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Global Spotlights

Low carbohydrate/ketogenic diet in the optimization of lipoprotein(a) levels: do we have sufficient evidence for any recommendation?

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Increased lipoprotein (a) [Lp(a)] concentration is a documented risk factor for atherosclerotic cardiovascular disease (ASCVD), independent of LDL-cholesterol (LDL-C).[1] Moreover, elevated Lp(a) levels have been recently shown to increase the risk of all-cause and cardiovascular mortality in the general population and ASCVD patients.[2] The relationship between Lp(a) concentration and the risk of mortality is linear. It was shown that each 50 mg/dL (∼125 nmol/L) increase in Lp(a) concentration was associated with a 31% and 15% higher risk of ASCVD mortality in the general population and in patients with already established ASCVD.[2] Increased Lp(a) levels are diagnosed in a significant proportion of people. According to the National Heart Lung and Blood Institute, an estimated 1.4 billion people globally have Lp(a) concentrations ≥50 mg/dL (≥125 nmol/L) with a prevalence ranging from 10% to 30%.[1] In Europe, 20% of women and 20% of men have serum Lp(a) concentration >50 mg/dL (>125 nmol/L).[3,4] It is recommended that serum Lp(a) concentration, both fasted and fed, should be lower than <50 mg/dL (<125 nmol/L), and some scientific societies suggest even <30 mg/dL (<75 nmol/L).[3,4]

The Lp(a) level is largely genetically determined, although several other non-genetic factors and conditions are indicated to modulate its level.[4] The consensus of experts from the European Society of Atherosclerosis indicates that the use of a low carbohydrate diet (LCD) high in saturated fat (ketogenic diet) may reduce the concentration of Lp(a) by ∼15%.[4] This information comes from a randomized clinical trial by Ebbeling *et al.*,[5] involving 164 people (body mass index: 32.4 ± 4.8 kg/m^2) with insulin-resistant dyslipoproteinaemia who were randomly assigned to three weight loss maintenance diets for 20 weeks. The diets used contained 20% of proteins and were characterized by a varied content of carbohydrates and saturated fats (low-carb: 20% carbohydrates, 21% saturated fats; moderate-carb: 40%, 14%; high-carb: 60%, 7%). After 20 weeks of intervention, it was shown that LCD use was associated with a significant Lp(a) reduction by nearly 15% [−14.9%; 95% confidence interval (CI): −22.0 to −7.1]. Other diets did not affect the Lp(a) concentration. Low carbohydrate diet in this study was also associated with the significant reduction of lipoprotein insulin resistance, reduction of triglycerides, and increase of HDL-cholesterol and adiponectin concentration.[5] In another study, the use of a ketogenic diet in healthy men allowed the reduction of Lp(a) concentration from 101 to 74 mg/dL (by 26%) after 3 weeks.[6] O'Neal *et al.*[7] assessed the effect of an LCD for 3 weeks on lipid parameters in middle-aged, trained male runners ($n = 8$), showing an Lp(a) decrease in six of the eight comparisons. While weight loss and attenuation of insulin sensitivity, inflammation, and oxidative stress could be hypothesized to mediate—at least in part, the reducing impact of LCD/ketogenic diet on Lp(a) levels—the exact mechanisms are yet to be explored.

From the clinical practice point of view, information on an LCD/ketogenic diet in the recommendations might cause some confusion and misunderstandings, especially taking into account somewhat unauthorized popularity of these diets. Moreover, this might have even harmful effects on the patients, who might have considered the application of a ketogenic diet in the absence of effective therapy for Lp(a) lowering at the present time. In this context, it is critical to emphasize several problems associated with the use of the ketogenic diet. In a meta-analysis of three studies by Joo *et al.*,[8] the use of a ketogenic diet significantly increased total cholesterol by 1.47 mmol/L (58 mg/dL) (95% CI: 0.72–2.22 mmol/L), LDL-C by 1.08 mmol/L (42 mg/dL) (95% CI: 0.37–1.79 mmol/L), and apoB by 0.35 g/L (95% CI: 0.06–0.65 g/L), which was also confirmed in other studies. Such an increase in LDL-C might be associated with the increased risk of cardiovascular events by even 24% (for the suitable long diet adherence).[3] On the other hand, a study by Mazidi *et al.*[9] of 24 825 National Health and Nutrition Examination Survey (NHANES) participants followed for

