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Dietary Fibers and Nutraceuticals for Primary Cardiovascular Prevention in Children and Adolescents: A Critical Review

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ABSTRACT

The roles of dietary fibers and nutraceuticals for primary prevention of cardiovascular disease from childhood are reviewed. Nutrition as an epigenetic modifier and the roles of endothelium, risk factors, epidemiological evidence and Mediterranean diet are critically analysed. Overfeeding in childhood can lead to the development of obesity and/or atherosclerosis in adult life. In particular, a high intake of nutrients affects the *in utero* programming with the adverse consequences of insulin resistance an endothelial dysfunction that lead to early atherosclerosis. Dietary fibers have important health benefits in childhood and research suggests that they may prevent obesity and lower blood cholesterol levels with a favourable impact on the risk of future cardiovascular disease incidence. However, it is for further studies to assess whether also in Southern European Countries, practicing Mediterranean diet as a normal habit, dietary fibers may contribute to modify the relatively low proportion of hyperlipemia observed in our population.

Keywords: Cholesterol; Hyperlipemia; Childhood; Dietary Fibers; Nutraceuticals; Prevention

1. Introduction

Numerous epidemiological and clinical studies performed in recent decades have brought an important contribution in understanding the pathogenesis of atherosclerosis. Although atherosclerosis is clinically manifest in adulthood, it is well recognized that it develops without symptoms in the earliest years of life. Fatty streaks, in fact, containing characteristic deposits of lipids, lipid peroxidation products, and white cells (monocytes/macrophages), can be observed in the aorta of premature human fetuses and intimal thickening has been demonstrated in fetal coronary arteries [1-3]. These early lesions may develop in advanced atherosclerotic lesions [4-8] and the progression may be influenced by risk factors promoting inflammation and plaque rupture [9].

In the last two decades a number of epidemiological and experimental studies aimed to understand the pathogenesis of atherosclerosis. Increased serum levels of LDL-cholesterol represent the most important risk factor for atherosclerotic cardiovascular disease; however, genetic and environmental factors interact in the onset and progression of the disease. This interaction emphasizes the key role of epigenetic mechanisms in the pathogenesis of early atherosclerosis. Epigenetics refers to a phenomenon of altered phenotypic expression without heritable variations in the nucleotide sequence of the DNA. The most frequent mechanisms in mammals include DNA methylation and histone modifications, resulting in a change in chromatin structure and pathway of small non-coding RNAs. The epigenetic modifications control embryonic development, differentiation, programming and reprogramming of stem cells. These changes are a biological response to environmental stressors (obesity, diabetes, smoking, etc.) and can be transmitted to the offspring influencing their risk of atherosclerosis [10-12].

2. Nutrition and Epigenetics

Nutrition is an important modifier of epigenetic profile, even before birth [13]. In fact, nutritional imbalances of the father before conception and of the mother during pregnancy, may predispose the fetus to the risk of cardiovascular and metabolic diseases in adulthood. Maternal nutrition can affect the epigenetic status of the fetal genome and can persist into adulthood [10,11]. There are many studies that suggest that most chronic diseases of adulthood, such as atherosclerosis, originate from an altered intrauterine growth and development. Among the classical risk factors for atherosclerosis, obesity and hypercholesterolemia seem to have the main role [10-12, 14-16].

2.1. Roles of Endothelium and Risk Factors

Endothelial dysfunction is considered an early stage of vascular damage and an early event in atherogenesis [17-19]. Until recently, the understanding of alterations in pediatric cardiovascular disease was mainly limited to autopsy studies and pathological findings in adolescents and young adults died from accidental causes. Recent advances in non-invasive diagnostic techniques have made it possible to detect early (anatomical, physiological, mechanical, proinflammatory and prothrombotic) changes of the vessel wall, which reflects the subclinical atherosclerosis [20-22]. The first changes of the arterial wall (intima-media thickening, IMT), can be observed with a technique of high-resolution ultrasound. IMT, preceding future clinical cardiovascular events, is considered a marker of systemic atherosclerosis. The arteries most commonly examined in adults, are the internal and common carotid arteries in the proximity of the carotid bulb and the carotid bulb itself. IMT in adults is associated with lesions, arteriografically documented, and the presence of cardiovascular risk factors such as diabetes, obesity and dyslipidemia.

The flow-mediated dilation (FMD) is the technique of choice for the study of endothelial function in adults and children and is the gold standard for research on endothelial function in cardiovascular pathophysiology [23]. It measures the changes in brachial artery diameter in response to increased shear stress produced by brief ischemia mechanics. Moreover, a significant reduction of FMD associated with increased oxidative stress in children with risk factors for cardiovascular disease (CVD) was demonstrated [24].

