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Mono unsaturated fatty acids for CVD and diabetes: A healthy choice

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Abstract

The focus of present scientific discussion is still the question on how to optimize the dietary fat intake in order to achieve maximum health benefits, that is, what is the optimum amount and composition of dietary fat. Over the past few years, there have been plenty of new findings concerning the various effects and modes of action of different fatty acids giving details on their specific role in health and diseases. Fatty acids are now known to not only play a role in the prevention of cardiovascular diseases via their effect on serum lipids but also because they directly influence a number of other risk factors in various ways and have direct effect on atherogenesis. Therefore, the health effects of dietary fat have to be judged according to its respective fatty acid composition. Epidemiologic evidence suggests that dietary monounsaturated fatty acids (MUFA) may have a beneficial health effect. This article summarizes present knowledge concerning the effects of mono unsaturated fatty acids with a focus on their role in coronary heart disease (CHD), diabetes, and their risk factors.

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Full Text

Introduction

Fats are one of the three major dietary components, which provide energy and play very relevant biological roles. A strong interest is devoted to the adequate quantitative and qualitative intake of fat, since unbalances have been associated with several degenerative pathologies, such as cardiovascular diseases (CVDs), diabetes, and cancer. Fatty acids, which are the main components of dietary fat, may be classified as saturated (saturated fatty acids, SFA) or

unsaturated, depending on the presence or absence of C = C double bonds in their acyl chain. Unsaturated fatty acids may present one (monounsaturated fatty acids, MUFA), or more (polyunsaturated fatty acids, PUFA) double bonds. Current guidelines recommend consuming no more than 25-35% of total daily calories from fat, with most coming from sources heavily endowed with MUFA and PUFA and no more than 10% of calories from SFA. [1] We are increasingly aware that many diseases that remain, whether killers or not, are related in some part to lifestyle of which diet, pollution of the environment, level of physical activity, and the role of fat in some disease conditions are all important factors.

CVD threatens to cripple India's workforce and stunt India's growth if timely and appropriate public health measures are not instituted. Epidemiologists in India and international agencies such as the World Health Organization (WHO) have been sounding an alarm on the rapidly rising burden of CVD for the past 15 years. [2],[3] It is estimated that by 2020, CVD will be the largest cause of disability and death in India. Of further concern is the fact that Indians are succumbing to diabetes, high blood pressure, and heart attacks 5-10 years earlier than their Western counterparts, in their most productive years. [4],[5]

Since the turn of the century, dietary fat has been recognized as a contributor to the development of coronary heart disease (CHD). More current research confirms this role and implicates specific lipoproteins in the development of CHD. [6] Further evidence suggests that specific fatty acids, including MUFA, tend to reduce the risk of CHD. Additionally, MUFA may rival carbohydrates in the management of diabetes mellitus (DM) in adults and adolescents, and may protect against some forms of cancer. [7],[8]

Historically, MUFAs were thought to have neutral effects on total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations [9],[10] but more recent evidence [11],[12], [13],[14] suggests that MUFAs not only lower TC and LDL-C when substituted for SFA and carbohydrates, but also maintain HDL-C concentrations.

A high-MUFA diet that replaces a high-carbohydrate diet appears effective in improving glycemic control and mitigating CHD-promoting dyslipidemia in diabetics. When carbohydrates are replaced with MUFA, LDL-C decreases without a concomitant decrease in HDL-C. Similarly, insulin sensitivity is constant on a MUFA-rich diet compared with a diet rich in SFA. [15],[16]

Dietary monounsaturated fats

The dietary fats exhibit a wide range of fatty acid types and varying ratios of PUFA:MUFA:SFA (P:M:S). What is important to note is that even though some dietary fats have the same P: S ratio, they contain differing amounts of MUFA and, in theory, would have significantly different effects on plasma lipoprotein concentrations. In addition to differences in the content of MUFA and stearic acid, some fats, such as butter oil, contain short-chain fatty acids (6-10 carbons) that are absorbed directly via the portal vein and are not transported through the bloodstream to the liver by chylomicrons. Thus, intake of short- and medium-chain fatty acids would be predicted to have different effects on the intravascular processing and inter-conversions of the lipoproteins compared with fats containing only long-chain fatty acids.

MUFA are classified as fatty acid chains with one double bond. MUFAs possess a higher melting point than PUFA, which contain two or more double bonds. Both MUFAs and PUFAs are liquid at room temperature, whereas MUFAs exist as semi-solids or solids when refrigerated. Conversely, SFA contain no double bonds and are solid at room temperature. Structurally, the common MUFAs, palmitoleic acid (16:1n-7) and oleic acid (18:1n-9), are both cis isomers of MUFA. Conversely the dietary trans isomer of MUFA is elaidic acid (trans18:1n-9). Oleic acid is the predominate MUFA in the diet, representing 92% of cis MUFAs. [17] [Table 1] outlines the fatty acid content of food rich in MUFAs.{Table 1}

In the Mediterranean diet, the majority of total fat intake is represented by MUFAs, ranging from 16% to 29%, with olive oil providing 60-80% of the oleic acid. [18],[19],[20],[21] The high MUFA intake of the Mediterranean diet is at the expense of SFA, with intakes of SFA < 8% of energy. Thus, an inverse relationship between the Mediterranean diet and CHD risk has been substantiated in both epidemiological studies and randomized clinical trials. [22]

Based on the emphasis of increasing the intakes of MUFAs in the diet, particularly at the expense of SFA, it is important to discuss the efficacy of MUFA rich diets, as well as the mechanisms of action of oleic acid, for reduction of chronic disease risk factors.

