AJFAND ONLINE
Formerly AJFNS
Volume 7 No. 1 2007
ISSN 1684-5374
AFRICAN JOURNAL OF FOOD AGRICULTURE NUTRITION AND DEVELOPMENT

ROLE OF FATTY ACIDS OF MILK AND DAIRY PRODUCTS IN CARDIOVASCULAR DISEASES: A REVIEW

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AJFAND ONLINE
Formerly AJFNS
Volume 7 No. 1 2007
ISSN 1684-5374
AFRICAN JOURNAL OF FOOD AGRICULTURE NUTRITION AND DEVELOPMENT

ABSTRACT

There are increasing global concerns about the role of foods in health and chronic diseases. Milk and dairy products are important sources of dietary protein and fat in the diets of many cultures including African communities. However, questions are being raised concerning the role of milk-nutrients in chronic diseases including CVDs. Also, the African public often does not have access to scientific information on the nutritional and health significance of nutrients in some of their major foods including milk and dairy products. This review of the literature was therefore conducted in order to provide information on the role of the fatty acids of milk and dairy products in respect of CVDs, with reference to some African communities. The fatty acids linoleic and alpha-linolenic are precursors of eicosanoids, whose excessive and/or imbalanced synthesis has been implicated in various pathological conditions including CVD. Due to the considerable amount of saturated fatty acids and cholesterol in milk, its consumption is often associated with mortalities from CVDs. Myristic and lauric acids are atherogenic, and raise the risk of CVD by increasing plasma cholesterol and LDL, although oleic, linoleic and linolenic reduce the increase. Palmitic acid does not seem to be strongly atherogenic, while stearic acid is largely neutral. Abundant intake of saturated fats increases plasma LDL and VLDL. Although considered high cholesterol foods, milk and dairy products may not be major contributors of dietary cholesterol, as whole milk contains 10-15 mg cholesterol/dL, while skimmed milk with 1% butter-fat contains less than 8 mg/dL cholesterol. *Trans* fats have been implicated as risk factors for CVD due to their hypercholesterolemic effect. The risks of CVD from *trans* fats intake in milk and its products are, however, lower compared to risks from the consumption of hydrogenated vegetable oils. Linoleic, α-linolenic and oleic acids are considered cardioprotective. The short and medium-chain fatty acids do not seem to influence plasma cholesterol levels; monounsaturated fats tend to have a neutral influence, while polyunsaturated fats tend to lower total cholesterol, but may also lower the "good" HDL. To lower cholesterol and saturated fatty acids intake from milk and dairy products, and to slow atherosclerosis progression, it is recommended that the consumption of full-fat milk be reduced while increasing that of skimmed milk and cheese. This can be achieved by integrating these findings into food processing practices, agricultural, and nutritional policy in Africa.

KEYWORDS: Milk, Diet, Fat, Fatty acids, Cholesterol, Cardiovascular diseases

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Formerly AJFNS
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AFRICAN JOURNAL OF FOOD AGRICULTURE NUTRITION AND DEVELOPMENT

French

LE ROLE D'ACIDES GRAS

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Les acides myristiques et lauriques sont athérogènes, et ils aggravent le risque de maladies cardiovasculaires en augmentant le cholestérol du plasma et la LDL bien que l'oléique, le linoléique et le linolénique réduisent l'accroissement. L'acide palmitique ne semble pas être pas fortement athérogénique, tandis que l'acide stéarique est largement neutre. La prise abondante de matières grasses saturées augmente la LDL et la VLDL du plasma. Tout en étant considérés comme des aliments contenant beaucoup de cholestérol, le lait et les produits laitiers ne peuvent pas être des contributeurs majeurs du cholestérol diététique, étant donné que le lait entier contient 10 -15 mg de cholestérol/dL, tandis que le lait écrémé à 1% de beurre – matière grasse contient moins de 8 mg/dL de cholestérol. Les acides gras trans ont été considérés comme des facteurs de risques de maladies cardiovasculaires à cause de leur effet hypercholestérolémique. Les risques de maladies cardiovasculaires provenant de la prise de matières grasses trans dans le lait et les produits laitiers sont, cependant, peu élevés en comparaison avec les risques de la consommation d'huiles végétales hydrogénées. Les acides linoléiques, a-linoléniques et oléiques sont considérés comme cardioprotecteurs. Les acides gras courts et moyens ne semblent pas influencer les niveaux du cholestérol du plasma; les matières grasses mono-insaturées tendent à avoir une influence neutre, tandis que les matières grasses poly-insaturées tendent à baisser le cholestérol total, mais ils peuvent également baisser la "bonne" HDL (lipoprotéine de haute densité). Pour diminuer le cholestérol et la prise d'acides gras saturés du lait et des produits laitiers et ralentir la progression de l'athérosclérose, il est recommandé que de réduire la consommation de lait entier en augmentant la consommation de fromage et lait écrémés. Ceci peut se réaliser en intégrant les présents résultats dans les pratiques de transformation des produits alimentaires, ainsi que dans la politique agricole et alimentaire en Afrique.