Several experimental and clinical studies have suggested that an increase in oxidative stress represents an important mechanism which leads to a reduced availability of endothelial NO in response to cardiovascular risk factors and, subsequently, promotes the development and progression of atherosclerosis. These non-invasive techniques have been used in recent years in pediatric age to investigate the association of the CVD risk factors with structure and function of the arterial wall. In particular, it was noted that IMT correlates positively with levels of total cholesterol and with BMI [25].

Among the classical risk factors for atherosclerosis, hypercholesterolemia, and obesity seem to be the main determinants of early atherosclerosis [6,7,26]. The endothelial dysfunction, assessed by the FMD has been recognized as a measure of systemic atherosclerosis [27]. The FMD depends on the release of nitric oxide (NO), a potent vasodilator and anti-aggregating molecule from the vessel wall [28,29]. Oxidative stress plays an important role in the modulation of the bioactivity of NO because it contributes to its rapid metabolism [29]. Children and adolescents with hypercholesterolemia and obesity have increased oxidative stress and impaired FMD [24, 30]. The coexistence of hypercholesterolemia and obesity, through the endothelial dysfunction and the activation of NOx2, represents, in addition, a trigger for the early atherosclerosis [31].

2.2. CVD Epidemiology: From Adulthood to Childhood

The primary prevention of non-communicable chronic degenerative diseases (such as CVD, cancer, neurodegenerative diseases) and infections should be the "main goal of modern medicine". Ancel Keys, about 60 years ago, was the first investigator to understand the close correlation between the intake of a cholesterol-rich diet and CVD [32,33]. The results of the Seven Countries Study confirmed this intuition showing that the campaign to reduce the cholesterol in the United States has significantly reduced CVD mortality. The Framingham Heart Study was the first longitudinal study population that allowed us to observe the development of cardiovascular events in relation to a number of variables and to show, after 10 years, multiple risk factors directly related to the occurrence of CVD events [34]. There is clear-cut evidence that hyperlipidemia, hypertension, obesity, diabetes and smoking are the main risk factors for atherosclerosis and subsequent CVD [34].

Many studies, including the Muscatine Study, the Bogalusa Heart Study, the Cardiovascular Risk in Young Finns Study, the Coronary Artery Risk Development in Young Adults (CARDIA), have demonstrated the tracking of cholesterol from childhood to adulthood, the family risk factor aggregation and the role of obesity and hypercholesterolemia in predicting vascular damage in young adults [35-38]. At present time, the scientific evidence indicates that primary prevention of atherosclerosis, related to classical cardiovascular risk factors, should be implemented as early as possible. Therefore it is necessary to screen healthy children at risk in the setting of a primary prevention program aimed to non-drug management: changes in dietary habits (limited intake of calories, saturated fat and salt, increase in the consumption of fruits, vegetables and fiber) associated with physical activity.

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Effective strategies for risk factors reduction in children are poorly investigated and only few studies evaluated the role of a healthy diet and individual nutrients. In fact, a relationship between fruit and vegetable consumption and prevention of atherosclerotic-related disease is based on observational and epidemiological analysis in adulthood [39]. Recently it has been observed that an adolescent population, consuming predominantly vegetarian foods, showed significantly better scores of markers of cardiovascular health and atherosclerotic progression, including body mass index, waist circumference, cholesterol/high-density lipoprotein ratio, and low-density lipoprotein-cholesterol [40].

2.3. Meditarranean Diet: Only for Mediterranean Countries?

The traditional Mediterranean diet is characterized by: a high intake of olive oil, fruit, nuts, vegetables and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats and sweets; a moderate wine consumption during meals [41]. A meta-analysis of 50 studies (approximately 500,000 individuals) suggests that adherence to the Mediterranean diet is associated with a lower prevalence and progression of metabolic syndrome (MS). In addition, a greater adherence to this dietary pattern is associated with positive effects on the individual components of the MS [42]. These results are extremely important for public health, because this alimentary model can be easily adopted by all population groups with different traditions and it has been shown to be more effective in modifying atherosclerosis-related risk factors then low-fat diets [43].

In a randomized trial for the primary prevention of cardiovascular events it was observed that an energy-unrestricted Mediterranean diet, supplemented with extra-virgin olive oil or nuts, resulted in a substantial reduction in the risk of major cardiovascular events among high-risk subjects. These results support the benefits of the Mediterranean diet for the primary prevention of cardiovascular disease [44]. Using the KIDMED (Mediterranean Diet Quality Index for children and adolescents) diet score on a population of 622 children Lazarou and colleagues found a positive correlation between lower levels of blood pressure and a higher KIDMED score [45]. Although the increased consumption of dietary fibers (fruits, vegetables, whole grains, legumes) is an important step in obesity control, dietary fiber supplements often represent a useful add-on, since lifestyle changes are difficult to follow after a while and high cholesterol levels may be resistant to these changes. On the other hand, different nutraceuticals have been studied for their ability to reduce cholesterol in humans [46]. Dietary supplement has been recognized as a starting point in the prevention and management of CVD and type 2 diabetes. Recent data show that about half of the US population and 70% of older people use every day dietary supplements [47].

