The Role of Nutrients in a Dietary Intervention in Improving Blood Cholesterol Profile and Lowering Cardiovascular Risk

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Abstract: Low-density lipoprotein cholesterol has been positively associated to an increase of cardiovascular risk by a large number of epidemiological studies. On the contrary, high-density lipoprotein cholesterol results inversely related to cardiovascular risk. In this contest plasma total cholesterol and low-density lipoprotein cholesterol concentration, and the total cholesterol - high-density lipoprotein cholesterol ratio seems to be able to predict cardiovascular risk. Diet and its composition affects various plasma cholesterol concentration and their ratios. Particularly, a reduction of saturated fat acids dietary intake is strictly related to both improve of blood lipid profile and reduction of cardiovascular events incidence. On the other hand, the evidences from epidemiologic and clinical studies are consistent in finding that the reduction of cardiovascular risk depends by nutrients used for replacing saturated fat acids. Specifically it has been demonstrated that replacement of saturated fat acids with unsaturated fat acids, either monounsaturated or polyunsaturated ones, is effective in improving cardiovascular risk. On the contrary, saturated fat acids replacement with high glycemic index refined carbohydrate actually increases cardiovascular risk. Despite that, many dietary guidelines do not give any tips about nutrients to use in replacement of saturated fat acids, underestimating the significance. In this perspective Mediterranean diet, represents an attractive dietary pattern for the improvement of blood lipid profile and the reduction of the cardiovascular risk.

Keywords: Mediterranean Diet, LDL-C, HDL-C, Glycemic Index, Glycemic Load, MUFA, PUFA, UFA, SFA.

INTRODUCTION

Blood cholesterol, and especially the low-density protein one (LDL-C), has been positively associated to an increase of cardiovascular risk (CVR) by a large number of epidemiological studies [1-4]. Moreover, reduction of plasma levels of total cholesterol (TC) and LDL-C induces a decrease of cardiovascular events incidence [3, 4]. A 10% reduction in LDL-C either with a pharmacological approach or with a dietary intervention is associated to a 25% reduction of the incidence of coronary artery disease in European population [5, 6]. Furthermore, a large study conducted on the US population reported 24% of the decrease in coronary deaths was due to a 6% reduction in total cholesterol [7].

On the contrary, high-density lipoprotein cholesterol (HDL-C) results inversely related to CVR [3, 8-10]. Despite these evidences, there is not always a direct correlation between a raising of HDL-C and reduction of cardiovascular events incidence. Moreover, it seems it is not only the quantity, but also the quality of HDL–C to be involved in cardiovascular protection: a person with high level of non-functional HDL-C will be at high risk of cardiovascular disease if compared with another one with a relatively low, but functional, HDL-C. Thus, the mere measurement of the HDL-C concentration does not seem to be sufficient for assessing CVR and HDL-C level may not be a optimal parameter. Furthermore, increase of HDL-C levels has led to conflicting results regarding CVR improvement. For these reasons, the effectiveness of raising HDL-C in reducing CVR is currently controversial [11, 12].

In this contest plasma TC and LDL-C concentration and TC/HDL-C ratio, seems to be predictive of CVR. The reduction of TC and LDL-C concentration following either pharmaceutical or nutritional interventions decrease TC/HDL-C ratio and cardiovascular events incidence [3-7, 10].

Cholesterol, synthesized, among others, by acetyl-CoA, is the most plentiful steroid in the human body and its plasma level is determined by balance of food intake absorption and endogenous synthesis, and this individual equilibrium is hereditary [13, 14]. However, such genetic bases can be modulated by metabolic factors such as body mass index (BMI) and the amount of visceral or liver fat [15]. Furthermore, diet and its composition affects various plasma cholesterol concentration and their ratios [16, 17].

In a dietary intervention, aimed to lower TC and LDC-C concentration and TC/HDL-C ratio, a reduction of saturated fat acids (SFA) intake is strictly related to both an improve of blood lipid profile and a CVR reduction [3, 5, 10, 16-22]. In addition, trans fat acids

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(TFA) intake has been associated with a variety of cardiovascular complications including atherosclerosis [18]. Moreover a lot of studies have been shown TFA raising LDL-C and lowering HDL-C levels, and the increase in the TC/HDL-C ratio induced by TFA is approximately twice than for SFA [18-20]. Therefore, reduction in SFA and TFA consumption is traditionally a major focus of dietary recommendations to reduce coronary heart disease risk. However, while the TFA are an insubstantial fraction of the diet, SFA are an important portion of the daily caloric intake, so a lower of habitual intake of SFA requires substitution with other macronutrients to maintain the energy balance [20]. Replacement of SFA with either carbohydrate or unsaturated fat acids (UFA), both monounsaturated (MUFA) and polyunsaturated (PUFA) ones, is effective in reducing blood concentration of TC and LDL-C. On the other hand, the evidence from epidemiologic and clinical studies is consistent in finding that the reduction of CVR depend by nutrients used for replacing SFA [21-23]. Although many dietary guidelines recommend reduction in SFA consumption, such guidelines often do not highlight any specific nutrient for replacing them, implying that all macronutrients have similar effects [21]. The aim of present review is to focus the actual role in the reduction of the CVR of the various nutrients used to replace SFA.

