ISSN: 2148-6832

MSD Medical Science and Discovery
February 2015, Vol. 2, No. 1, p:125-32

Review Article Doi: 10.17546/msd.25609

Effects of oleic acid

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Abstract

Content of fatty diet plays a significant role in the development and progression of chronic diseases. Generally, it is accepted that unsaturated fatty acids are beneficial. According to literature review, oleic acid (C18:1n-9) has positive impacts on various tissues in general and has negative impacts rarely. Olive oil composition includes high amount oleic acid. Considering of the effects of oleic acid on the cardiovascular system, it was determined that decreasing of the myocardial infarction rate, platelet aggregation and secretion of TXA2, plus reduce of the systolic blood pressure. LDL cholesterol was decreased. In terms of effects on the liver, while some studies suggest that oleic acid has beneficial effects, unlike other studies proved that exposed to oleic acid of hepatocytes induce ER (endoplasmic reticulum) stress in long - term period. The several studies which were investigating the efficacy of the oleic acid on the tumor tissue proved that OA increased to hepato-tumorigenesis in vivo as a potential. On te other hand, another research showed that oleic acid blocked the action of HER-2 / neu oncogene that led to breast cancer. Although some researchers reported that OA develop neutrophil phagocytic capacity and candidacidal activity, other researchers point out that these fatty acids didn't cause any changes on bactericidal activity and fatty acids caused moderate decreases on phagocytosis and chemotaxis only in extremely high concentrations, and they suppressed to T lymphocytes. Although, most of studies have indicated to beneficial effects of oleic acids, also the adverse effects of oleic acid have been reported in a few studies. This situation requires further researches for detail information about oleic acid

Keywords: Oleic acid, Cancer, Liver, Immune system, Cardiovascular system disease

Introduction

Lipids, in addition to being an important component within the structure of the cell membrane, they also act for storage and transmission of energy. So, they constitute significant part of our diet. Fats obtained from natural sources by diet are composed of a mixture of fatty acids. Most of these fatty acids are included within the structure of triglycerides. (1) Fatty acids are categorized in two groups as saturated fatty acids and unsaturated fatty acids. Both solid and liquid fats contain a mixture of saturated and unsaturated fatty acids. In general, fats obtained from animal products are more saturated while vegetable oils contain unsaturated fatty acids.

Contents of dietary fat play an important role in the development and progression of chronic diseases such as obesity. In general, saturated fatty acids (SFAs) and trans- fatty acids are considered to be harmful while unsaturated fatty acids are considered as beneficial for cardiovascular health in diets. Conventionally unsaturated fatty acids are classified according to their chemical structures as either monounsaturated fatty acids with one double bond (MUFAs) or polyunsaturated fatty acids with more than one double bond (PUFAs). If the first double bond is three carbons from the methyl end, the fatty acid is classified as n-3 fatty acid and if the first double bond is six carbons from the methyl end, the fatty acid is classified as n-6 fatty acid. Most dietary fats contain a part or all of the 18-carbon fatty acids sequence -having both saturated and unsaturated fatty acids- such as stearic acid (C18: 0; SFA), oleic acid (C18: 1n-9; MUFA), linoleic acid (C18: 2n-6, n-6 PUFA) and α-linolenic acid (C18: 3n-3 ; n-3 PUFA). Oleic acid has one double bond in N-9 position, linoleic acid has two double bonds in n-6 and n-9 positions and α-linolenic acid has three double bonds in n-3, n-6 and n-9 positions and these double bonds have cis configuration. Oleic acid, in general, is found in animal oils such as tallow and lard as well as in vegetable oils such as olive oil and sunflower oil and canola oil which have high oleic acids (2). Studies conducted on oleic acid have revealed the fact that oleic acid has positive or negative effects on various tissues.

