reaction, lisophospholipids are formed (such as lisosphosphatidylcholine), which drastically stimulate inflammation and take part in several stages of the formation of the atherosclerotic plaque. Therefore, it may be observed that Lp-PLA2 activity favors the inflammatory process and the evolution of atherosclerosis (37).

The activity of Lp-PLA2 in the plasma is mainly associated with its presence in LDL (83%); a small amount of this enzyme is found in HDL (11%) (38). Because of this, some researcher raised a hypothesis that when linked to LDL, Lp-PLA2 would be pro-atherogenic, whereas its action in the HDL particle would be anti-atherogenic (39). Other researchers observed that the greater the LDL/Lp-PLA2 and HDL/Lp-PLA2 ratio, the greater the levels of LDL-C, TG, glucose, insulin, and lower the levels of HDL-C in individuals with polycystic ovary syndrome (40). Rallidis and cols. (41) observed that the concentration and activity of Lp-PLA2 in a longitudinal study were predictive of death by CVD. The mass and activity of the enzyme associated with the HDL particle are linked to lower risk of death by CVD, even after adjustment for the traditional risk factors.

Several cohorts showed that the blood level and activity of Lp-PLA2 are associated with cardiovascular events, independent of other risk factors (42). Packard and cols. (42) found greater risk of coronary events

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**Table 1. Emerging cardiovascular risk markers and their respective physiopathological effect**

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among individuals in the higher quintiles of Lp-PLA2 throughout a seven-year period. The Malmö Diet and Cancer Study, which followed individuals in a cardiovascular program between 1991 and 1994, observed that individuals in the higher tercile of Lp-PLA2, compared individuals in the lower tercile, showed higher relative risk for cardiovascular events (43). In a follow-up carried out for 6 months in 142 patients with acute coronary syndrome, it was observed that those with high Lp-PLA2 presented greater risk for important adverse cardiac events (44).

Based on this evidence, the authors proposed the use of Lp-PLA2 as a cardiovascular risk marker (45). However, the standardization of reference values, the reduction in the cost of the analyses, and the greater understanding of its effect when associated with the different particles are some questions that need to be answered before the practical use of this determination is suggested.

### Apolipoproteins

The evaluation of the plasma apolipoprotein profile is not part of the local monitoring of cardiovascular risk factors. As the concentration of apo B100 is high in atherogenic lipoproteins (VLDL, IDL and LDL), whereas apo A-I is basically part of HDL, laboratory analysis of these lipoproteins may complement the analysis of this dyslipidemia. More commonly, the apo B/apo A-I ratio, which shows the balance between the atherogenic (apo B) and anti-atherogenic cholesterol particles (apo A), has been employed in the evaluation of cardiovascular risk. In fact, several investigators confirmed its usefulness in the prediction of cardiovascular events (46).

Apo A and B are easy to be measured and showed to be useful in the prediction of cardiovascular events in some studies (45-48). The meta-analysis carried out with 23 studies showed that the greatest concentrations of apo B determined a relative risk of 1.99 for events, whereas the lowest levels of apo A-I raised the risk in 62% (47). The apo B/apo A-I ratio was also predictive, with a risk of 1.86. A multicentric study conducted in the USA confirmed the association between apo B with heart disease and cardiovascular death; similarly the apo B/apo A-I ratio, as well as the CT/HDL-C ratio, were associated with fatal coronary events. It should be emphasized that only the apo B and the apo B/apo A-I ratio remained significantly associated after the adjustment for traditional risk factors (46). Similarly, the association of the same parameters with the media-intima thickness suggest they may be early predictors of atherosclerosis (48).

In spite of the evidence, apolipoprotein dosage is not recommended by scientific societies for the diagnosis of dyslipidemia or risk estimation (3,49). However, recent studies suggest that the quantification of apo B should be added to clinical practice to refine the evaluation of plasma lipids in individuals at increased risk (50). The indication for apo B determination is expected to be included in the next NCEP guidelines (ATP IV) (11,51).

### Lipoprotein(a)

Lipoprotein(a), Lp(a), is a particle with similar structure to LDL, containing one apo-B combined with an additional apo(a). Its, cholesterol content, density and depuration are also very similar to those of the LDL particles. The structure of the apo(a) particle is similar to plasminogen, including a common gene sequence. Therefore, the presence of apo(a) shows prothrombotic potential, and it is able to interfere with the physiological role of plasminogen. Apo(a) inhibits plasminogen activation in plasmin, which is responsible for fibrin degradation (52,53).

Lp(a) concentrations are associated, therefore, with the atherogenic characteristics of the particles that contain apo B and the thrombogenic properties determined by apo(a). There are distinct classes of apo(a); they differ by a small number of aminoacids. These classes are defined by genetic characteristics that also determine the rate of apo(a) synthesis. As a function of the strong genetic components, the concentration of Lp(a) in the bloodstream are weakly influenced by age, sex, and environmental factors (52).