REPLACEMENT OF SFA WITH CARBOHYDRATE

For many years, replacement of SFA with carbohydrate promoted, especially in US, low-fat/high-carbohydrate diets leading to a compensatory increase in consumption of refined carbohydrates and added sugars. This change in dietary habits may have contributed to the current epidemics of obesity and diabetes in the United States [24]. A recent meta-analysis of prospective cohort studies did not found association between decreased CVR and substitution SFA for carbohydrates but a correlated to a modest increased of the risk [25]. However, the effects of substitution of carbohydrates may vary depending on the quality of carbohydrates consumed. Traditional classification of carbohydrate as simple and complex is not sufficient to determine a healthy alternative to dietary fats. In fact, many complex carbohydrates, like potatoes and white bread, produce glycemic response similar to those of simple sugars [26]. Thus, the term complex carbohydrates is not useful in characterizing the quality of carbohydrates [24]. More useful indicators of carbohydrate quality include the amount and type of fibers, the extent of food processing (whole vs refined grains), glycemic index (GI) and glycemic load (GL).

Increased dietary fibers intakes are associated with lower prevalence of cardiovascular disorders in prospective studies. Soluble fibers, when included within a saturated fat and cholesterol poor diet, lower LDL-C concentration of about 5–10% in hypercholesterolemic and diabetic patients [5, 27]. These findings support the routine use of soluble fibers in the recommended diets for adults with hypercholesterolemia [5].

GI compares blood glucose concentrations after ingestion of a food and a reference carbohydrate (usually glucose or white bread), and is an index of the rate of absorption of a given food compared to the standard carbohydrate considered [18, 24]. Lowering GI enhanced the reduction in TC and LDL-C concentrations, furthermore it has been found a direct association between high-GI values and CVR, so dietary GI would be used as an indicator of the average quality of carbohydrates consumed [18, 24, 26, 28, 29].

GL, defined the product of the GI value of a food and its carbohydrate content, has been used to represent both the quality and quantity of the carbohydrates consumed. Dietary GL is strongly associated with higher fasting triglycerides and lower HDL-C levels; moreover it has been shown a positive association between GL and CVR [18, 23, 30, 31].

Typically whole grain (brown rice, spelt, whole meal bread) are digested at a slower rate and therefore have lower GI and GL values than refined carbohydrates like potatoes, white rice and white bread. Numerous epidemiologic studies have found that higher intake of refined carbohydrates is associated with greater risk of type 2 diabetes and ischemic heart disease, whereas higher consumption of whole grains protects against these disorders [18, 24].

Lack of effectiveness on reducing CVR of replacement of SFA with carbohydrate is mainly because most carbohydrates in western diets are highly refined, including bread, rolls, pizza, white rice, and most ready-to-eat cereals and sugar [24]. Moreover high consumption of this type of carbohydrates is particularly harmful, increasing weight and predisposing to insulin resistance thus negating the reduction of SFA intake benefits.

REPLACEMENT OF SFA WITH PUFA

Replacement of SFA with PUFA, lowers the TC/HDL-C ratio largely than carbohydrate, reduces blood triglyceride concentration and CVR. Furthermore,

PUFA consumption may also improve insulin resistance and reduce systemic inflammation [32, 33]. These effects on risk factors suggest that PUFA may be a good replacement for SFA in the western population. Although many epidemiological studies have analyzed the replacement of SFA with PUFA as a whole, recent studies have highlighted a different role on reducing CVR of PUFA of the n-6 and n-3 series [34-36].

PUFA of n-6 Series

Replacement of SFA with PUFA of n-6 series seems to be able to decrease TC and LDL-C by either lowering LDL-C production rates or increasing LDL-C clearance rates [20, 37]. Although the replacement of SFA with PUFA is able to decrease HDL-C, this decreasing is substantially lesser than LDL-C reduction, so, the HDL/LDL-C ratio is increased and the TC/HDL-C ratio is reduced [37]. Furthermore, some findings suggested that n-6 PUFA, especially linoleic acid, modulate the cholesterol raising due to SFA: with low levels of linoleic acid, SFA increase LDL-C, but hypercholesterolemic effect of SFA is reduced by high levels of linoleic acid [36]. According with this role of n-6 PUFA in improving blood lipid profile the replacement of SFA with n-6 PUFA has been shown to lower CVR, by about 10% -13% for each 5% energy substitution [38, 39].