Mots-clés: Lait, régime alimentaire, matières grasses, acides gras, cholestérol, maladies cardio-vasculaires.

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INTRODUCTION

Cows, sheep, goats and camels are the milk-animals in Africa. The camel is important in North Africa, the Horn of Africa, Somalia, northern and northeastern Kenya.

Milk is a source of protein, lactose and fats in the diets of many African communities. Dietary fats supply energy, carry the fat-soluble vitamins, and are a source of antioxidants and bioactive compounds [1]. Fatty acids (FAs) mainly comprise saturated (SAFAs), monounsaturated (MUFAs) and polyunsaturated fatty acids (PUFAs). The latter are classified into essential and nonessential fatty acids. The essential fatty acids linoleic (9, 12-octadecadienoic acid-18:2n-6) and alpha-linolenic (9, 12, 15-octadecatrienoic acid-18:3n-3) are precursors of eicosanoids [2, 3]. Excessive and/or imbalanced synthesis of eicosanoids has been implicated in various pathological conditions, including thrombosis, inflammation, asthma, ulcers and kidney disease [4]. An inadequate dietary intake of essential fatty acids (EFAs) precipitates essential fatty acid deficiency disease. Five to 10% of an adult's calories need to come from fat to maintain health, and 2-3% of these calories have to be supplied by the EFAs or 1-2% energy as linoleic acid (LA) [5, 6]. FAs are needed for infant nutrition, growth and development. Maternal milk, from mothers of preterm infants, contains higher concentrations of long-chain polyunsaturated fatty acids (LC-PUFAs)-in particular, docosohexaenoic acid (DHA, 22:6n-3), than either cow's milk or most infant formulae [7], implying the essentiality of DHA for preterm infants. Phospholipids are incorporated as structural components of the brain and all cell membranes [5]. The PUFAs from animal feed are hydrogenated as they pass through the cow's four stomachs by resident intestinal microflora. PUFAs and MUFAs are prone to autooxidation under adverse processing and storage conditions. Lipid peroxidation products have been shown to cause endothelial damage both in vivo and in vitro [8]. They may therefore promote atherogenecity. Cholesterol performs many important roles in the body despite the bad publicity associated with it [9]. It is the backbone of steroid hormone synthesis, synthesis of bile acids, and is essential for stabilizing cell membrane constituents, plasma lipoproteins and myelin. The American Heart Association (AHA) recommends limiting dietary cholesterol to less than 300 mg/day due to its role in atherosclerosis [10].

GENERAL RISK FACTORS FOR CARDIOVASCULAR DISEASES (CVDs)

CVD refers to any disease that affects the cardiovascular system although it usually refers to atherosclerosis, systemic hypertension, syphilitic heart disease, and rheumatic heart disease. Coronary atherosclerosis develops with the formation of fatty fibrous plaques that narrow the lumen of the coronary and peripheral arteries and may lead to thrombosis or myocardial infarction. CVD is multi-faceted, and the course of its pathology is influenced by physiology, genetics, the environment and psychosocial stresses [11]. The non-modifiable risk factors for

CVD include increasing age, the male sex (gender), heredity (including race), while the major identified modifiable risk factors include cigarette smoking, elevated blood pressure, elevated plasma cholesterol, obesity, diabetes mellitus and elevated plasma triglycerides [12, 13]. Diet is an important part of the control and management of CVD; diet involves a modifiable set of factors, which if well managed can reduce the risk of CVD as most variables including diabetes mellitus, obesity, low-density lipoprotein (LDL) levels, triacylglycerol levels, alcohol and blood pressure are all connected to diet.