Epidemiological evidence on the CVD risk reduction

An impressive body of evidence from epidemiological studies has demonstrated the healthful effects of the

Mediterranean diet in reducing many risk factors for CVD. The Mediterranean diet contains olive oil as one of its focal components, and many population studies have confirmed the numerous cardio protective abilities of olive oil in promoting health and reduction of the mechanisms involved in the pathogenesis of atherosclerosis; including inflammation, LDL-C oxidation, dyslipidemia and disregulation of glucose, and endothelial dysfunction. In a landmark study of 12,763 adults in seven countries, Keys et al. presented important data that revealed that areas that consumed a Mediterranean diet rich in olive oil, even though higher in total fat (33-40%) led to significantly decreased plasma cholesterol and incidence of CHD. [23] Indeed, in a 15-year follow up led by Keys, data continued to emphasize the strong negative association between a Mediterranean diet, high in monounsaturated fats, and incidence of CHD. Similarly, the Lyon Heart study led by De Lorgeril et al. [24] concluded after 5 years follow-up that people with previous myocardial infarction (MI) who consumed a Mediterranean diet had a 3-fold reduction in second occurrence of cardiac events; 1.24 occurrences in every 100 subjects in the Mediterranean group compared with 4.07 occurrences in control. De Lorgeril et al. [24] and Fung et al. [25] concluded in their 20-year prospective investigation of 78,886 women in the Nurses' Health Study that nurses who were at the highest quintile of Mediterranean diet consumption had the lowest occurrence of CHD when compared with those in the bottom quintile. Alpha-linolenic, eicosapentaenoic, and docosahexaenoic acids, constituents of Mediterranean diet - MUFA are associated with one of the lowest reported incidences of CVD. [26]

Similarly, women in the highest quintile had the lowest occurrence of stroke and CHD mortality compared with those consuming an average American diet, which is high in saturated fats and low in monounsaturated fats. The Medi-RIVAGE study was a prospective evaluation of 212 volunteers in France with risk factors for CVD comparing the effects of a low fat diet and a Mediterranean diet. [27] After 3 month follow-up, those who consumed a Mediterranean diet had 15% reduction in CVD risk factors, whereas only a 9% reduction was seen in subjects consuming a low-fat diet. Recently, the AARP-NIH and ATTICA studies examined the correlation between a Mediterranean diet and CVD risk; the authors observed significant decreases in CVD mortality. [28],[29] The HALE project followed a cohort of 2339 elderly European adults for 10 years to determine the protective effect of a Mediterranean diet, physical activity, smoking cessation, and moderate alcohol consumption on CVD risk reduction. [30] Adherence of a Mediterranean diet was related significant reduction in CVD risk (hazard ratio (HR) =0.77).

Epidemiological evidence and monounsaturated fats

The MUFA content of Mediterranean diets accounts for 15-30% total energy, of which 80% is oleic acid. [23] Similar to the Mediterranean diet, the cardioprotective effects of MUFAs have been well established in numerous epidemiological studies. A systematic review of 507 prospective cohort studies confirmed the significant relationship between a Mediterranean diet and decreased risk of CHD (risk ratio (RR) =0.32) and although many studies have demonstrated beneficial effects of polyunsaturated fats, the distribution of total fats and α-linolenic acid, only the Mediterranean diet has been confirmed as effective through pooled analysis of randomized control trials (RCTs) (n = 94). [22] Additionally, a significant inverse relationship was found between MUFA consumption and CHD risk (RR = 0.80). Conversely, Mente et al. [22] also identified that consumption of foods high in trans fatty acids (TFAs) and glycemic load are attributed to increased CHD risk [RR = 1.32 for both]. Clearly, the evidence associating a Mediterranean diet, high MUFA intake, and CHD is compelling and well supported, and the results from RCTs corresponds with evidence from epidemiological studies, including data earlier reported from the Lyon Heart Study.

