Reviews

Lipoprotein(a): Current Evidence for a Physiologic Role and the Effects of Nutraceutical Strategies

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ABSTRACT

Purpose: Cardiovascular (CV) diseases account for most worldwide mortality, and a higher level of lipoprotein (Lp)-(a) is recognized as a prevalent contributing risk factor. However, there is no consensus regarding nutritional strategies for lowering Lp(a) concentration. Thus, the purposes of this literature review were to: (1) critically examine data concerning the effects of dietetic interventions and nutraceutical agents on Lp(a) level; and (2) review the feasibility and utility of their clinical use.

Methods: A literature search was conducted for studies published between August 2018 and March 2019. The search was performed using the Cochrane, Medline, and Web of Science databases. In order to expand the research, there were no delimitations on the type or year of the studies. A total of 1932 articles were identified using this search procedure. After duplicates were eliminated, 740 abstracts of articles written in English were screened to identify those of highest relevance. In the final tally, a total of 152 full-text articles were included in this review.

Findings: Several foods and decreases in saturated fat and ethanol intake, especially red wine intake, may lower Lp(a) concentration, but limits are necessary. Coffee and tea intake may decrease Lp(a) level; further investigation is crucial before they can be considered potent Lp(a)-lowering agents. Among supplementation strategies, only L-carnitine and coenzyme Q10 are promising clinical candidates to lower Lp(a) level. Since both L-carnitine and coenzyme Q10 supplementation are commonly used for CV support, they deserve further exploration regarding clinical applicability. In contrast, despite potential CV benefits, current research fails to justify use of higher intakes of vitamin C, soy isoflavones, garlic, and ω-3 for decreasing Lp(a) concentration.

Implications: Definitive long-term clinical trials are needed to confirm the effects of dietetic interventions and nutraceutical agents on Lp(a) concentration when anticipating improved CV outcomes. (*Clin Ther*. 2019;41:1780–1797) © 2019 Published by Elsevier Inc.

Key words: atherosclerosis, cardiovascular disease, lipoprotein, lipoprotein(a), lipid profile.

INTRODUCTION

Cardiovascular diseases (CVDs), especially those related to ischemic heart disease (IHD), have been considered epidemics for decades.[1] Together with stroke, included within the umbrella of CVD, these diseases account for most worldwide mortality, exceeding the burdens of chronic respiratory diseases, diabetes mellitus, and even cancer.[2,3] Although the management of CVD has improved remarkably, the associated high incidence, prevalence, and mortality continue unabated.[4] In most developed countries, wide use of statins, antihypertensives, and other

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drugs, along with a diminution in tobacco use, have been credited with much progress in improving patients' prognoses. The complex task of disentangling individual risk factor contributions to better outcomes remains a challenge.[4]

One long-neglected potent risk factor now attracting substantial interest is excess lipoprotein (Lp)-(a) in the peripheral blood. The Lp(a) molecule is a fundamentally different genetic variant of low-density lipoprotein (LDL), exhibiting a diameter and density very similar to those of LDL and with considerable dyslipidemic potential.[5] The molecule Lp(a) was first identified as a genetic "trait" by Berg in 1963.[6] Described as a new antigen associated with low-density lipoproteins, the molecule was named, as was then the custom, as Lp(a), referring to the "a" antigen linked with lipoproteins. In other words, there was no intent to describe a new kind of lipoprotein *per se,* since it was before the adoption of the apolipoprotein (apo) terminology used in lipidology today. This antigen is present in the sera of most individuals in low amounts, with wide interpersonal variation in concentrations, and its identification by immunoassay persists. The function of this lipoprotein has been enigmatic and still remains unknown.[7]

As a public-health challenge,[7] the measurement of blood Lp(a) from pediatric to elderly individuals deserves more attention.[8–10] Given that there has been an attenuation in the decline of all CVD, heart disease, and stroke mortality rates with existing approaches, perhaps tighter control of Lp(a) concentration may mitigate the future burden of CVD.[11] This global concern is indeed challenging as concentrations of Lp(a) show large individual variation within various populations, ranging from 0 to 200 mg/dL. For example, most European people have an Lp(a) concentration of ~10 mg/dL, while only about 25% have concentrations near 30 mg/dL.[12] In the current European Atherosclerosis Society opinion statement, Nordestgaard et al[13] recommend that patients at intermediate to high risk for CVD achieve an Lp(a) target of <50 mg/dL. More specifically, Lp(a) level can be categorized as normal (≤30 mg/dL or 75 nmol/L), borderline (30−<50 mg/dL or 75−<125 nmol/L), or high (≥50 mg/dL or ≥125 nmol/L).[10,14] Measurement of blood Lp(a) accurately and in a standardized fashion is a further challenge.[15–17] Moreover, without knowing a patient's Lp(a) level, it is impossible to know the true LDL-C level because the two are independent yet are reported together as the number of "LDL-C." In patients with "normal" LDL-C, Lp(a) may be elevated, raising the CV risk.[17] Since apo(a) size is variable, one also cannot convert a result in mg/dL of Lp(a) to mmol/L of Lp(a).