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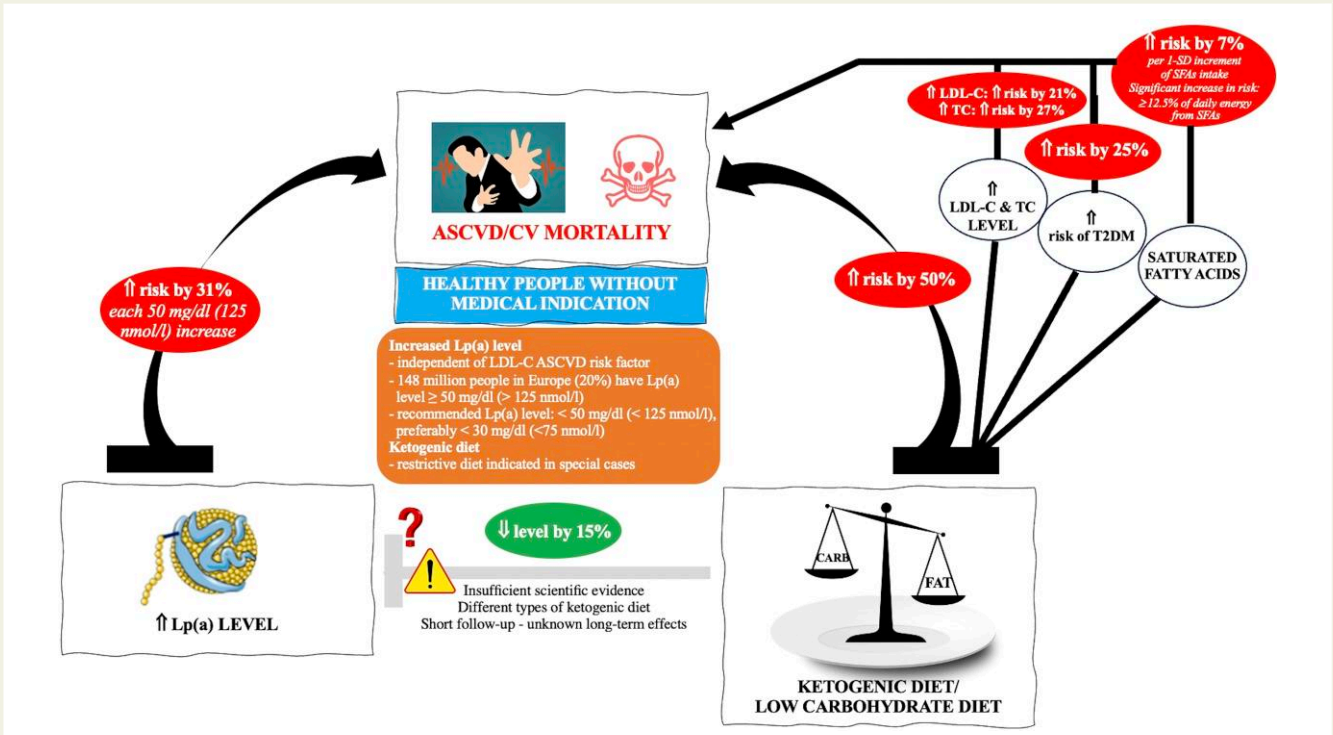

Figure 1 The current state of knowledge about the role of lipoprotein (a) in cardiovascular risk, the impact of the ketogenic diet on lipoprotein (a) concentration, and the risks associated with the use of this diet in healthy people without medical indication. Lp(a), lipoprotein (a); LDL-C, LDL-cholesterol; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; TC, total cholesterol; T2DM, Type 2 diabetes mellitus; SFAs, saturated fatty acids; carb, carbohydrate.