3. Dietary Fibers

The American Dietetic Association (ADA) position paper uses ADA's Evidence Analysis Process and information from ADA's Evidence Analysis Library [48]. Four topics were included in the evidence analysis for dietary fibers (DF): cardiovascular disease, gastrointestinal health and disease, weight control, and diabetes. The Evidence Analysis Library does not include the topic of dietary fibers and cancer. The Institute of Medicine defines DF as the "non-digestible carbohydrates and lignin that are intrinsic and intact in plants." [49]. DF are usually divided into 2 major categories based on water solubility and viscosity. The physical properties of viscous and non-viscous DF in food determine their physiologic effects, which in turn are related to their known and potential health benefits [50].

Recently, the National Academy of Sciences (NAS) proposed a new definition for fiber [49]. The new definition proposes that total fiber = dietary fiber + functional fiber. Under this new definition, fiber consists of non-digestible carbohydrates and lignin (a non-carbohydrate substance bound to fiber), which are intrinsic and intact in plants (e.g., gums, cellulose, oat bran, wheat bran), and functional fiber consists of isolated, non-digestible carbohydrates that have beneficial physiological effects in humans. Functional fibers may be extracted or modified from plants (e.g., resistant starch from green bananas and cooked, cooled potatoes) or may be derived from animal sources (e.g., chitin and chitosan found in crab and lobster shells). Functional fiber also must have a beneficial physiological effect in humans.

The health benefits of DF are determined, in part, by their physical attributes, particularly solubility and viscosity. DF can be differentiated by the chemical properties of their components and the processes used to extract those component and can be classified as insoluble DF, which do not dissolve in water, and soluble DF, which dissolve in water [51,52]. Soluble DF can be further divided into viscous (*i.e.*, gel-forming) or non-viscous types. The viscous DF in turn, can be totally soluble (oligosaccharides, prebiotics) or gel forming. Those forming gels are characterized by their viscosity and fermentability that vary widely from fiber to fiber and characterize their action. The viscosity exerts its action at the metabolic-hormonal level, while the fermentation improves the formation of short-chain fatty acids (SCFA) and increases the proliferation of bacteria in healthy colons improving the trophism [53].

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Observational studies in adults showed that the consumption of large amounts of DF is associated with lower rates of CVD, stroke and peripheral vascular disease and that the main cardiovascular risk factors (hypertension, diabetes, obesity and dyslipidemia) are less common in subjects with increased consumption of DF [51].

The known or potential health benefits of DF in childhood include: promotion of normal intestinal function and prevention of gastrointestinal disorders, prevention and treatment of childhood obesity, reduction of blood cholesterol, modulation of postprandial hyperglycemia and glucose intolerance and possible effects on reducing the risk of future chronic diseases, such as cancer, cardiovascular disease, and adult-onset diabetes.

A daily total dietary fiber intake from food sources of at least age plus 5 g for young children up to 14 g/1000kcal for older children and adolescents is recommended [54]. Recent European guidelines on the management of dyslipidemias also recommend some nutraceuticals as potentially useful lipid-lowering substances [55]. As cardiovascular disease prevention needs a life-course approach, both the tolerability and safety of dietary supplements/nutraceuticals used to control plasma cholesterol levels have to be adequately defined as well as the risk/benefit ratio of their assumption. A relatively large number of recent reviews already described the mechanism of action and the efficacy of the different nutraceuticals and botanicals with lipid-lowering effects [56-58].

4. Nutraceuticals and Obesity

Childhood obesity has increased 3-fold in the last 20 years, with potentially long-lasting effects on health. Childhood obesity affects a considerable part of the world's population across gender and ethnic groups [59]. In Italy, 22.1% of infants are overweight and 10.2% are obese, with the highest rates in central and southern regions [60]. The reasons for this escalation are not fully determined; however, sedentary lifestyle and dietary changes in combination with genetic predisposition are probably involved.

Many studies, including the Bogalusa Heart Study, have convincingly shown that childhood obesity is correlated with risk factors for CVD in adulthood, MS and early development of atherosclerosis [6]. This emphasizes the importance of prevention and early management of obesity in the young, including both dietary and physical activity modifications, as well as pharmacologic interventions. Intake of DF is inversely associated with body weight, body fat, and BMI [61]. DF are capable of promoting satiation, decreasing the absorption of macronutrients, and altering the secretion of gut hormones [62]. Although the increase of fiber consumption with meals is an important step to control the obesity, the addition of fiber supplements should also be considered. Data from the NHANES III study showed that 13 - 18 years old boys and girls with a low fiber intake were three to four times more likely to be overweight compared to those with higher fiber intake [63].