Received: 16-11-2014, **Accepted** 24-11-2014 **Available Online** 10-01-2015
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Cardiovascular Effects of Oleic Acid

Cardiovascular diseases such as hypertension, aneurysm, thrombosis and MI are responsible for 30% of deaths according to 2005 data of the World Health Organization. Cigarette consumption, low physical activity, obesity and malnutrition constitute the risk factors for cardiovascular diseases. Myocardial infarction rate in Mediterranean countries is lower compared to Northern Europe, USA or Australia (3, 4, 5). Olive oil is major component of the Mediterranean diet and has high oleic acid ratio (3, 6). Hence, US Food and Drug Administration have recommended 23 grams of olive oil per day in 2004 against the risk of coronary heart disease due to MUFAs content (7).

Numerous studies state that oleic acid is effective in prevention of ischemic heart diseases (3,8). It has been shown that oleic acid inhibits platelet aggregation induced by platelet aggregation factor (PAF) as well as the secretion of serotonin. It has been discovered, as a result of the studies which were carried out for understanding of the molecular mechanism of this effect, oleic acid inhibits the aggregation of platelets induced by PAF by reducing the phosphatidylinositide (PIP) and PIP2 levels (3-9). It has been shown in several studies that oleic acid inhibits platelet function, reduces the aggregation of platelets, reduces the secretion of TXA_2, increases thrombocyte membrane oleic acid content significantly and decreases levels of arachidonic acid. The inhibiting effect of oleic acid on platelet function in various ways may be associated with its lowering of the risk of heart diseases as well as the protective role (3, 10).

The beneficial effects of olive oil are related to the high level of oleic acid in the composition of its own (%70-80). This composition of olive oil helps the regulation of lipids in the membrane structure by increasing the oleic acid level in the cell membrane. In this way it leads to signal-dependent G protein control and reduces the blood pressure (3-11). Cardiovascular tissues which are applied to 2-OHOA (hydroxyl oleic acid) in rat's shows the cAMP activation as a response to activation of the Gs-α protein which is thought to increase the expression of Gs-α proteins. Consequently, there is a significant fall in systolic blood pressure. (3).

In 1985, Mattson and Grundy are found that olive oil increases HDL cholesterol which has antiatherogenic function, supports the elimination of LDL cholesterol, and plays a protective rol. Sirtori et al. have suggested in 1986 that olive oil plays a protective role against thrombosis and platelet aggregation in addition to the effects thereof on cholesterol and atherosclerosis. Accordingly, consumption of olive oil in high levels is not harmful since it reduces only LDL cholesterol but not HDL levels (3).

Effects of cardiovascular, hepatic and metabolic parameters of macadamia oil (63% oleic acid, 17% palmitoleic acid) rich in MUFAs(monounsaturated fatty acids), safflower oil rich in n-6 PUFAs (polyunsaturated fatty acids) and flaxseed oil rich in n-3 PUFAs (polyunsaturated fatty acids) have been compared in the study conducted by Poudyal et al. in 2013 (2).

They have determined that the groups which are rich in both oleic acid and alpha linolenic acid reduce weight gain unlike linoleic acid when compared with the control groups. There was reduction in plasma total cholesterol in COA (corn starch + Macadamia oil rich in oleic acid) and HOA (high carbohydrate, high fat + Macadamia oil rich in oleic acid) groups compared to the control groups (2).

Eccentric hypertrophy has been found characterized with preload defined by increase in inner diameter of left ventricle in diastole without change in wall thickness was identified in H group rats fed by a high-carbohydrate and high-fat diet compared to the control group rats (C). Deterioration in systolic function as decreased fractional shortening, increased wall stress, increase in diastolic resistance and decrease both in pressure increase and dP/dt were also observed in H group rats. Furthermore, high diastolic, systolic and stroke volume, and cardiac output were found in H group rats compared to C group rats (2).