A second pooled analysis of 11 cohort studies conducted by Jackobsen et al., [31] did not find a causal link between monounsaturated fat intake and decreased CHD risk. These authors reported that a 5% substitution of PUFAs for SFAs of daily energy intake resulted in a HR of 0.87, supporting a significant link between PUFA intake and decreased CHD risk. However, the authors do identify information bias as a possible limitation to their analysis as they only examined baseline food consumption data, and not subsequent data consumption information. Results of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study revealed that although there was a significant positive relationship between trans-fat consumption and risk of CHD mortality (top quintile, RR = 1.39), there were no positive protective effects of MUFAs. [32] Omega-3 fatty acid intake specifically from fish sources was also significantly related to risk of CVD mortality. Much evidence from cohort studies has supported the positive effects of MUFAs on CVD risk.

The Adventist Health Study analyzed a population of 31,208 Seventh-Day Adventists for 6 years, and those who consumed six or more servings of nuts/week had a significant decrease in CHD events when compared with those consuming nuts less than once/week. [33] The MUFA content of almonds consumed within this population was 49%, whereas 23% of MUFAs were found in walnuts. SFA in almonds and walnuts attributed to 10% and 9% total energy, respectively. These subjects received 13.9% of their oleic acid and 19.3% linolenic acid from nut consumption. In the Omni Heart trial, Appel et al. [34] investigated 164 subjects with hypertension on diets rich in protein, carbohydrates (CHOs), and MUFAs on CVD risk factors. After a 2-year follow-up period, they revealed that a high MUFA diet produced significant decreases of 9.6 mg/dL in triacylglycerols (TAGs) while increasing HDL-C by 1.1 mg/dL. There was a significant association between high MUFA consumption and 10-year decrease in CHD mortality; lowering CHD

risk by 21%. Similarly, a prospective study of 6863 Spanish subjects compared consumption of olive oil and CVD risk. [35] After a 2-year follow up, only 1.7% of subjects presented hypertension in women, and 4.7% in men. In male subjects consuming olive oil amounts greater than 9 g/day, there was reduced incidence of hypertension (odds ratio (OR) = 0.46, 95% confidence interval (CI)), this effect was not seen in women.

It is clear that intake of a Mediterranean diet rich in MUFAs contributes to reducing CVD in both healthy adults and those with hypertension or hypercholesterolemia. Past epidemiological data and prospective cohort trials contribute to demonstrate and emphasize the cardio protective activity of MUFAs.

Dietary monounsaturated fat and plasma lipids

The primary MUFA in the diet are palmitoleic (C16:1, n-9) and oleic (C18:1, n-9) acids, which are found in olive oil, rapeseed oil (canola oil), groundnut oil, and cocoa butter. In addition, humans have the ability to synthesize MUFA from SFA. Conventional wisdom notes that MUFA when substituted for SFA in the diet, effectively lower plasma LDL cholesterol concentrations and could play an important role in dietary fat modifications to lower plasma cholesterol levels.

It is well known that several parameters within the dyslipidemic state contribute to the risk of atherosclerosis and ultimately CVD. Raised plasma LDL-C, TC, and TAG levels all have detrimental effects on the accumulation and formation of atherosclerotic plaques in humans. SFA found in foods of meat and full-fat dairy origin are of particular concern as they raise LDL-C and TC levels, while lowering HDL-C. The National Cholesterol Education Program (NCEP) ATP III guidelines have outlined risk factors, which increased CVD risk over a 10-20 year period; elevated LDL-C remains the strongest primary factor in predicting CVD (Anonymous). Secondary clinical intervention is urged if patients have plasma TAG levels >2.26 mmol/L along with the presence of metabolic syndrome. Indeed, a combination of raised LDL-C levels and low HDL-C levels (<40 mg/dL) is an important clinical indicator of CVD risk and the concomitant need for dietary intervention (NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults). [36]

A meta-analysis conducted by Mozaffarian and Clarke [37] evaluated the effects of trans fatty acids versus diets rich in SFA, MUFA, or PUFA substitution of butter, normally part of the Western Diet with canola oil produced a decrease in the TC/HDL ratio by 0.54, the Apo-B/Apo A1 ratio by 0.010, and lipoprotein A by 1.39 mg/L. These effects, along with clinical markers of inflammation showed that canola substituted into the diet starting at only 2% can produce an overall coronary artery disease (CAD) risk reduction of 21%.

Dietary monounsaturated fat and blood pressure

Dietary interventions for the prevention and treatment of hypertension have increased due to the alarming rates of affected people seeking effective and safe methods of treatment. Recent focus has shifted to the cardiovascular benefits of MUFAs. Indeed, many clinical studies have shown that MUFAs have the distinct ability to lower systolic and diastolic blood pressure in normotensive adults when compared with diets rich in SFA or even compared with diets further supplemented with n-3 PUFAs. [38] Specifically, in a study comparing hypertensive subjects consuming MUFA and PUFA rich diets show that virgin olive oil (VOO) high in oleic acid resulted in significant decreases in total blood pressure. [39] The hypotensive effect of MUFAs also decreased the need of antihypertensive drug therapy by 48%, whereas all subjects on a PUFA rich diet required further drug therapy. In contrast, a study conducted by Mutanen et al. [40] failed to observe hypotensive effects of either MUFA or PUFA rich diets. Additionally, a study of 100 obese subjects with metabolic syndrome was conducted for 5 months; subjects consumed diets of high MUFA or high CHO content. At study cessation, although both groups showed significant reductions in all components of metabolic syndrome, only the diet high in MUFAs produced significantly lower systolic blood pressure as well as heart rate. [41]