While Lp(a)-lowering pharmaceutical agents have been proposed, there is no established consensus for their use.[18] Among nonpharmaceutical treatments, both a healthy diet and regular physical exercise are associated with favorable changes in lipoproteins and play a crucial role in decreasing the risk for CVD and mortality.[19–21] Surprisingly, physical exercise, *per se,* does not seem to influence Lp(a) concentration, as in one study low-aerobic athletes (resistance trainers, bodybuilders) and high-aerobic athletes (long-distance or endurance runners) both had elevated plasma Lp(a) concentrations regardless of androgenic−anabolic steroid use,[22] which, despite their well-known disturbances in lipid markers, promote a reduction in Lp(a) concentration.[23–25] Regarding the effect of nutrition on Lp(a) level, little is known about specific dietary factors that influence Lp(a) metabolism.

Hence, the aims of this literature review were to: (1) critically examine data concerning the effects of dietetic interventions and nutraceutical agents on Lp(a) level; and (2) review the feasibility and utility of their clinical use.

MATERIALS AND METHODS

For the current report, we examined several different electronic databases, such as Medline (Pubmed), Embase, Web of Science, and Cochrane, and manually perused references of studies published between August 2018 and March 2019. The research was composed of and associated with the following terms (and their respective related terms): *lipoprotein(a) or Lp(a) and diet, and vitamin C, and soy, and garlic, and omega 3, and fat diet, and ethanol, and coffee, and tea*. In order to expand the search, there was no delimitation of type or year of the studies. We initially identified 1932 articles, and after duplicates were eliminated, 740 papers written in English were further examined, ultimately leaving us 152 articles for this review.

RESULTS

Structural, Metabolic, and Pathophysiologic Properties of Lp(a)

Lp(a) is a spherical macromolecular complex particle with a diameter of ~25 nm, a size range of 200 to >1000 kDa, and a density ranging of 1.05−1.12 g/mL with both atherogenic and thrombogenic properties.[26,27] Lp(a) is a combination of a protein similar to plasminogen, known as apolipoprotein (apo)-(a), covalently attached by a disulfide bond to apoB-100, the atherogenic component of LDL and other lipoproteins.[28] Apo(a) is not structurally related to Apoa-I, and Lp(a) is not a separate class of lipoproteins, since it cannot be separated by ultracentrifugation. However, the density of Lp(a) is similar to that of LDL, and Lp(a) circulates as a part of LDL-C. Lp(a) is composed of 30%−45% cholesterol by mass, and is included in the usual LDL-C number (in mg/dL or mmol/L) reported in standard lipid profiles.[5] While LDL-C and Lp(a) levels are independent of each other, a high Lp(a) concentration has the potential to increase CV risk by 22% or more.[29]

The apo(a) gene, *LPA*, evolved from the plasminogen gene, contains multiple Kringle (K) domains, which are units of structure and function allowing molecular recognition.[30] Typically, this domain is found in coagulation factors with proteinase activity associated with blood clotting and fibrinolysis such as thrombin, plasminogen, and plasminogen activators. The primary and tertiary structures of the Kringle domain are highly conserved and hence readily recognized. Apo(a) shares homology with plasminogen, but differs in that the Kringle domains are different (no KI to KIII, with types of domains diversified and expanded into 10 subtypes of KIV, including one copy of KIV_1, one copy of $KIV_{3\text{-}10}$, and KIV_2 in 1 to over 40 copies).[31] By occupying sites on fibrinogen, apo(a) interferes with plasminogen binding and impedes fibrinolysis. Yet, due to structural amino acid differences precluding an active protease domain, evolved and mutated apo(a) cannot participate in physiologic activation of plasminogen into the fibrinolytic enzyme plasmin by tissue plasminogen activator, which is essential for hemostasis.[32−34] By releasing inhibition of smooth muscle proliferation by plasmin, Lp(a) indirectly increases atherogenesis through an additional mechanism.[35]

Over 90% of the population are heterozygous for the copy number of KIV_2 and hence apo(a) size. An apo(a) allele with a high variation number of KIV_2 will generate a longer apo(a) associated with a lower plasma level, and those with a small variation number will generate a shorter apo(a) and a higher Lp(a) level. The latter will result in a higher risk for CVD.[34] The apo(a) molecule is transcribed in the liver, and the older hypothesis that the Lp(a) molecule is assembled in the plasma is challenged. Mature Lp(a) consists of a lipid bilayer containing phospholipids, membrane proteins, free cholesterol, and some triglycerides.[34] Part of the atherogenic potential of Lp(a) likely relates to its high content of proinflammatory oxidized phospholipids (oxPL) and the increased oxidative stress generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and other enzymes.[36]

Recent data suggest that some of the proatherogenic properties of Lp(a) may be explained by the oxPLs it carries or by the oxidative modification of Lp(a).[37] In human plasma, oxPLs preferentially associate with Lp(a) rather than LDL particles, and are very active immunologically.[38] In one study, both oxPL on apoB particles and Lp(a) level were related to the degree of atherosclerosis, inversely related to the size of the apo(a) isoforms, and independent of CV risk factors.[39] In another study, levels of both Lp(a) and oxPL provided cumulative predictive value for IHD when added to conventional risk factors for IHD.[40] In other words, a greater cargo of oxPL carried by Lp(a) confers additional atherogenicity.