CVD is currently the commonest global cause of death for mankind, with an estimated 17 million deaths/year, which are projected to reach 25 million by 2020 [14]. It is the number one cause of death in the U.S., U.K., Australia and Europe (except in France) [12, 15, 16, 17]. It is responsible for 33, 40, 39, 40 and 39% of all deaths in the World, U.S., U.K., Australia and Europe, respectively. The 2004 World Health Report estimates that CVD is the largest cause of death in the lowest socioeconomic groups in developed countries and 85% of all deaths in low-income and middle-income countries are due to it [14]. However, deaths from HIV/AIDS related illnesses are currently greater in some sub-Saharan African countries than those due to malaria, tuberculosis and/or CVD. In Kenya, HIV/AIDS claims 100 000-150 000 lives annually compared to over 42 000, 30 000 and 20 000 by CVD, malaria and tuberculosis, respectively [14]. In 2002, cerebrovascular disease, ischaemic stroke and other CVDs represented 31.9, 37.1 and 31.1% of 20 000 deaths attributed to CVDs in males, and 37.0, 27.5 and 35.6% of 24 000 female deaths in Kenya [14]. Ischaemic stroke and cerebrovascular disease were the main CVD sub-type killers of Kenyan males and females, respectively.

In developing countries, there are indications that deaths from CVD are rising with changes in lifestyles, "modernization," urbanization and occupational sedentarization [14].

Hyperlipidemia, which is associated with elevated levels of cholesterol, cholesteryl esters and triglycerides, has been identified as a major risk factor for atherosclerosis [18]. These lipid components are transported in the circulatory system in association with proteins, carbohydrates and phospholipids in various micelle forms, e.g., chylomicrons (CMs), very low density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), lipoprotein A (LpA) and various micelle remnants [13]. HDL (the "good" cholesterol) carries cholesterol back to the liver from the bloodstream and is thought to be protective by taking the extra cholesterol out of the blood. LDLs (the "bad" cholesterol) transport cholesterol through the blood to the cells and usually comprise most of the blood cholesterol. VLDLs also keep cholesterol in circulation and may contribute to atherosclerosis [18]. The LDL, total cholesterol/HDL and/or the LDL/HDL ratios are often assumed to be relative measures of CVD risk. A ratio of LDL/HDL above 5.0, total cholesterol, LDL, and triglyceride levels above 200, 150, and 150 mg/dL, respectively, and HDL below 35 mg/dL are believed to indicate elevated CVD risk [19].

It is well established that individuals with premature CVD exhibit some or all of the following: a) increased LDL levels; b) increased cholesteryl esters and triglycerides, primarily as VLDLs; and c) increased triglycerides with normal cholesterol, primarily as VLDLs [13]. Several prospective studies have found a positive correlation between serum LDL and atherosclerotic events, and this appears to be inversely related to serum HDL [20]. However, the cardioprotective effect of HDL does not contribute to explain CVD mortality differences between populations. Also, despite the widespread acceptance of the role of LDL-cholesterol, it remains true that many patients suffering from myocardial infarction have relatively normal levels of LDL-cholesterol [18]. This underlines some lack of clarity and knowledge on the specific roles and interaction of CVD risk factors. Also, there is still ongoing debate as to whether high LDL-cholesterol or low HDL-cholesterol is the better predictor of CVD risk.