The Omni Heart trial was a randomized clinical study of 164 participants that consumed diets with varying dietary fats, and subjects were followed over 2 years to determine their subsequent risk of hypertension. [34] Compared with a high CHO diet, consumption of high protein and MUFA diets produced significant reductions in systolic blood pressure and TAGs. Additionally, consumption of the high MUFA diet also resulted in increases in HDL-C levels. The SUN study cohort of nearly 7000, consumed olive oil and showed similar decreases in the incidence of hypertension, but this effect was seen only in men and not women. [35] Indeed, olive oil in Mediterranean countries is known to contain up to 80% oleic acid content and has potent hypotensive effects. [21]

Degradation of varying oils has been studied for their hypertensive effects. The deleterious end products from the frying process yield polar compounds and polymers. [42] A study of 1226 normotensive and hypertensive adults consuming dietary oils high in MUFAs, PUFAs, or a mixture revealed the use of PUFA rich sunflower oil was directly associated with the risk of hypertension, whereas intake of MUFA rich olive oil was inversely associated. Conversely, a

study cohort of Swedish men were followed-up for 20 years to investigate risk factors for left ventricular hypertrophy (LVH); a 1-standard deviation rise in blood pressure, cholesterol ester proportion of oleic acid, and SFA at age 50 were among the risk factors for LVH 20 years later. [43]

Oleamide (cis-9, 10-octadecenoamide) is a primary fatty acid amide analogue of oleic acid with powerful vasodilatory effects and is involved in regulatory effects of gap junction permeability and communication in vascular and endothelial tissue. [44],[45],[46] This MUFA is in the cis-formation and has an amide group attached. Of particular interest is the ability of the brain to synthesize oleamide utilizing endogenous oleic acid and ammonia. In a murine model, oleamide has been proven to induce vasorelaxation at concentrations of 1.2 μM, and has further been shown to induce vasorelaxation in a concentration-dependent manner (0.1-10 μM) [44] ; however, its antihypertensive potency has yet to be elucidated in human clinical trials. Importantly, oleamide activates endothelial-cell synthesis of nitric oxide (NO) and consequently, its activity is impaired by a NO synthase inhibitor called L-NAME, thereby demonstrating the direct activity of oleamide on NO production. In turn, NO regulates vascular tone and function, promotes vasodilation, inhibits nuclear factor kappa-B (NF-κB) expression, impairs oxidation of LDL-C and hinders the abnormal growth of vascular smooth muscular cells. [47] Conversely, linoleic acid administered in a cell culture decreased the activity of NO synthase (eNOS), an enzyme essential for the synthesis of NO, while also decreasing the amount of MUFA content within the plasma lipid membrane. [48],[49],[50] Additionally, oleamide can act on the endothelium by stimulating Na + and Ca 2+ sensitive K + ion channels through interaction with endothelium-derived hyperpolarizing factors, acting on cardiac excitability, [45],[46] and has activity in both sensory nerves and vascular smooth muscle cells.

2-Hydroxyoleic acid (2-OHOA) is a compound derived from oleic acid. New research has revealed the potent hypotensive activity of 2-OHOA, related to its ability to lower systolic blood pressure. [51],[52],[53] In the presence of hypertension the plasma lipid membrane undergoes structural modifications; alterations to signaling proteins and reduced capability of signal transduction systems, cation transport organization malfunction and impaired Ca 2+ cytosolic control all culminating in loss of blood pressure control. An important class of proteins that helps regulate blood pressure is guanine nucleotide regulatory proteins (G-proteins). These G-proteins in turn aid in the modulation of signal transduction pathways, including the adenylyl cyclise (AC)/cAMP signaling pathway that promotes vascular functions such as vasodilation, vascular permeability, and heart contractibility. In a murine model, 4 hours after administration of 2-OHOA of 10 and 30 mg/kg, systolic blood pressure was lowered by 16 ± 4 mmHg and 18 ± 4 mmHg, respectively. Additionally, rats that received 2-OHOA treatments had increased levels of Gαs protein, 65 ± 14% in cardiac tissue, and 52 ± 12% in aortic tissue, as well as upregulation of Gαq/11 protein by 31 ± 9% in cardiac membranes. In AC signaling, 2-OHOA administration significantly increased cAMP accretion to 20 ± 3% and 76 ± 31% in cardiac and aortic tissues, respectively. Thus, 2-OHOA has powerful and impressive effects on many hypotensive mechanisms involving regulation, modification and control of G-proteins, and cardiac cell signaling pathways to promote vasorelaxation. [54],[55]

Alterations to the plasma lipid membrane structure exist as another beneficial activity of 2-OHOA. Animal studies have confirmed the ability of 2-OHOA to raise the cholesterol and sphingomyelin content while simultaneously decreasing the content of phosphatidylserine-phosphatidylinositol lipids. [52] Repair of nonlamelar H II -phase membranes, necessary for G-protein binding, was also observed by administration of 2-OHOA. [53] Indeed, in a study of spontaneously hypertensive rats, investigators confirmed the acute and chronic blood pressure lowering activity of olive oil to be solely attributed to its oleic acid content. In contrast, soybean oil and elaidic acid, the trans isomer of OA and stearic acid did not exert hypotensive effects.