6.4 years showed that participants on an LCD had a significantly higher risk of all-cause mortality [hazard ratio (HR) 1.32; 95% CI: 1.14–2.01], ischaemic heart disease (1.51; 95% CI: 1.19–1.91), cerebrovascular disease (1.50; 95% CI: 1.12–2.31), and cancer (1.35; 95% CI: 1.06–1.69). Accompanying meta-analysis of 9 prospective studies, including 462 934 participants who were followed for 16.1 years, also showed that the use of an LCD was associated with a higher risk of all-cause (HR 1.22; 95% CI: 1.07–1.39), cardiovascular (1.13; 95% CI: 1.02–1.24), and cancer mortality (1.08; 95% CI: 1.01–1.15).[9] The results of this meta-analysis confirm that the use of an LCD/ketogenic diet increases the risk of mortality and should be used in medically justified cases, such as obesity, diabetes, and epilepsy in children. This was also confirmed in the mentioned NHANES study analysis, as the link between overall mortality and LCD was significantly stronger in the non-obese than in the obese participants (P-interaction < .001).[9] In a prospective study by Wang *et al.*,[10] involving 203 541 healthy men and women, it was additionally shown that the use of a ketogenic diet was associated with higher Type 2 diabetes risk in a dose-response manner (HR comparing highest vs. lowest quintile was 1.28; 95% CI: 1.22–1.34). Another concern is the saturated fat content of a ketogenic diet. In the aforementioned study by Ebbeling *et al.*,[5] the saturated fat content of the LCD/ketogenic diet was 20%. The current American and European guidelines indicate that saturated fatty acids should account for <10% of total energy intake (the lower, the better).[3] In the meta-analysis of 29 prospective cohorts with 1 164 029 participants, the authors found a significant association between saturated fatty acid intake and coronary heart disease mortality (HR 1.10, 95% CI: 1.01–1.21).[11] Zhuang *et al.*[12] showed that the next quintiles of saturated fatty acids (SFAs) consumption were significantly associated with all-cause mortality (increasing the risk by up to 52%), and every increase in energy from SFAs by 1 SD was associated with a 7% increase in the risk of cardiovascular mortality (HR 1.07; 95% CI: 1.05–1.09). Another problem is the differences in the definition of the ketogenic diet. Currently, there are at least four types of ketogenic diet (classical ketogenic diet, Atkins diet, modified Atkins diet, and medium-chain triglyceride ketogenic diet or low-glycaemic index treatment), which differ in the content of protein, carbohydrates, and fats. The classical ketogenic diet is the most restrictive and is characterized by the fat-to-protein and carbohydrate ratio of 4:1, with ~80%–90% of energy derived from fat.[5–10]

To conclude, the use of an LCD/ketogenic diet may be beneficial in patients with medical indications, such as obesity, diabetes, metabolic syndrome, or refractory epilepsy. In healthy people, apart from possible weight loss, the harmful complications presented in *Figure 1*, as well as muscle wasting, may occur. Therefore, the use of an LCD/ketogenic diet should not be recommended as a part of a healthy lifestyle.[3,9] The data are also insufficient to use an LCD/ketogenic diet in people with elevated Lp(a) concentration, especially since the risk of cardiovascular events and death seems to outweigh the potential Lp(a) and metabolic-associated benefits. Moreover, further evidence from larger randomized trials with long-term follow-up considering inter-individual differences in responses to ketogenic diets and genetic variations in Lp(a) isoforms is still needed to draw a more robust conclusion. In patients with elevated Lp(a) levels, the use of forthcoming targeted drugs (e.g. pelacarsen, olpasiran, zerlasiran, or new LY-3819469, and muvalaplin) and other available lipid-lowering drugs (proprotein convertase

subtilisin/kexin type 9 [PCSK9]-targeted therapies) should be considered.[1,3,4]

Declarations

Disclosure of Interest

S.S.: honoraria from: Novartis/Sandoz; A.S.: none; M.B.: speakers bureau: Amgen, Daiichi Sankyo, KRKA, Pfizer, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, Pfizer, Sanofi-Aventis, Teva, and Zentiva; consultant to Adamed, Amgen, Daiichi Sankyo, Esperion, MSD, NewAmsterdam, Novartis, Novo-Nordisk, and Sanofi-Aventis; grants from Amgen, Daiichi Sankyo, Viatris, and Sanofi; CMO at the Nomi Biotech Corporation (till December 2022) and Dairy Biotechnologies; CMDO at the Longevity Group.

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