PUFA of n-3 Series

The most important n-3 PUFA are α-linolenic acid, hosted in nuts and vegetable and eicosapentaenoic acid that can be found in fish. Their intake tends to decrease plasma triglyceride levels reducing synthesis of triglyceride-rich very low-density lipoproteins (VLDL). This effect is more pronounced in patients with elevated basal plasma triglyceride levels and can be accompanied by a low increase in plasma LDL-C levels; on the other hands, some studies showed a modest increase in HDL-C levels. However the effects of n-3 PUFA on TC, LDL-C and HDL-C are negligible [36, 40].

REPLACEMENT OF SFA WITH MUFA

Replacing SFA with MUFA has uncertain effects, based on mixed evidence within and across different research paradigms. Substitution of MUFA for SFA decreases plasma LDL-C and TC/HDL-C ratio, although the effect is not so evident than with PUFA replacement. Some studies showed that increased of MUFA intake is related to decrease of LDL-C and increase of HDL-C, concurrently was found an increase in Apo A1 concentrations, and interestingly high sensitivity C-reactive protein was significantly reduced by an high MUFA intake [41, 42]. These findings suggest that increased MUFA intake should reduce CVR. However, results from studies in nonhuman primates and mice have suggested that replacement of SFA with MUFA may not protect against the development of coronary artery atherosclerosis, despite favorable changes in serum lipoprotein lipids [33, 43].

The pooled analysis of observational cohort data suggested a trend in the opposite direction, but these findings can be explained taking into account that MUFA and SFA coexist in many foods and furthermore monounsaturated TFA and MUFA were sometimes categorized together in epidemiological study [20, 21, 44]. On the other hand the use of no hydrogenated vegetable oils (including olive oil rich in MUFA) decreases the CVD compared with animal fats [45, 46]. Furthermore, many epidemiological studies provide direct evidence that Mediterranean diet, characterized by an high percentage of MUFA is effective in reducing CVR [47-50]. Particularly a recent Spanish randomized trial, PREDIMED (PREvenciòn con DIeta MEDiterranea) showed a significant role of Mediterranean diet in the reduction of incidence of major cardiovascular events among persons at high CVR. PREDIMED study found a role of both virgin olive oil and nuts in cardiovascular prevention [51]. This trial did not demonstrate the role of MUFA in reducing cardiovascular events, but showed a preventive effect of integration with Virgin Olive Oil (rich in MUFA). Furthermore, the food pattern of Mediterranean diet, provides a characteristic profile of nutrient intake with a high MUFA/SFA ratio, which, probably could be involved in the reduction of CVR [50-52]. Obviously, in a synergic effect with its other nutritional characteristic: high intake of α-linoleic acid, moderate ethanol intake (mostly from wine), high intakes of fiber, vitamins, folate, and natural antioxidants and low intake of animal protein. These data lead to suppose a role of MUFA in the reduction of CVR, thus, many indications suggest that SFA could be replaced with MUFA although the evidence is stronger for PUFA, but further investigations are needed to clarify their role in CVR protection, certainly at the time underestimated.

CONCLUSION

In the perspective of a healthy dietary pattern directed to the improvement of the blood lipid profile

and to the reduction of the CVR all findings are unanimous in underlining the importance of the quality of macronutrients used in the replacement of SFA. Particularly it has been shown the importance to replace SFA with UFA, both MUFA and PUFA, and not with carbohydrate: replacement of SFA with Carbohydrate, while improving blood lipid profile, is not correlated with a reduction of CVR, actually, some studies showed an increase of the risk. Furthermore it has also been demonstrated an involvement of GI and GL of individual meals in increasing CVR. It is important underline that many international dietary guidelines, though recommend reduction in SFA consumption, do not highlight any specific nutrient for replacing them, implying that all macronutrients have similar effects, in contrast to the epidemiological evidence. Instead, it is clear that intake reduction of SFA and TFA is effective in reducing the CVR only if these fatty acids are replaced with UFA, and the GI and GL of individual meals is kept low. In this perspective Mediterranean diet, characterized by a good compliance, a low consumption of meat and meat products and a high consumption of whole grain, fish, vegetable fibers and vegetable UFA, represents an attractive dietary pattern for the improvement of blood lipid profile and the reduction of the CVR.

ABBREVIATIONS

BMI = Body Mass Index

CVR = cardiovascular risk

GI = glycemic index

GL = glycemic load

HDL-C = high density lipoprotein cholesterol

LDL-C = low density protein cholesterol

MUFA = monounsaturated fat acids

PUFA = polyunsaturated fat acids

SFA = saturated fat acids

TC = total cholesterol

TFA = trans fat acids

UFA = unsaturated fat acids

VLDL = very low density lipoproteins

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