In further biological activity, 2-OHOA demonstrates the ability to regulate Ca 2+ ion channels in cardiomyocytes, therefore promoting electrical stability, vascular contractibility, and ultimately mediating blood pressure. [56] Due to its remarkable hypotensive effects, there is current investigation into the feasibility and application of 2-OHOA into a pharmaceutical agent for treatment of hypertension and CVD.

There are physiologically important constituents of oleic acid that contribute to improving the plasma lipid profile while simultaneously activating RCT. These crucial derivatives of oleic acid exert their antiatherogenic and cardioprotective effects at a cellular level, acting on both enzymes, transporters and signaling proteins to improve vascular health.

Dietary monounsaturated fat and LDL oxidation

Atherogenesis is initiated with the transport of circulating oxidized lipoproteins, namely LDL-C, into the subendothelial space of the arterial wall. [57] Antioxidants play a fundamental role in the protection of LDL-C from oxidized modification. However, reactive oxygen species can impair native LDL-C, depleting antioxidant stores, initiating the peroxidation of its PUFA stores and the generation of breakdown products, namely reactive aldehydes such as malondialdehyde. [58] The derivatization of the apolipoprotein B-100 lysine residues by these reactive aldehydes

results in the oxidation of LDL-C. [59],[60] Furthermore, scavenger receptors of macrophages have an increased affinity for the uptake of oxidized LDL-C versus native LDL that has not undergone modification. [61],[62],[63] As more oxidized LDL-C is taken up by macrophages on the arterial wall, there is an increase in the generation of foam cells, accumulation of intracellular lipids forming fatty streaks and plaques, and thus accelerating the process of atherosclerosis. [58],[64] Therefore, it is both critical to reduce the quantity of circulating LDL-C, as well as the rate of LDL-C oxidation in the amelioration of atherogenesis.

Oxidation status is commonly measured by lag time, the rate of oxidation, propagation rate, and conjugated diene formation [65] . Lag time is an in vitro method that measures the resistance of LDL-C particles to copper-induced oxidation, thus the time elapsing until the onset of conjugated diene production. The extent of oxidation can be quantified by measuring the amount of conjugated dienes formed. An increase in oxidation and propagation rate is directly correlated with an increase in oxidizability of LDL-C particles.

It has been well documented that qualitative dietary fatty acid intake influences LDL-C susceptibility to oxidation. As previously discussed, diets rich in PUFAs have been considered beneficial in cardiovascular health due to their hypocholesterolemic effects, on the contrary since PUFAs are readily oxidized, they may be contribute to atherogenesis. The majority of evidence supports MUFA rich diets reducing the susceptibility of LDL-C to undergo oxidation versus diets rich in n-6 PUFAs in healthy, [66],[67],[68],[69],[70] overweight, [71] and hypercholesterolemic subjects. [72] Baroni et al. [72] supplemented hypercholesterolemic subjects with either a MUFA rich diet or a PUFA rich diet for 4 weeks. The MUFA rich diet led to an increase in LDL-C phospholipid concentrations of MUFA by 11% and a decrease in PUFA by 10%, thus decreasing both the PUFA/MUFA ratio and the unsaturation index of the LDL-C particle. Furthermore, the PUFA/MUFA ratio was directly correlated with the LDL-C oxidation rate, as well as the oleic content in LDL-C correlating with the lag phase of conjugated diene formation. Other studies have observed similar results reporting that the LDL-C content of oleic acid and linoleic acid being correlated with its susceptibility to oxidation. [68],[70],[73],[74],[75],[76],[77] However, some studies have either observed no difference between dietary MUFA and PUFA intake on lag time, [74],[78],[79] or the rate of oxidation. [71] Schwab et al. [80] reported that when low fat diets providing ~ 30% energy replaced MUFA or PUFA intakes with SFA there was no significant effect on LDL-C oxidation as measured by lag time, however, SFA diet was associated with higher circulating total and LDL-C cholesterol levels. Although SFA are not prone to oxidation, unlike PUFA, when incorporated into LDL phospholipid membrane, it is evident that SFA rich diets lead to an increase in circulating LDL-C and the duration of LDL-C in circulation, which may induce oxidative stress. [81] Furthermore, an increase of circulating LDL-C, as a result of SFA rich diets, is correlated with the quantity of LDL-C flux into the arterial wall. [57],[81]