Lp(a) catabolism likely occurs in multiple sites, the renal arteries and veins among them, but direct evidence is lacking. However, there is also strong evidence that the hepatic LDL-receptor plays a role in Lp(a) catabolism, accounting for the reduction in Lp(a) level by proprotein convertase subtilisin/kexin type 9 inhibitors.[15,41] Interestingly, individuals without the LDL receptor and with a deletion of the LDL receptor and homozygous familial hypercholesterolemia do not exhibit a higher Lp(a) level. The wide variety of Toll-like and scavenger receptors, lectins, and plasminogen receptor ligands poses a particular challenge in elucidating those

which are involved in Lp(a) removal.[16] However, no specific receptor for Lp(a) catabolism has been described.

Relationship Between Lp(a) and HDL

In human liver cells, a relationship between Lp(a) and high-density lipoprotein (HDL) has been suggested, wherein Lp(a) plays a role in the expression of the PPARγ–LXRα heterodimer (peroxisome proliferator-activated receptor γ and liver X receptor α, respectively), molecules that regulate ATP-binding cassette transporter A1 (ABCA1) production.[42]

Scavenger receptor class B type 1 (SR-B1) has been identified as a receptor of Lp(a).[43] In addition to Lp(a) *per se*, its derivatives such as oxPL avidly bind to SR-B1.[44] Subsequently there is a transduction process in the hepatocyte nucleus, possibly mediated by SR-B1–mediated internalization of oxPL and Lp(a) contents, to activate the PPARγ–LXRα axis, and, in turn, to upregulate ABCA1 RNA and ABCA1 production.[42] ABCA1 is involved in transporting cholesterol and phospholipids to lipid-poor apolipoproteins from the liver and peripheral tissues. At the plasma level, additional cholesterol from the liver and peripheral tissues is incorporated to nascent HDL mediated by ABCA1. Lecithin–cholesterol acyltransferase (LCAT) converts free cholesterol into cholesteryl ester (a more hydrophobic form of cholesterol), which is then sequestered into the core of the lipoprotein particle; both processes furnish substrate for HDL production.[45–47] Some evidence exists that the Lp(a)-oxPL complex does promote cholesterol efflux and there is a mechanism for the interaction of Lp(a) with HDL (Figure 1). Thus far, the clinical effect size has not been significant. More work is needed because of the many confounders possible, including measurement and other interactions (eg, interleukin-1 interactions), and dysfunctional HDL.[48–50] Notably, both the

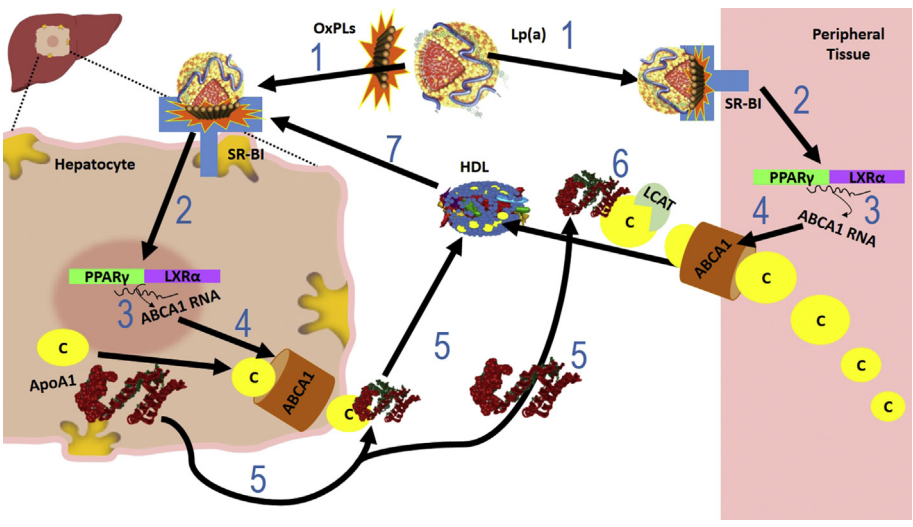

Figure 1. Possible relationship between lipoprotein (Lp)-a and high-density lipoprotein (HDL). 1) Oxidized phospholipids (oxPLs) are released by Lp(a). 2) oxPLs bind to scavenger receptor class (SR)-BI. 3) Through a transduction response of the binding of Lp(a) derivatives to SR-BI, activation of the peroxisome proliferator-activated receptor (PPAR)-γ– liver X receptor (LXR)-α axis occurs in the hepatocyte nucleus, promoting the expression of ATP binding cassette transporter (ABC)-A1 RNA. 4) ABCA1 is stimulated by hepatic cholesterol uptake. 5) Apolipoprotein(a) produced in the liver on release into the plasma captures the cholesterol supplied by ABCA1. 6) HDL takes apo(a) up substrates, which is rich in cholesterol released through by ABCA1 in liver and peripheral tissues, as well as lecithin–cholesterol acyltransferase (LCAT).

promotion of ABCA1 activity and the avid association of oxPL with Lp(a), effectively functioning as a "sink" for potentially harmful oxPL, have been considered possible functions of Lp(a).