There was increase in inner diameter of left ventricle in diastole in COA (corn starch + Macadamia oil rich in oleic acid) and CLA (high corn starch+ rich in linoleic acid) groups with oleic and linoleic acid supplementation. There was increase in inner diameter of left ventricle in systole in all groups except HLA (high carbohydrate, high fat, rich in linoleic acid) group and decreasing left ventricular internal diameter in systole in HLA was compensated by left ventricular posterior wall dimension, left ventricular internal diameter of which has increased. These effects were accompanied by low fractional shortening in the COA and CLA groups in contrast to HLA. Furthermore, diastolic, systolic and stroke volume and cardiac output were significantly higher in CO and CLA group compared to C rats. Diastolic volume, stroke volume and cardiac output remained unchanged in the HOA and HLA groups compared to H group rats while systolic volume increased in the HOA group and decreased in the HLA group. The addition of alpha-linolenic acid has normalized systolic and diastolic left ventricular internal diameter and all the volumes. In addition, systolic blood pressure has been normalized in HOA and HALA (flax seed oil with high volume of oil + rich in α-linolenic acid) groups in contrast to the HLA group (2).

However, oleic acid supplementation has increased the systolic wall stress in COA, compared to the C (corn starch) and H (high carbohydrate,

high fat) group rats and maintained the high wall stress in HOA (2). Wall stress did not change in the CLA group while it decreased in CALA (corn starch + flax seed oil rich in α-linolenic acid), HLA, and HALA groups (2).

Oleic acid has decreased the total plasma cholesterol, however it has not changed plasma triglycerides and non-esterified fatty acids. Oleic or linoleic acid supplementation did not change the left ventricle structure induced by H diet, however both of the fatty acids have caused left ventricular enlargement and subsequently led to impaired function in rats fed with low-fat (C) diet. However, oleic acid supplementation has normalized the systolic blood pressure (2).

It was observed that inflammatory cell infiltration as well as collagen deposition increased in H group rats compared to C group rats after 16 weeks in the histological evaluation of the left ventricle. It was observed that inflammatory situation induced by H diet did not change in oleic acid supplemented HOA group but collagen deposition decreased (2). Inflammatory situation normalized in linoleic acid and alpha-linolenic acid supplemented HLA and HALA groups and collagen growth decreased. Tissue histology was found normal in COA, CLA and CALA rats (2).

Effects on Liver

Decrease was observed in plasma ALT, AST aminotransferase, alkaline phosphatase and creatine kinase activity in the HOA group compared to H group rats in the study of Poudyal et al. in terms of liver structure, functionality and fatty acid composition. There was increase in the hepatic lipid accumulation and inflammatory cell infiltration in H group rats compared to C group rats, and oleic acid supplementation has decreased significantly portal inflammation and macrovesicular steatosis in HALA and HOA rats. Plasma bilirubin concentrations have decreased in both COA and HOA groups (2).

It was revealed in the study of Fuchs et al. conducted in 2011 that OA (oleic acid) has protective features against PA (palmitic acid) which induces toxicity. Both WT (wild type) rats and ATGL KO (adipose triglyceride lipase knock out) rats were stimulated by TM (tunicamisin) to induce ER (endoplasmic reticulum) stress. It was found that by the adjustment of PIK3IP1 (phosphoinositide 3-kinase - inhibitor-1), OA (oleic acid) inhibited PA (palmitic acid) which induces the ER (endoplasmic reticulum) stress. It was seen in ATGL KO rats that OA amount may have a protective function against PA resulting from ER stress. In summary, it can be said that these data has revealed the fact that WT rats exposed to ER stress rats cannot create TG form as a result of the high PA levels and reduced hepatic OA and additionally due to increase of PIK3IP1 (phosphoinositide-3-kinase-inhibitor-1) expression and increase of ER stress in relation with it. On the contrary, it was determined that TM inducing hepatic ER stress in ATGL KO rats inhibited the growth of OA in hepatic TG pool (12).