Additionally, the antioxidant level of the LDL-C particle, commonly measured by vitamin E or coenzyme Q10 content, plays an important role in the resistance of PUFA peroxidation and the defense against oxidation. [82],[83] Thus the antioxidant content of MUFA rich oils may contribute to the protective effects against oxidation. The majority of studies investigating the benefits of MUFA use VOO in their intervention. There is evidence that the polyphenolic components of VOO, primarily oleuropein and hydroxytyrosol, may contribute directly to the reduction in oxLDL. [84],[85],[86],[87] Although VOO is rich in polyphenols other MUFA rich oils have elicited similar effects, with respect to longer lag times and reduction of LDL-C oxidation, as compared with low-fat/high-CHO diets, [88],[89] PUFA rich diets, [68],[71],[90] NCEP Step-1, [73] NCEP Step-2. [75]

The uptake of oxidized LDL-C by macrophages on the arterial wall is the critical step in the initiation of atherosclerosis. Recently, Moreno et al. [81] reported that consumption of MUFA rich diets significantly reduced the uptake of oxidized LDL-C by macrophages. In this study after a wash-in SFA rich diet, 20 healthy young men consumed either a high CHO diet or a high MUFA diet rich in olive oil for 4 weeks using a randomized crossover design. As compared with the SFA rich or high CHO diet, intake of a MUFA rich diet was associated with a significant decrease in LDL-C susceptibility to oxidation, as measured by a decrease in lag phase and an increase in the rate of propagation. Furthermore, intake of the SFA rich diet increased plasma LDL-C levels and the authors reported an inverse relationship between plasma LDL-C cholesterol and lag time. The MUFA diet reduced the macrophage uptake of oxidized LDL-C as compared with the SFA diet, however, there was no difference in oxidized LDL-C uptake by macrophages between the CHO diet and the other two diets. Furthermore, there was a direct relationship between the production of conjugated dienes and the uptake of oxidized LDL-C by macrophage, with the MUFA diet significantly reducing moderately oxidized LDL-C conjugated diene content as compared with SFA or CHO diets. In summary, the majority of evidence favors the beneficial effects of MUFA rich diets, as compared with PUFA or SFA rich diets, to reduce the susceptibility of LDL-C oxidation and these effects are mostly attributed to increasing the unsaturation index of the LDL-C particle, specifically replacing linoleic acid with oleic acid.

The therapeutic benefits of monounsaturated fats in treatment of diabetes mellitus-II

The increase in prevalence of diabetes has reached alarming rates; dietary therapeutic interventions have become a

primary focus for clinical practitioners. MUFAs have gained attention for their ability to increase insulin sensitivity while regulating postprandial glucose levels, minimizing increases in blood TC and LDL-C and promoting elevated HDL-C levels. [91],[92],[93],[94],[95] They also exert potent antiinflammatory and regulatory effects, which have been previously discussed. The American Diabetes Association is currently recommending that 60-70% of total calories in the diet of those affected with DM-II should be obtained from monounsaturated fats and CHOs, emphasizing individualization of macronutrients by a healthcare professional. [96] Minimizing fat intake and reducing body fat help insulin do its job much better. The new approach focuses more attention on MUFA compared with other fats to maintain healthy blood glucose levels. [97],[98]

Insulin resistance

Insulin resistance is characterized as a state in which the body requires additional insulin beyond normal levels to maintain glucostatic control. [99] In DM-II, pancreatic β-cells that secrete insulin to counteract postprandial rises in blood glucose become overwhelmed and as a result, fail to effectively provide the necessary insulin to regulate glucose levels. This is a condition that is mostly preventable; emphasis has been placed on a balanced diet, promoting appropriate dietary fat composition and intake. [100] It has been observed that SFAs raise insulin resistance. [101]

When compared with high CHO (50% CHO) and high SFA (>15% SFA) diets, diets high in MUFAs (>20% MUFA) have been shown to significantly decrease fasting glucose by 3% and insulin by 9.4%, and improve insulin sensitivity by 12.1%. [92] MUFAs have been shown to have direct action on β-cell function and lower insulin resistance in a study of 14 healthy men in a randomized, crossover design. [102] With the incremental substitution of MUFAs for SFAs, direct linear decreases in insulin resistance were observed. Similarly, a study of DM-II subjects comparing the effects of MUFA (25% MUFA) and CHO-rich (50% CHO) diets on postprandial lipids revealed that a MUFA rich diet reduced both Very Low Density Lipo Protein (VLDL) and TC TAG content by 35% and 16%, respectively, compared with a high CHO diet. [103]