Lp(a) as a Biomarker and Cause of CVDs

Human senescence is a physiologic process in which CV damage caused by Lp(a) may be substantial and unrecognized, materially raising the risk for arterial lesions in older individuals without a diagnosis of CVD.[8] Hence, in a study involving 136 elderly individuals without a diagnosis of CVD, carotid artery intimal thickness was greater in patients with higher oxidized Lp(a) content.[51] Likewise, genetic variation is vitally important in understanding Lp(a) biology. As observed in a multicenter case–control study in which 3355 individuals with IHD and 3352 controls from four European countries (United Kingdom, Italy, Sweden, and Germany) were enrolled, the genotype variants of Lp(a) (rs10455872 and rs3798220) associated with high levels of Lp(a) and, significantly, participants classified with those genetic disturbances, had a greater prevalence of IHD.[52]

Viewed collectively, Lp(a) excess contributes to the occurrence of stroke, cardiac ischemia, thrombosis, and atherosclerosis, as summarized in Figure 2.

Manifestations of the Relationship Between Lp(a) Concentration and CVD

IHD and Stroke

A meta-analysis of data from 20 studies, totaling 90,904 patients with 5029 cases of stroke, compared high with low Lp(a) levels and reported a pooled estimated odds ratio of 1.41 from case–control studies (n = 11), and a pooled estimated relative risk of 1.29 from prospective studies (n = 9), with relative risk particularly evident in younger stroke patients.[29] Similarly, another meta-analysis of data from 31 observational studies, including 56,010 individuals, corroborated that an elevated level of Lp(a) is indeed a risk factor for stroke.[53]

During a 10-year follow-up of 5436 CVD cases in a meta-analysis of 27 prospective studies, a high level of Lp(a) was also associated with IHD.[54] In a meta-analysis of data from 126,634 participants without a previous history of IHD or stroke, Lp(a) concentration was positively correlated with total

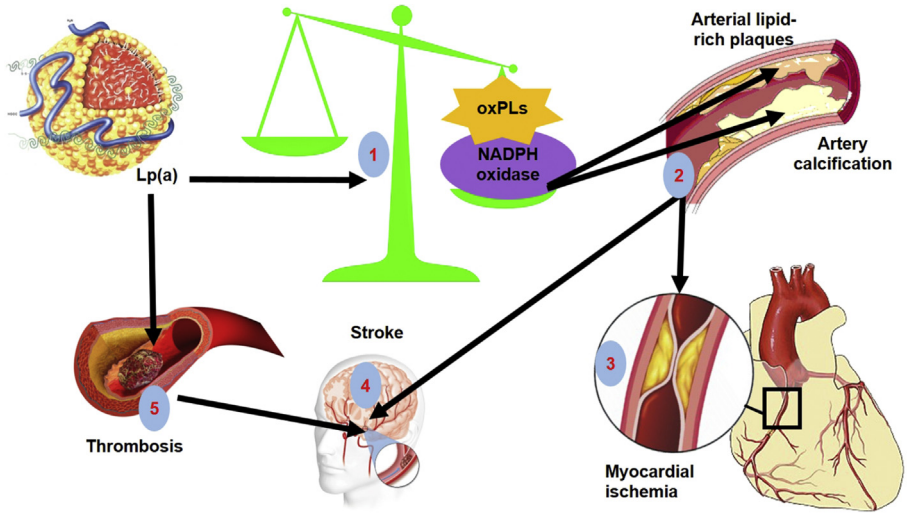

Figure 2. Lipoprotein (Lp)-a and cardiovascular outcomes. 1) Redox imbalance caused by increasing oxidized phospholipids (oxPLs) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. 2) Formation of lipid plaque and arterial calcification by redox imbalance. 3) Progression to atherosclerosis and possible cardiac ischemia. 4) Arterial dysfunctions caused by Lp(a) can affect brain sites leading to stroke. 5) Thrombotic process as a consequence of the Lp(a).

cholesterol, non-HDL cholesterol, apo B-100, and fibrinogen.[55] Paradoxically, Lp(a) concentration was inversely related to the level of serum triglycerides. The meta-analysis also showed that Lp(a) value was associated with the risk for vascular diseases, such as IHD and stroke. In contrast, the Lp(a) values were not related to nonvascular mortality and cancer. Interestingly, the overall median Lp(a) in the baseline studies included in that meta-analysis was 12.6 mg/dL (interquartile range, 4.9−32.1 mg/dL), providing support for the ranges previously presented.[55]

Furthermore, a high Lp(a) level is now an established cause of premature acute coronary syndrome in young adults.[56] In individuals <45 years of age, every 20-mg/dL rise in Lp(a) is associated with a 4% higher risk for acute coronary syndrome. An Lp(a) value of >50 mg/dL triples the risk for acute coronary syndrome in this age group. The likelihood decreases to 2% between the ages of 45 and 60 years, but during this midlife period, IHD typically begins a steep rise from LDL-C−associated disease.

Indeed, Lp(a) measurement is relevant not only in middle-aged and elderly individuals,[8,51] but also in the pediatric population.[9] In this age group, rare strokes are due to ischemia accompanied by plaque. Children afflicted with pediatric familial hypercholesterolemia are particularly vulnerable. Zawachi et al[10] recently demonstrated that in this population the Lp(a) value may predict early CVD in family members better than LDL-C.