Lp(a) blood levels behave as independent risk factor for CVD (54). In most individuals, these values are lower than 30 mg/dL; those with values above 100 mg/dL present very high risk, in general related with familial hypercholesterolemia and DM2 (55). In the Emerging Risk Factors Collaboration, in which 36 prospective studies involving 126,634 participants were analyzed, it was observed that the concentration of Lp(a) was associated with increased risk for CVD. After adjustment for cholesterol and other established risk factors, the association were only slightly attenuated, reinforcing the hypothesis that this is an independent risk factor for coronary disease (54). Similarly, in the
European Prospective Investigation of Cancer cohort, it was observed that the associations of the Lp(a) concentrations with arterial coronary and cerebral disease were not modified by adjustment for LDL-C (56).

The third report of the National Cholesterol Education Program for the Detection, Evaluation and Treatment of Hypercholesterolemia in Adults (NCEP-ATP III) stated that, in spite of the measurement limitations, Lp(a) dosage is an useful parameter. Its high concentration aids the identification of those individuals with even higher cardiovascular risk. It is suggested that Lp(a) should be used as a second risk factor to support lower LDL cholesterol targets (3). The American College of Cardiology and the American Heart Association, in a recent publication on the treatment of dyslipidemias in adults, understand that the future recommendations for the control of blood cholesterol will include Lp(a) as a marker of therapeutic effects and as a form of monitoring CVD evolution (51).

CETP and its lipoprotein subclasses
CETP activity (an enzyme mainly found in HDL particles) results in the transfer of a cholesteryl ester from HDL to the lipoproteins that contain apo B (VLDL, IDL, LDL), which in their turn, transfer TG to HDL (57). This CETP action is, therefore, responsible for important changes in lipoproteins, transforming LDL in small and more dense particles (phenotype B), and generating smaller HDL particles (HDL$_2$ in HDL$_3$).

CETP concentrations are increased in obesity, dyslipidemia and atherosclerosis, and are directly associated with inflammatory markers (57). However, their use as a risk biomarker is still controversial. Some researchers (58,59) observed, in high risk individuals, associations of CETP with cholesterol efflux capacity, which is in agreement with the protective role of the enzyme in atherosclerosis. In a longitudinal study with 6,780 individuals, variation in the concentrations of CETP did not affect the importance of the effect of apo B/apo A-I and CT/HDL-C ratios for the occurrence in the first cardiovascular event (60). Schierer and cols. (61), similar to other authors (58,59), proposed that low CETP is associated with higher cardiovascular risk.

In spite of the recognition that CETP action is directly related to its size and density of the LDL-C e HDL-C fractions, it is not clear how its effect, mainly on HDL-C, affects cardiovascular risk. The meta-analysis suggests that CETP activity is inversely associated with the concentration of HDL-C, which would favor atherosclerosis (62).

LDL subclasses may be identified by means of ultracentrifugation or electrophoresis, enabling the definition of dyslipidemic individuals according to different phenotypes. In relation to the proportion of LDL subclasses, individuals with greater concentrations of small and dense particles are carriers of phenotype B, which is associated with higher risk of atherosclerosis. Small and dense LDL contains greater proportions of cholesterol, being more susceptible to oxidation, presenting lower affinity with the B/E receptor, and passing more easily through the intima layer. Larger and less dense LDL particles (phenotype A) present opposite characteristics and, thus, lower cardiovascular risk (63).

Increased proportions of small and dense LDL have been consistently associated with cardiovascular risk (64), and some special groups of individuals, such as DM (65) or metabolic syndrome (66) carriers, show this phenotype more frequently. Several researchers consider that more specific dosage of LDL particles is a promising technique to refine the prediction of cardiovascular risk (64,67). However, this measurement still needs to become easier to be more widely used in clinical practice.

As for HDL, existing data gathered with different methodologies demonstrate that the subclasses present heterogeneous biological activities. Small and dense fractions seem to exhibit atheroprotective properties. This effect is probably due to the greater antioxidant, anti-inflammatory, anti-cholesterol and cholesterol efflux capacity compared with the larger and less dense fraction (68,69). However, its protective ability is attenuated in atherogenic dyslipidemia, probably due to the lipid and protein changes caused by this condition (69). There are few studies in the literature that definitely clarify the role of HDL subfractions, specially changes in composition and structure of the atherosclerotic process.

CONCLUSION
Based on this analysis of the lipid metabolism, its importance in the prediction of cardiovascular risk is reiterated. Classic measurements, such as LDL-C, HDL-C and triglycerides are established in clinical practice as important tools in risk prediction and therapy follow-up (3). Besides them, it is important to find other markers, due to the considerable number of individuals...
that suffer cardiovascular events with few or none of the risk factors (20,70).

Lipid metabolism has several elements with a potential role in the risk prediction and monitoring that are targets for the development of new therapeutic strategies for CVD, as many of these makers take part in the physiopathology of atherosclerosis. Among them, promising ones are measurements of changes in LDL particles, Lp-PLA2, apolipoprotein (apo B and apo A-I), Lp(a), CETP, and LDL and HDL subclasses for a more rigorous evaluation of risk in specific strata of the population. Among the markers, Lp(a) dosage is already contemplated in NCEP (5) as a second risk factor to justify more strict lipid targets. The next guidelines of ATP IV are being determined, and possibly Lp(a) will be included as a reference measure for the treatment and monitoring of CVD. There are great expectations for apo B, non-HDL cholesterol, and total cholesterol/ HDL-C ratio as aids in the evaluation of cardiovascular risk (11,51). It may be concluded that the fast evolution of knowledge on the subject may justify periodic reassessment of lipid metabolism.

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