A study conducted by Paniagua et al. [104] demonstrated that when compared with CHO-rich diets (65% energy), insulin-resistant subjects consuming a MUFA-rich diet (38% energy; 23% MUFA) had significantly increased fat oxidation rates and decreased abdomen-to-leg adipose ratios, which were initially induced by a CHO rich diet. This has important implications for those at risk for metabolic syndrome. An increase in visceral adiposity promotes insulin resistance and causes a concomitant increase in adipokines, which promote inflammatory activity. [100] Similarly, compared with subjects on a SFA rich diets (38% energy; 23% SFA), subjects on a MUFA rich diet had significantly lower fasting glucose concentrations and increased insulin sensitivity compared with groups on CHO and SFA rich diets. Interestingly, leptin concentrations were lowest for those on a MUFA rich diet. Leptin is a hormone responsible for signaling satiety and subsequent energy expenditure and storage status of adipose tissues to the lateral hypothalamus. [105]

Hyperleptinemia has been associated with obesity and insulin resistance. The regulation of leptin levels is governed also by the concentrations of insulin present in adipocytes. [105] A study conducted by Paniagua et al. [94] revealed insulin-resistant subjects consuming MUFA rich diets displayed significantly higher levels of HDL-C and glucagon like peptide-1 (GLP-1) compared with those on a CHO rich diet, presented decreased fasting serum glucose concentrations compared with a SFA rich diet and finally demonstrated increased insulin sensitivity compared with those on high CHO diets and SFA diets. GLP-1 is another hormone implicated in the balance of energy expenditure versus storage; its release after a meal signals the concomitant rise of insulin levels. GLP-1 can interact on β-cell synthesis and function; thereby restoring insulin sensitivity in treatment of diabetes. [94],[106],[107] These compounds act synergistically to either maintain satiety and energy homeostasis or when overwhelmed, result in insulin resistance, abdominal obesity, and DM-II culminating to the metabolic syndrome condition.

Clearly consumption of a MUFA rich diet improves insulin sensitivity, reduces the hyperglycemic state, promotes β-cell proliferation and favorably mediates plasma lipids. In fact, oleic acid molecules in the cis configuration exert the most potent antiapoptotic effect against β-cells among the MUFAs, whereas SFAs promote apoptosis. [108]

Insulin control of monounsaturated fat in skeletal muscle cells

Another important property of MUFAs is their ability to mediate insulin levels in skeletal muscle cells. [109] Since skeletal muscle cells are one of the primary uptakes sites for insulin-stimulated glucose levels, they are further implicated in insulin resistance. [110] When oleate was compared with palmitate in vitro, oleate inhibited the pro-inflammatory activation of NF-κB and IL-6. Palmitate encouraged these inflammatory pathways and further inhibited of peroxisome proliferator-activated receptor-gamma (PPAR γ)-coactivator 1α while additionally suppressing TAG synthesis. When both fatty acids were co-incubated, oleate preferentially channeled palmitate toward TAG synthesis and promoted β-oxidation through the increase of related genes, decreasing the amount of palmitate added into

diacylglycerols (DAGs), ultimately decreasing inflammation and DAG accumulation. The presence of DAGs in skeletal muscle cells activates protein kinase C-0 (PKC0), which then in turn enhances insulin resistance through a series of enzymatic reactions and promotes inflammation through signaling of NF-κB. [109],[111] The impact of palmitate on their incomplete breakdown into β-oxidation and the citric acid cycle, and subsequently the promotion of acylcartinites into mitochondria may enhance generation and activity of ROS. [109],[112] Thus, oleate is crucial in promoting insulin sensitivity and reversing the deleterious effects of palmitate on insulin resistance in skeletal muscle.

Inflammation and diabetes mellitus-II

Another pro-inflammatory cytokine involved in the progression of insulin resistance is TNF-α. It has been established that adipose tissue secretes TNF-α, and in the presence of obesity, can in turn impair insulin sensitivity and promote insulin resistance. [113] In a murine model, pancreatic cells treated with oleic acid at concentrations of 5 and 10 μM showed significant increases in insulin sensitivity. [114] Cells pretreated with 5 and 10 μM oleic acid reversed the pro-inflammatory effect of TNF-α. Additionally, DM-II rats treated with oleic acid had decreased glucose concentrations compared with control. [114] PPAR-γ gene expression was significantly increased with administration of oleic acid, signifying the regulatory effect of PPAR-γ on inflammation and the concomitant activity of oleic acid on promoting translocation of PPAR-γ to the cellular nucleus for gene regulation. This effect has important implications in the pathogenesis of insulin resistance, which is characterized by a chronic state of inflammation in adipocytes, chiefly induced by activation of TNF-α.

Monounsaturated fats, vascular function and diabetes mellitus-II

However, evidence has been found that oleate incorporated into TAGs can support the growth of insulin-like growth factor-I (IGF-I), a molecule that is abundantly found in arterial lesions of smooth muscle cells in a porcine model, which accelerates the rate of atherosclerosis in the presence of DM-II. [115] In addition, supplementation of MUFAs for patients with DM-II produced significantly decreased flow-mediated dilation rates, compared with further supplementation with 3-5 g/day of Eicosapentaenoic acid/Docohosahexaenoic acid (EPA/DHA). [116] This may correspond to the concomitant rise in plasma TAGs postconsumption of a high MUFA meal. Overall, the FMD rate at 4 hours postprandial increased by 17% irrespective of the diet consumed.