Stent Failure

Lp(a) concentration may be associated with disorders of coagulation. According to Nordestgaard et al,[13] although Lp(a) has intrinsic thrombotic potential, a high plasma concentration of Lp(a) may induce an antifibrinolytic effect through apo(a). After stent implantation, Lp(a) can accumulate in the vessel walls at lesion sites and inhibit normal plasminogen activation to impede plasmin-induced fibrinolysis. Deposition of Lp(a) also appears to be linked with dedifferentiation and proliferation of smooth muscle.[57] In a meta-analysis composed of 9 cohort studies involving 1834 patients, those with the highest Lp(a) level had the greatest frequency of in-stent restenosis.[57]

Venous Thromboembolism

Concerning disturbances in the coagulation system, significant association between a high level of Lp(a) with occurrence of venous thromboembolism was reported in a meta-analysis of data from 6 case−control studies. Data from ~1800 patients with venous thromboembolism and 1100 healthy controls were analyzed. Compared with healthy controls, patients with an Lp(a) level of >300 mg/dL had approximately double the risk for venous thromboembolism.[58]

Calcific Valvular Aortic Stenosis

In humans, Lp(a) is associated with inflammation and calcific valvular aortic stenosis.[59] In one study, each log-unit rise in genetically determined Lp(a) level was associated with a 62% rise in the risk for aortic valve calcification.[60] The relationship between lifelong exposure to high Lp(a) level and drastically increased prevalence of aortic-valve calcification in adulthood support Lp(a) as the cause. Elevated Lp(a) and oxPL-apoB levels are linked with progression of calcific valvular aortic stenosis and sooner need for valve replacement, endorsing the notion that oxPL on Lp(a) mediates calcification.[61] Calcium deposits in the lipid-rich area of the aortic valve lead to stenosis of the orifice.[62] These findings suggest that Lp(a) mediates progression of aortic stenosis through its oxPL cargo. Lp(a) increases alkaline phosphatase activity, releases phosphate, and effects calcium and hydroxyapatite deposition, followed by cell apoptosis.[62] The mechanism is related to a compound lysophosphatidic acid, which is formed by the action of an enzyme, autotaxin. Lysophosphatidic acid is a very bioactive proinflammatory compound that triggers fibrosis. The sequence is that autotaxin is overexpressed in mineralized aortic valves, which acts on phosphocholine-containing oxPLs carried on Lp(a) to form the excess lysophosphatidic acid.[63]

Renal Disease

Raised Lp(a) concentration may be associated with specific pathologies in the kidney.[64] In a cohort of 560 patients with type 2 diabetes followed up for over 10 years, 125 participants developed chronic kidney disease (CKD). A subgroup with an Lp(a) level in the highest tertile (mean, 43.5 mg/dL) had a

significantly greater prevalence of CKD as compared with a subgroup with Lp(a) in lowest tertile (7.1 mg/dL)—a risk ratio of 2.12.[65] Hence, measurement of Lp(a) concentration may be useful in assessing patients for CKD, especially in those with CV risk factors.

Dietetic Interventions

A diet prescribed for weight loss is a respected strategy for improving the lipid profile.[66,67] Dietary patterns rich in animal-derived protein and fat may be associated with higher risks for CVD and mortality as compared with plant-derived protein and fat intake, which is considered protective.[68–70] Continuing this theme, a recent study showed that a plant-based diet reduced Lp(a) level in conjunction with improved inflammatory and atherogenic biomarkers.[71] After 4 weeks of following a plant-based diet, overweight and obese individuals (n = 31) had a mean decrease in Lp(a) concentration of 32 nmol/L.[71]

On the other hand, Berk et al[72] noted that diet-induced weight loss programs may be accompanied by an increase in Lp(a) level regardless of favorable effects on conventional CV risk factors. The investigators studied 4 independent cohorts consisting of obese individuals with and without type 2 diabetes. After 3–4 months of a calorie-restricted diet, there were improvements in conventional CV risk factors, including a lower LDL-C level and a weight loss of 9.9% in the primary cohort (cohort 1), which encompassed 131 predominantly obese patients with type 2 diabetes; however, the Lp(a) level was increased by 14.8 nmol/L. In cohorts 2 and 3, consisted of 30 obese patients with type 2 diabetes and 37 obese individuals without type 2 diabetes, respectively, weight losses of 8.5% and 6.5% were accompanied by median increases in Lp(a) of 13.5 and 11.9 nmol/L. In cohort 4, comprised of 26 obese individuals without type 2 diabetes who underwent bariatric surgery no significant change in Lp(a) was found despite considerable weight loss (14%).[72]

Bariatric surgical procedures produce significant improvements in serum lipids,[73,74] and calorie restriction is the physiologic mechanism by which bariatric surgery achieves weight loss[75]; hence, it is reasonable to expect a reduction in Lp(a) concentration. Recently, however, Gómez-Martin et al[76] found that sleeve gastrectomy and gastric bypass induced a similar beneficial effect on serum lipids in women with high CV risk at 1 year after surgery, decreasing total cholesterol, triglycerides, and oxidized-LDL, but unaccompanied by a change in Lp(a) level.