CVD RISK FACTORS ASSOCIATED WITH MILK AND DAIRY PRODUCTS

Milk is considered a risk factor for atherosclerosis and coronary heart disease (CHD) because of its cholesterol content, SAFAs and possibly lactose [21]. However, while epidemiological data to support these assertions are scanty and inconclusive, there is almost complete lack of clinical data. Triacylglycerols compose 97-98% of milk lipids with the rest being sterols (mainly cholesterol, 1.1%) and phospholipids (0.45%) [22]. Bovine milk therefore contains 15 and 7-8 mg/dL cholesterol and phospholipids, respectively. Ross proposed the "response to injury hypothesis" as the primary cause of atherosclerosis [23]. Injury to endothelial cells can arise from exposure to endotoxins, vasoactive amines, viral infections, lipid oxides, hypercholesterolemia, mechanical injury (hypertension), carbon monoxide, and/or hyperlipidemia [13]. Serum cholesterol levels in a given population are closely related with increased risk for atherogenesis [18, 24]. However, skepticism still remains regarding the relationship between dietary cholesterol intake and serum cholesterol concentrations [25, 26].

The seven-country study [27] gave rise to the idea that saturated fats contribute to high plasma cholesterol and atherogenesis, but skepticism still remains about the degree of such an effect [28]. Merskey and Marcus in a review concluded that there was no evidence that the type of saturated dietary fat had any influence on coagulation [29]. Among 350 rural Maasai men of Kenya over the age of 40 who were examined for CVD, only one had an equivocal ECG-based evidence of a myocardial infarction [28]. Dietary evaluations showed a daily intake of 300 g animal fat, with 25% young men showing plasma cholesterol of 600 mg/dL, all from fermented milk and meat. The serum cholesterol level among the warrior age-group of the Maasai averaged 150 mg/dL, and did not significantly rise with age. In another group of 400 rural Maasai men and women, the mean plasma cholesterol was 120 mg/100 mL despite the consumption of large amounts of full-fat milk and meat containing considerable amounts of saturated fats [28].

According to Shaper, the Samburu, another group of nomadic livestock herders in northern Kenya consumed about 200-400 g fat/day, mainly saturated fat from milk but did not show evidence of a high incidence of clinical CVD similar to the rural

Maasai [30]. All Samburu age-groups consumed more milk than the Maasai but their blood lipid profiles resembled those of populations living on low-fat diets. In autopsies of the hearts and aortae of 50 Maasai men, who died suddenly from natural causes, examination of the aortae showed extensive atherosclerosis with lipid infiltration and fibrous changes but with very few complicated lesions [28]. It was evident that although their arteries showed intimal thickening by atherosclerosis which equalled that of old U.S. men, the Maasai blood vessels enlarged with age to more than compensate for this disease. It was postulated that they are protected partially from atherosclerosis by physical fitness (from the extensive walking in the course of herding), which causes their coronary vessels to be capacious [28]. A recent large prospective study involving 47 721 Finnish subjects 25-64 years of age, without a history of coronary heart disease, stroke, or cancer at baseline, supported Mann's assertions; the study spanning over 19 years established an inverse correlation between the level of physical activity and ischaemic heart disease [31]. It is established that a high level of leisure time physical activity including active commuting reduces the risk of all subtypes of stroke. The absence of salt in their low carbohydrate, high-protein dairy and meat diets, the beneficial effect of the probiotic natural cultures that ferment their milks, and low levels of stress may also have contributed to the low incidence of CVDs in the above livestock-herding populations.

Three recent case-control studies concluded that a high-carbohydrate, low-fat diet offers no more protection against atherosclerosis than does a low-carbohydrate, high-fat diet [32]. While these studies did not seem to have controlled all confounding variables, they disprove the conventional wisdom that animal fat is the primary dietary cause of coronary diseases. Nevertheless, it is increasingly being demonstrated on the basis of convincing evidence that saturated fats and high serum cholesterol levels may indeed contribute to the build up of atherogenic plaques in arterial walls thereby possibly leading to CVDs. A review of clinical trials and dietary interventions revealed that it is possible to reduce the incidence of coronary death and nonfatal myocardial infarction, as well as manifestations of atherosclerosis in cerebral and peripheral arteries, by reducing the dietary intake of saturated fat and cholesterol [33]. Also, cholesterol oxidation products, cholestane-3ß, 5α, 6ß-triol and

25-hydroxycholesterol, produce endothelial damage both in vivo and in vitro [8]. This is likely to lead to CVD.