Glucomannan is a natural gel forming fiber (composed of beta-1, 4-linked d-glucose and d-mannose) extracted from Amorphophallus Konjac tubers. There are many kinds of glucomannan but only the one with high viscosity is effective in the treatment of metabolic disorders, overweight and obesity. This soluble highly viscous fiber can promote weight loss and improve lipid and glucose profile in adults but currently no data on weight loss in children are available [62,64]. Several other fibers are marketed as dietary supplements, including use in children; however, their weight-lowering effects have not been studied yet.

5. Nutraceuticals and Hypercholesterolemia

Hypercholesterolemia can be diagnosed in childhood [65,66] and requires an early management to prevent future CVD [24,65-67]. Lipid-lowering drugs are not usually recommended for children since no data are currently available about long-term effects and safety. The NCEP recommends that drugs should be administered only in patients above 10 years of age (ideally at pubertal Tanner stage II or higher, preferably after onset of menses in girls), and only after failure of an aggressive diet over a 6 - 12 months period. Therefore, the current management of children and adolescents with high LDL-cholesterol includes diet changes and increased physical activity [68,69].

Dietary changes are the cornerstone for the management of children with elevated blood cholesterol levels. The Expert Panel on Blood Cholesterol Levels in Children and Adolescents recommends a dietary intervention in two steps. The Step-1 diet calls for an average intake of total fat less than 30% of total calories, of saturated fat of no more than 10% and of dietary cholesterol less than 300 mg per day. If cholesterol reduction is not achieved after a minimum of 3 months on this diet, the child progresses to the Step-2 diet, which calls for further reduction of saturated fat to less than 7% of total calories and of dietary cholesterol to less than 200 mg per day [70]. However, the dietary changes result in a relatively small reduction of cholesterol concentrations; nevertheless, these changes would be difficult to be maintained over a long period. A low-fat and fiber-rich diet is the first treatment in all hypercholesterolemic children [71]. The quality of dietary fiber is important: water-soluble fibers such as pectin, gums and mixed-linked β-1, 3- and 4-D-glucans

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have a significant cholesterol-lowering effect [72]. The high viscosity glucomannan has shown a lipid-lowering capacity 3 to 5 times greater than that of psyllium, guar and oat products [73]. This fiber may decrease serum levels of total cholesterol and LDL-cholesterol without changes in HDL-cholesterol. Previous studies demonstrated these positive effects in adults [74,75] and in children [76,77]. A meta-analysis of 14 studies ($N = 531$ subjects) showed that glucomannan seems to have beneficial effects on total cholesterol, LDL-cholesterol, triglycerides, body weight, fasting blood glucose but not on HDL-cholesterol or blood pressure [78].

The action of high viscosity glucomannan in decreasing and maintaining the targeted cholesterolemia is also validated by the European Food Safety Authority (EFSA) report and many clinical trials [72,74-76,78-80]. Other nutraceuticals as chromium-polynicotinate and policosanol were investigated in the treatment of lipid disorders showing cholesterol-lowering effects [79-81]. Unfortunately, subjects taking high doses of these products experienced adverse effects. Glucomannan alone or in combination with low-dose chromium-polynicotinate or policosanol was able to significantly reduce total cholesterol and LDL-cholesterol without changing HDL-cholesterol, triglycerides and glucose. The highest reduction was obtained in children treated with a combination of glucomannan and low-dose chromium-polynicotinate and no adverse effects were reported, however the concomitant use of glucomannan with resistant starch inhibited its effectiveness [82].

Dietary supplementation with 6 g/day of psyllium over 6 weeks improves fat distribution and lipid profile (6% reduction in LDL cholesterol) in a population at risk of adolescent males. Conversely, psyllium supplementation did not improve insulin sensitivity [83]. However, Dennison *et al.* found no additional lowering effect of psyllium fiber on total or LDL-cholestertol in children who were following a low total fat, low saturated fat, and low cholesterol diet [84].

6. Conclusions

Overfeeding in childhood can lead to the development of obesity and/or atherosclerosis in adult life. In particular, a high intake of nutrients affects the *in utero* programming with the adverse consequences of insulin resistance an endothelial dysfunction that lead to early atherosclerosis.

DF have important health benefits in childhood: research suggests that DF may be useful in preventing and treating obesity and in lowering blood cholesterol levels with a favourable impact on the risk of future CVD. It remains for further investigation to assess whether also in Southern European Countries, practicing Mediterranean diet as a normal habit, DF may indeed contribute to modify the relatively low proportion of hyperlipemia observed in our population [85]. Clearly, adequately powered and controlled trials are needed.

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