Dietary Fats

A high level or increase in dietary trans fatty acids does not appear to increase Lp(a) level, whereas saturated fat has been reported to decrease Lp(a) level.[77] Hydrogenated soybean oil resulted in a significantly higher Lp(a) level than that achieved with a diet in which butter was the major fat source.[78] However, Lp(a) concentration did not change in a randomized crossover study in hypercholesterolemic patients who followed a 6-week diet high in butter or margarine.[79]

Intake of meals high in specific dietary fatty acids can increase postprandial plasma lipids differently,[80–83] including Lp(a) concentration. After 6 weeks of consuming a diet high in saturated fat (equivalent to 16% of total energy intake and composed of lauric, myristic, and palmitic acids), both women and men had significantly lowered blood Lp(a) concentrations, by 8%–11%, respectively.[84] In comparison, long-chain stearic and palmitic acids led to the highest increases in postprandial Lp(a) level after an oral fat test in young healthy men.[85]

Additionally, coconut oil may have more favorable effects on Lp(a) concentration compared with unsaturated oils containing longer carbon chains. Researchers conducted a controlled crossover study in female students with 2 types of high-fat diets over a 3 week period.[86] Lp(a) level was reduced by 17 mg/L after the consumption of coconut-oil–based fatty acids, but after the consumption of highly unsaturated long-chain fatty acids, the Lp(a) level increased by 25 mg/L.[86] Albeit coconut oil is a saturated fat, it should be noted that the main content (50%) is medium-chain fatty acid (eg, lauric acid) and, therefore, it may elicit a different response on Lp(a) concentration.[87] Despite the modest advantage regarding Lp(a) level associated with coconut oil ingestion, current guidelines recommend that dietary unsaturated fats account for <10% of total energy consumption,[88,89] since their excess is linked with greater morbidity and mortality from cancers and CVD.[68,90]

Replacing energy from saturated fats with equivalent energy from unsaturated fats is associated with reductions in total mortality.[90] Nut consumption is a feasible approach for increasing unsaturated fats in the diet, since they are associated with lower all-cause and cause-specific mortality, especially CV-related mortality.[91] A diet rich in walnuts, containing α-linolenic acid, plant sterols, polyphenols, and tocopherol improves the standard blood lipid profile.[92] Contrary to expectations, however, in a randomized, controlled, prospective crossover study involving 194 healthy individuals, a regimen of 43 g of walnuts daily for 8 weeks showed no effect on Lp(a) concentration, although other lipid parameters, such as non−HDL-C, apoB, total cholesterol, LDL-C, very low-density lipoprotein cholesterol, and triglycerides were improved.[93]

Popular Beverages

Worldwide, drinking tea, coffee, and moderate amounts of alcohol are habits that may play a role in CV health.[94−96] Thus, potential effects of popular beverages on Lp(a) concentration deserves consideration. In a cross-sectional study in 300 middle-aged men, the Lp(a) concentrations in the subgroups with low (<39 g/wk), intermediate (39−132 g/wk), and high (>132 g/wk) ethanol intake were 137, 109, and 94 mg/L, respectively ($P < 0.05$). Interestingly, Lp(a) concentration was higher (median, 206 mg/L) in the abstainers than in the drinkers.[97] Nonetheless, in another cross-sectional study, which included 402 patients with untreated hypertension, light (1−20 g/d), moderate (>20−50 g/d), and heavy (>50 g/d) ethanol drinkers had, respectively, 21%, 26%, and 57% lower median Lp(a) concentrations than did abstainers and occasional drinkers.[98]

Red wine consumption apparently has more ability to decrease the Lp(a) value than white wine. Twenty healthy male volunteers consumed 200 mL of red wine per day for 10 days and, following a 6-week washout, the protocol was repeated with white wine.[99] A reduction in Lp(a) level from 18.6 to 13.2 mg/dL ($P < 0.001$) was detected after the intake of red wine but not white wine.[99] In a 4-week randomized crossover study in 67 men with high CV risk, Lp(a) levels were compared after the ingestion of red wine (30 g alcohol/d), the equivalent amount of dealcoholized red wine, and gin (30 g alcohol/d).[100] The Lp(a) level fell from 54.4 mg/dL at baseline to 50.2 md/dL only after the red wine intervention.[100] Adverse health effects of more than minimal alcohol intake far outweigh any potential benefit in lowering Lp(a) level.[101,102]

An accumulating body of evidence recognizes the potential benefits of coffee in the CV system,[103−106] but its effects on Lp(a) level remain unclear. More research is needed, especially with respect to the number of tea preparations commercially available. In a meta-analysis of data from 640 participants, the consumption of coffee or coffee diterpenes was associated with either a reduction in serum Lp(a) of ≤11 mg/dL (6 trials, 275 participants), or no effect (2 trials, 56 participants).[107] Present in unfiltered coffee brews, coffee diterpenes are among the few dietary constituents that may modulate Lp(a) level.[108]

In mildly hypercholesterolemic adults (209 and 135 mg/dL of total cholesterol and LDL, respectively) receiving 5 cups daily of black tea prepared with 180 mL of water per serving, Lp(a) fell 16% as compared with placebo, although the sample size was only 15 subjects.[109] Mozaffari-Khosravi et al,[110] in turn, randomly assigned patients with diabetes to consume Hibiscus tea (n = 27) or black tea (n = 26) for 1 month. Patients were instructed to consume 2 g of tea sachet with 240 mL of boiling water per serving, twice daily. The Lp(a) concentration remained unchanged from the baseline value of 26 mg/dL.[110]

Nutraceutical Supplementation

The use of nutraceutical agents may be an alternative strategy for approaching elevation in blood Lp(a) concentration. To date, 2 substances with positive effects—L-carnitine and CoQ10—have been identified.[111,112]

L-Carnitine

L-Carnitine is an amino acid found in foods, especially in meat.[113] The doses made possible through supplementation (1−2 g/d) that lead to decreased Lp(a) level cannot be attained through dietary sources (Table I). Both oral and intravenous L-carnitine administration may provide benefits in individuals with CVD.[116−118] As such, it is an interesting option because of improvements in energy metabolism and antioxidant support that have been

Table I. L-Carnitine and coenzyme Q10 contents in food items. Data are given as milligrams per 100-g serving.