Although there is general agreement that reducing dietary cholesterol, saturated fats and possibly *trans* fatty acids would be beneficial, controversy still remains as to what constitutes beneficial dietary fats. The long-chain ω-3 PUFAs, eicosapentaenoic acid (EPA) and DHA, commonly found in seafood, are the only FAs that have consistently been shown to significantly reduce the risk of CVD in human kinetic studies [6]. Some dairy fatty acids are also cardioprotective.

Milk is not a high-fat food and yet due to its considerable cholesterol and SAFA content, its considerable consumption is suspected to lead to higher risk for CVD. The major fatty acids in bovine milk-fat are palmitic (26.3%), oleic (25.1%), stearic

(12.1%), myristic (10.1%), butyric (3.2%), lauric (2.8%), decanoic (2.4%) and linoleic (2.3%) [34]. Camel milk contained palmitic (31.5%), oleic (25.0%), stearic (14.0%), palmitoleic (10.4%) and myristic (10.1%) [35], while goat milk contained oleic (28.1%), palmitic (21.3%), stearic (14.4%), myristic (7.7%) and capric (5.4%) [36]. Due to the higher content of stearic and oleic acid as well as MUFA in camel milk, it may be more favourable for human nutrition than cow's and/or goat milk. Myristic, lauric and palmitic are atherogenic and raise the risk of CHD by increasing plasma cholesterol and LDLs [22]. However, 18:0, 18:1 and 18:2 reduce the increase [37]. Palmitic does not seem to be strongly atherogenic and has not been shown by some workers to raise LDL-cholesterol [38, 39]. However, Grundy showed it potentially raises plasma cholesterol [40]. Although considered high cholesterol foods, milk and dairy products are minor contributors to dietary cholesterol as whole milk contains 10-15 mg cholesterol/dL [9, 22], while 1% fat skimmed milk contains less than 8 mg/dL cholesterol [9]. The cholesterol intake from bovine milk in Kenya as calculated by this author based on a fat content of 3.3% is 71 and 89 mg/day/person from the production of 2.8 and 3.5 billion litres full-fat milk in 2000 and 2004, respectively. However, the 2000 milk production excluded milk from camels, while the 2004 milk production excluded that from sheep, goats and camels [41, 42]. Cholesterol intake from milk and dairy products in Kenya is therefore likely to be higher than 89 mg/person/day and the consequences for the health of the consumers are currently undetermined. The cholesterol intake by Kenyans from meats is also unaccounted for. The current per capita consumption of milk in Kenya is 113 litres or 310 mL/day [42], which is similar to the American per capita consumption [43]. Milk and cheese consumption and consequently of calcium did not seem to increase the risk of non-fatal acute myocardial infarction (AMI) in an Italian population characterized by comparably low milk consumption of 137 mL/day among cases and 148 mL/week among controls, but a high intake of cheese (average intake of 36.4 g/day among cases and 40.0 g/day among controls [21]. However, in a small controlled trial over a 6-week period, consumption of 236 mL/day skim and whole milk by 8 healthy males showed that substitution of skim milk for whole milk decreases the risk of CHD [44]. The daily cholesterol and SAFAs intake has recently been estimated in British adults as 223 mg and 42 g in males, and 223 mg and 31 g in females, respectively [45]. This compares with the American daily intake of 337 mg cholesterol and 35 g saturated fat by males and 217 mg cholesterol and 22 g saturated fat by females [46]. Unlike the rural Maasai and Samburu of Kenya, plasma cholesterol rises with age in both American and British adults [45, 46]. Furthermore, despite the reduction in the intake of meats and milk, and therefore of cholesterol and saturated fats in the U.S. and British diets between 1965 and 1995, CVD mortality still remains high [45, 46).