Effects of monounsaturated fats on fat metabolism in diabetes mellitus-II

The chronic rise in free fatty acids contributes to altered fat metabolism; freely circulating fat cannot be effectively incorporated within adipocytes, nor can they easily be lipolyzed for elimination from the body. Consequently, their presence reduces insulin-stimulated glucose uptake into cells and therefore contributes to β-cell exhaustion, hyperglycemia, enhanced VLDL synthesis, lipotoxicity, and ultimately culminating insulin resistance. [108],[117] However, it has been recently noted that the chain length and unsaturation of fatty acids play a major role in promoting lipotoxicity; specifically oleate has been observed to inhibit β-cell exhaustion and can counteract the lipotoxic effects of SFA. [108] A study of healthy subjects ingesting either SFA or MUFAs subsequently participated in oral glucose tolerance and triglyceride tests; data revealed that MUFAs preferentially increased insulin sensitivity and β-cell function when compared with SFAs. [102] An in vitro test of rat adipocytes evaluated differential effects of oleic acid, AA, EPA, DHA, and stearic acid on basal glucose and insulin-stimulated uptake. [111] The authors observed that after 30 minutes of administration, oleic acid along with EPA and DHA increased basal glucose adipocyte uptake by 30-40%, whereas all tested fatty acids with the exception of stearic acid decreased insulin-sensitive glucose uptake. However, a 30-day clinical trial revealed that subjects consuming high oleic acid diets demonstrated significantly high insulin-sensitive glucose uptake when compared with control. [118]

Nonesterified fatty acids and monounsaturated fats in diabetes mellitus-II

Elevated free fatty acids otherwise known as nonesterified fatty acids (NEFAs) have also been implicated in stimulation of macrophage lipoprotein lipase (LPL); the presence of this macrophagic enzyme is key factor in atherosclerotic development within the vascular endothelium and is present in elevated amounts of patients with diabetes. [119],[120] For people with diabetes, circulating levels of NEFAs are significantly higher, which reflects ineffective fat metabolism causing hypertriglyceridemia and increased VLDL production. Additionally, they disrupt the insulin-signaling cascade, a series of events that normally provide glucose transport and incorporation into peripheral cells, all of which further accelerates insulin resistance. NEFAs are also important in regulating basal insulin secretion through a glucose-dependant process. In these ways, NEFAs prohibit effective delivery of glucose into peripheral cells, while simultaneously raising blood NEFA and glucose concentrations, all of which contribute to insulin resistance.

Monounsaturated fats, plasma lipids in diabetes mellitus- II

Eleven DM-II patients were administered either a SFA rich (17%) or MUFA rich (23% MUFA) diet in a randomized crossover design. [121] At study cessation, while postprandial TAG concentrations were quickly elevated with consumption of a MUFA rich diet, these values soon returned to normal levels at 4-6 hours after meal consumption. The amount of TAGs and TCs contained within small, dense VLDLs was significantly lower in the MUFA rich group, with LDL-C levels also significantly decreased. While CM-TAG levels rapidly increased postprandially, there was also a concomitant increase in the Apo B-48 content of CMs during the initial postprandial phase, suggesting that MUFAs exert a swift assembly of CMs in the GIT compared with SFAs. Of particular interest were the significant increases in both LDL and hormone-sensitive lipase (HSL) while subjects consumed the MUFA rich diets. It has been postulated that the oleic acid content of MUFAs up-regulates the activity of HSL and is preferentially handled by adipocytes. [122] Both lipases are insulin sensitive and are implicated in fat metabolism, with HSL specifically responsible for lipolysis within adipocytes. [121] These results suggest the positive effects that MUFAs exert on fat metabolism for subjects with DM-II, both with favorable and rapid modifications to blood lipids and with increased activity of lipases in fat metabolism and concurrent regulation of insulin secretion and control.

Overall, MUFAs can beneficially promote insulin sensitivity, regulate fat metabolism, and attenuate inflammation in those with DM-II. The impressive cluster of effects that MUFAs exert on subjects with DM-II highlights their implications in treatment and prevention of DM-II.

Conclusions

The beneficial or detrimental effects of dietary fats on our health and well-being largely depends on their fatty acid composition. It is therefore important to develop more specific recommendations concerning the dietary intake of different fatty acid groups instead of postulating a general decrease in overall fat consumption. It is still mostly recommended not to exceed a total daily fat intake of 30% of total energy. The major source of dietary fat should be those fats and oils rich in MUFA, while the consumption of products with SFA should be low. Simultaneously, plant-derived foods should be the main component of the daily diet. The health benefits of the traditional Mediterranean diet are indisputable as per the research data available worldwide. It can be adapted to country specific preferences by integrating country specific foods to get maximum health benefits as well as excellent taste.

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