Food Item	L-Carnitine	CoQ10
Meat products		
Beef steak	64.6–87.5	1.61–3.65
Pork (muscle)	13–53.5	2.43–4.11
Chicken	10–10.4	1.4–2.1
Fish		
Salmon (cooked)	5.8	0.43–0.76
Cod (Atlantic)	1.8	0.37
Dairy products		
Yogurt, regular (3.2% fat)	12.5	0.07–0.11
Milk 2%–4% fat	2.3–2.9	0.07–0.12
Cheese	1.4–1.8	0.12–013
Butter	0.85	0.71
Chicken egg		
Whole	Not evaluated	0.07–0.37
Egg Yolk	0.8	Not evaluated
Egg white	0.3	0.52

Adapted with permission.[114,115]

recognized, in addition to a decrease in Lp(a) level.[117,118] In a meta-analysis of data from randomized clinical trials of 2–6 months' duration, with L-carnitine administration, Lp(a) concentration fell a mean of 8.8 mg/dL.[111] Interestingly, oral 1–2 g/d ingestion was more potent with respect to Lp(a) than the intravenous route.[111] In subjects with mixed hyperlipidemia, Florentin et al[119] showed that 12-week coadministration of 2 g/d of L-carnitine together with 20 mg/d of simvastatin reduced the Lp(a) level from 56 to 42 mg/dL. Since this did not occur with simvastatin monotherapy, the Lp(a) benefit could be attributed to L-carnitine. Unfortunately, L-carnitine supplementation may raise trimethylamine N-oxide production in the liver[120–122]; trimethylamine N-oxide is a potent CV risk factor, and blood levels predict incident cases of CVD.[123] Therefore, longitudinal studies are needed in order to provide information about whether potential benefits of L-carnitine on Lp(a) level outweigh or modulate the atherosclerotic and metabolic damage associated with a higher trimethylamine N-oxide level.[111]

Coenzyme Q10

Similarly, CoQ10 supplementation may benefit individuals with CVD,[124,125] but doses likely to benefit cannot be attained through food alone (Table I). CoQ10 has several antioxidant properties, and is a key molecule in the production of cellular energy by the mitochondrial electron transport chain.[126,127] Statin drug therapy blocks mevalonate production and depletes CoQ10 stores, and while CoQ10 administration does not eliminate statin-induced myalgia, ensuring physiologic CoQ10 levels may be prudent.[126,128]

In a meta-analysis of data from clinical trials, CoQ10 supplementation was associated with a modest 3.5 mg/dL fall in Lp(a) level.[112] However, a greater Lp(a) reduction of 11.7 mg/dL was observed in patients with an increased baseline Lp(a) level (≥30 mg/dL) than in patients with a lower Lp(a) level. A proportionately larger effect has also been evident in patients with a high baseline Lp(a) level in drug trials. Another interesting note: Lower CoQ10 doses (<150 mg/d) were associated with greater reductions in Lp(a) level than were higher doses (≥150 mg/d). CoQ10 has been associated with improvements in the general lipid profile, particularly in patients with CKD. CoQ10 regulates several genes controlling inflammation, and together with its antioxidant properties, may account for multiple beneficial effects. The explanation for this finding remains unclear,[112] and in many instances the clinical effect size is small.

The selected use of these nonpharmacologic agents may be reasonable in individuals with an elevated Lp(a) level. All things considered, the effects of L-carnitine and CoQ10 on Lp(a) level deserve further investigation.

Vitamin C

Hypoascorbemia leads to Lp(a) accumulation in the vascular wall and parallels atherosclerotic lesion development in experimental animal models.[129] However, the recommended dietary allowance of vitamin C is easily achieved by diet[130] (Table II). A randomized, placebo-controlled trial reported that 1.0 g/d of vitamin C ingested by healthy subjects for 8 months did not change the Lp(a) concentration.[132] In

Table II. Vitamin C contents in food items. Data are given as milligrams per 100-g serving.

Food Item	Vitamin C
Fruits	
Kiwi	93.2
Papayas	60.9
Strawberries	58.8
Oranges	53.2
Pineapple	47.0
Mangos	36.4
Tangerines	26.7
Blueberries	9.7
Vegetables	
Peppers, sweet	127.7
Kale	93.4
Cauliflower	48.2
Cabbage	36.6
Spinach	28.1
Tomatoes	13.7
Pumpkin	9.0
Onion	7.4

Adapted from the US Department of Agriculture.[131]

patients with premature CVD who were administered 4.5 g/d of vitamin C for 12 weeks, Bostom et al[133] did not find a decrease in the Lp(a) level. Taken together, the use of pharmacologic doses of vitamin C for decreasing Lp(a) concentration is not evidence based,[133] as a recent meta-analysis confirmed.[134]