Butter with 80% fat contains 190-200 mg cholesterol/100 g [9, 22]. However, because butter is consumed in small quantities it should not be a major nutritional concern; nevertheless, the large amounts of atherogenic fatty acids could along with those from other dietary sources hasten atherogenesis in susceptible individuals [22].
The presence of *trans* fatty acids in foods has recently elicited scrutiny from the scientific community. Most unsaturated fatty acids in nature are found in the *cis* double-bond configuration, but during the hydrogenation of vegetable oils, and food

processing in oil at high temperatures (e.g., in deep-oil frying), inversions of the double bonds occur resulting in *trans* fatty acid isomers. Hydrogenated vegetable oils are currently a major source of *trans* fats in human diets. Despite trends towards reducing *trans* fats in margarines and hydrogenated vegetable oils in developed countries, the applicable technologies are not yet widely used in edible oils processing in Africa. *Trans* fats have been shown to be nearly as hypercholesterolemic as myristic or palmitic acids [20]. It was shown recently that palmitoleic acid, 16:1, alters serum lipoproteins in a manner similar to 14:0 and 12:0 [47]. However, *trans* FAs appeared less hypercholesterolemic than 14:0, the most hypercholesterolemic SAFA, and 12:0 [47]. It was also shown that Lpa was increased by a high *trans* fat diet compared to a stearic-enriched diet [47]. Since Lpa is a strong independent risk factor for CVD, a high *trans* fat diet may contribute to the risk of CVD [48]. Mensink and Katan concluded that since *trans* FAs raise LDL-cholesterol and decrease HDL-cholesterol, they are as unfavourable as the SAFAs [49]. The AHA recommends lowering their dietary intake [12]. Due to the small amounts of unsaturated fatty acids in dairy fats, the dietary intake of *trans* fats in milk, butter and ghee is likely to be insignificant, while those with existing adverse cardiovascular risk factors are often advised to avoid margarine [5]. Milk from cattle, goats, sheep and camels also contain 0.8-19% C_4-C_{10} fatty acids, whose roles in CVD have not been reported much in the literature, despite indications that they may inhibit hepatic cholesterol synthesis and/or redistribute cholesterol from plasma to the liver.

28% of bovine milk-fat comprises oleic, linoleic and linolenic acids. Oleic increases cholesterol esterification in hepatocytes, diminishes the free cholesterol pool, and enhances LDL-receptor activity [50]. However, epidemiological studies have not shown consistent effects of MUFAs on the risk for coronary arterial disease. Replacement of dietary SAFAs with oleic-rich diets has been shown to be as effective as substitution with PUFAs in lowering plasma LDL [51, 52]. It also has the advantage that it does not simultaneously lower HDL-cholesterol in hypercholesterolemic subjects [51, 52]. HDL has also been demonstrated to inhibit oxidative modification of LDL [53]. Because there may be an exchange of fatty acids and oxidized fatty acid products between LDL and HDL, HDL particles enriched with PUFAs may offer less protection to LDL. Thus, diets enriched with oleic rather than PUFAs might confer additional protection by generating both LDL particles that are more resistant to oxidation and HDL particles that inhibit oxidative modification, while optimizing both LDL and HDL-cholesterol levels [54]. Oleic acid is beneficial as regards atherosclerosis, as ecological studies have shown an inverse association between the intake of MUFAs and CVD mortality [55].

Several epidemiological studies suggest that low tissue levels of LA might be an independent risk factor for CVD [56]. However, as a n-6 fatty acid, a dietary LA deficiency would be expected to lower both thromboxane A_2 and prostaglandin I_2 concentrations due to the synthesis of less arachidonic acid [13]. Both thromboxane A_2 and prostaglandin I_2 particles are antiaggregatory and vasodilatory, pointing to the likely beneficial effects of consumption of adequate but low levels of LA. Conjugated linoleic acid (CLA), a fatty acid in milk and dairy products protects against atherosclerosis in hamsters and rabbits [22]. These animals are regarded as reasonable