Soy Isoflavones and Garlic

It is generally believed that soy isoflavones (daidzein and genistein) and the allicin in garlic (*Allium sativum*) may decrease LDL-C values.[135–138] At best, an intake of 25 g of soy or a half-clove of garlic (900 mg purified) may lower LDL-C by up to 5% and 9%, respectively, but the effects are inconsistent and controversial. However, meta-analyses of these agents have not shown any significant alteration in plasma Lp(a) level.[115]

ω-3 polyunsaturated Fatty Acids

With respect to supplementation with marine ω-3 polyunsaturated fatty acids (PUFAs), doses ranging from 2 to 4 g/d are recognized as a measure of preventing the development of CVD,[138] particularly in the presence of hypertriglyceridemia.[139] PUFA-associated improvements in lipid profiles have been investigated in heterogeneous populations, including those with kidney disease,[139] in whom physiopathology is associated with elevations in Lp(a) level.[140] However, ω-3 supplementation did not affect Lp(a) concentration in patients with chronic glomerular disease being treated with hemodialysis.[141,142]

Plant-derived α-linolenic acid is a shorter-chain PUFA with weaker CV and other properties different from those of longer-chain marine PUFAs. Both walnuts and flaxseed are rich in α-linolenic acid; the ineffectiveness of walnuts in lowering Lp(a) concentration was mentioned earlier.[143] In a randomized, double-blind, placebo-controlled trial, 68 women with polycystic ovary syndrome were randomized to receive either 1000 mg ω-3 fatty acids from flaxseed oil (400 mg α-linolenic acid) plus 400 IU vitamin E or placebo for 12 weeks.[143] Compared with placebo, α-linolenic acid and vitamin E cosupplementation downregulated Lp(a) mRNA in addition to oxidized-LDL mRNA. Concomitantly, the supplemented group also had decreased levels of serum triglycerides, very low-density lipoprotein, and LDL, and increased plasma total antioxidant capacity compared to the placebo group. Women with polycystic ovary syndrome have high plasma levels of androgen and insulin, as well as insulin resistance, among other hormonal abnormalities. Flaxseed oil contains lignans, capable of reducing androgen levels. Therefore, ascribing the benefits reported in this study to α-linolenic acid may be premature, and generalization of the results is tenuous.

Niacin Versus Lp(a)-Lowering Drugs

Niacin, also known as nicotinic acid or vitamin B_3, is an essential human nutrient, but achieving benefits on lipid metabolism requires medical doses.[144,145] At an intake of 2 g/d, niacin raises HDL-C by as much as 25%, and lowers triglyceride levels by 25%, LDL-C by ~16%, and Lp(a) level by up to 30%. The cutaneous "flushing" experienced by patients taking high amounts of niacin was severely limiting. Niacin therapy has also lost favor because of 2 disappointing, but inconclusive, studies attempting to

raise HDL-C and improve CV outcomes.[146] Although niacin was formerly recommended for lowering Lp(a) level,[13] it does not appear in the latest guidelines due to inconsistent effects in long-term studies.[147]

For comparison, other pharmacologic effect sizes on Lp(a) reduction are as follows: cholesteryl ester transfer protein inhibitors, 24%–36%; apoB antisense agents, 26%–27%; microsomal triglyceride transfer protein inhibitors, 17%; proprotein convertase subtilisin/kexin 9 inhibitors, 25%; anti–interleukin-6 receptor agents, 30%–37%; lipid apheresis (removing blood from the body, chemically trapping circulating apo B-100 lipoproteins, and returning the blood intravenously), 70%; and apo(a) antisense therapy, up to 78%.[18]

The effects of statin drugs and proprotein convertase subtilisin/kexin 9 inhibitors have produced monumental impacts clinically.[148,149] Large reductions in morbidity and all-cause and CV mortality followed.[150–152] Although the adverse effects of high Lp(a) concentration have been known since the 1960s, the full atherogenic potential of these particles has become more apparent. It is reasonable to anticipate that the additional ability to control Lp(a) level in at-risk individuals will result in meaningful improvements in future patient outcomes.[17]

CONCLUSIONS

Associations between high concentrations of Lp(a) and CVD are stronger than previously believed, and several lines of evidence implicate the molecule itself and its cargo of oxidized phospholipids as a cause. Measuring Lp(a) is now recommended in some conventional medical guidelines, and clinical use of Lp(a) level in assessing CV risk may assist in refining risk stratification. This application is already evident in particular subpopulations: young adults with premature IHD and those with familial hypercholesterolemia or a strong family history of IHD. In addition to proposed Lp(a)-lowering drugs, dietetic interventions and nutraceutical agents are being investigated. Although there is a paucity of specific approaches, the use of L-carnitine and CoQ10 are promising Lp(a)-lowering supplements, but the mechanisms of action are unclear. Regarding macronutrients and alcohol-containing beverages, the consumption of saturated fat as well as ethanol, especially from red wine intake, may decrease the Lp(a) concentration, but should not be encouraged. The intake of other beverage types, such as coffee and tea, may decrease Lp(a) level, although more investigation is necessary for recommending a lower Lp(a) concentration. Despite CV benefits, the intake of vitamin C, soy isoflavones, garlic, and ω-3 are unsubstantiated for decreasing Lp(a) level. Long-term clinical trials would be decisive in confirming the effects of Lp(a)-lowering nutraceutical agents on CV outcomes.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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