animal models from which the metabolic effects of dietary fatty acids can be extrapolated to human beings. It can therefore be postulated that LA as found in milk-fat may decrease the risk of CVD, despite the rarity of data on humans [22]. In a prospective and nested case-control study of 7450 Japanese participants aged 40-85 years, and using frozen serum samples from cardiovascular risk surveys collected from three communities from 1984-1992, it was found that the nature of fatty acids in the diet influenced the occurrence of stroke [57]. The study showed that a high intake of LA may protect against ischaemic stroke, possibly through potential mechanisms of decreased blood pressure, reduced platelet aggregation, and enhanced deformability of erythrocytes. Furthermore, it has been shown that CLA fed to rodents can predispose to the formation of fatty streaks-the presumed precursors of atherosclerotic lesions in the aorta [18]. CLA may play a role in slowing the formation of atherosclerotic plaques in blood vessels. However, it is recognized that dietary LA favours oxidative modification of LDLs, increases platelet response to aggregation, and suppresses the immune system [55]. Also, a high LA intake reduces apolipoprotein A-1 production [6]. This lowers HDL thereby decreasing reverse cholesterol transport, and possibly increasing the risk of atherosclerosis. Biochemical evidence also suggests that increased levels of LA in vascular cells favours lipid peroxidation due to its unsaturation [13]. Increased n-6 PUFA dietary intake may reduce the cellular incorporation of n-3 PUFAs, thereby leading to unhealthy imbalances in tissue lipids, by influencing the activity of the delta desaturase enzyme through competitive inhibition. This results in greater formation of the aggregatory and inflammatory series 2 eicosanoids [13]. LA hydroperoxides have also been shown to have potential cytotoxic effects in vitro [58]. In 2000, the Board of the International Society for the Study of Fats and Lipids (ISSFAL) could not recommend an upper limit for LA intake beyond 2% of total energy due to controversy, inconsistency and lack of adequate data. Therefore, more research is necessary to resolve the controversies and establish a clear role for LA in CVDs.

Alpha-linolenic acid (ALA) can be elongated to the long-chain EPA and DHA, but its other exact functions in the human body are not characterized in detail. Eicosanoids derived from EPA have different biological properties in contrast to those derived from arachidonic acid. Their effects result in decreased vasoconstriction, platelet aggregation and leukocyte toxicity. However, the exact mechanism of action of ALA in reducing coronary disease recurrence is unknown; nevertheless, the AHA Dietary Guidelines recommend increasing its intake, as for the long-chain n-3 fatty acids from fish [10]. ALA has been found in several studies to exert positive effects in reducing CVD mortality risk [59, 60]. Due to competition between LA and ALA for entry into the elongation and desaturation pathways for the synthesis of their respective eicosanoids, emphasis should be on a favourable dietary ratio of LA to ALA.

CONCLUSIONS

Regarding CVDs, it seems beneficial to reduce the dietary intake of SAFAs and cholesterol, since it is well established on the basis of convincing evidence that reduction in serum total cholesterol results in reduction of coronary morbidity and mortality, as well as in regression of other atherosclerotic manifestations. Abundance

of dietary cholesterol expands the small regulatory hepatic intracellular pool of free cholesterol, resulting in reduced LDL-receptor activity, reduced LDL-cholesterol catabolism, and increased serum total cholesterol and LDL-cholesterol. The long-chain SAFAs ($C_{12:0}$-$C_{16:0}$) interfere with the esterification process of free cholesterol, and by this mechanism enlarge the hepatic regulatory free cholesterol pool. Similar to the situation with dietary cholesterol excess, LDL-receptor transcription is reduced, resulting in diminished LDL catabolism. Oleic acid increases cholesterol esterification in hepatocytes, diminishes the free cholesterol pool and enhances LDL-receptor activity. *Trans* fatty acids increase serum total cholesterol and LDL-cholesterol levels, but their importance as independent risk factors for CVD has not consistently been verified. MUFAs have a neutral influence on cholesterol levels, while PUFAs tend to lower both total cholesterol and HDLs. It is advisable to reduce the consumption of full-fat milk, and rely more on skimmed milk in order to lower cholesterol and SAFAs intake. Further research into the relationship between milk intake and risk for CVD using case-control, clinical, and pathological approaches, rather than relying largely on epidemiological studies (which are often conflicting) seems necessary.

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