In the study made by Caviglia et al. (13) it was found that although short-term incubation of hepatocytes with oleic acid stimulated APOB100 (apolipoprotein B100) secretion (13,14,15), long-term and high doses of oleic acid application induced ER (endoplasmic reticulum) and as a result of this it reduced the secretion of APOB100 (apolipoprotein B100) (13,16) and although palmitic acid (PA) triggered the ER stress its effects on apoB100 secretion was uncertain(13,16) and although it was shown that docosahexaenoic acid (DHA) inhibited apoB100 secretion, they made comparison as to apoB100 secretion in McArdle RH7777 (MCA) cells and the effects of OA and PA and DHA on ER stress because effects on the ER stress was not studied (13). OA and PA induced ER stress in high doses and inhibited apoB100 secretion and PA was found to be more because its effect increased synthesis of ceramides. It has been shown that DHA did not stimulate ER stress however it was the strongest inhibitor of apoB100 secretion by stimulating autophagy. These specific effects of each fatty acid have been confirmed by infusing C57BL6J rats. These results have shown that both VLDL and apoB100's increase of liver secretion accompanied hepatic steatosis, however ER stress was reduced and hepatic steatosis was alleviated at the expense of VLDL secretion. In contrast, it was determined that increased autophagy could reduce the secretion of VLDL without causing steatosis. They have concluded that different fatty acids has suppressed APOB100 (apolipoprotein B100) secretion in different ways such as ER stress, ceramide synthesis and autophagy (13). Other studies have shown that apoB100 may undergo degeneration through autophagy which is one of the nonproteosomal ways (13, 17, 18)

In the study carried out by Wu et al. steatosis was induced by incubating the HepG2 cells with oleic acid and it was found that oleic acid caused a significant increase in PPAR gamma expression in a calcium-dependent way. It was also understood that oleic acid regulated the sensitivity of insulin because PTEN (phosphatase and tensin homolog) increasing insulin resistance in hepatic steatosis is regulated by PPAR gamma (19).

Over expression of liver PPAR gamma has increased the liver steatosisin diabetic db/db rats. Finally, it has been proven that OA increases the PPAR gamma expression by the way of GPR40-PLC-calcium and in steatotic situation PPAR gamma increase has proven to have higher role in the regulation of lipid metabolism of and insulin sensitivity (19).

In a study made in 2011, the effects of the high-fat diet rich in oleic acid on rat liver and the role in weight gain were examined (20). When body weight, liver weight and epydidimal fat weight of rat groups was compared with each order, there was no significance difference found among groups. As a result of the biochemical analysis LDH was found to be significantly higher in the 16-week high carbohydrate group while ALT was found to be significantly higher in the 20-week high carbohydrate group. Although fibrosis, inflammation and steatosis findings were observed in all groups in the portal area in the histological examination, a statistically significant difference was not determined (20).

The effect of oleic acid on tumor tissue

Kudo et al. focused on fatty acids as additional pro-tumorigenic factors that contribute to in vivo hepato-tumorigenesis in Tg (transgenic) rats. OA or PA was applied to BNL-CL2 cells to investigate the potential of OA (oleic acid) or PE (palmitic acid) which downregulated the expression of the tumor suppressors containing PTEN (phosphatase and tensin homolog deleted on chromosome 10). It was found that OA suppressed the expression of PTEN, AridB5, Xpo4 (exporting 4 gen) and Dlc1 (deleted in liver cancer-1) while PA did not create such an effect. Moreover, BNL-CL2 cells exposed to OA became significantly more colonized in soft agar. These findings have revealed the fact that OA increases the in vivo tumorigenesis potentially (21).

A study carried out by Mendez has revealed that oleic acid blocked the action of HER-2/neu an oncogene causing cancer which % 30 of patients have breast cancer and 1 or 2 tablespoons of olive oil per day has been recommended to adults (22,23).

The role of oleic acid in the immune system

Effects of oleic acid on neutrophil functions

Numerous studies have evaluated the effect of OA on adhesion of leukocytes. According to some authors, in vitro studies have revealed the fact that micromolar quantities of oleate inhibit expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin and intercellular adhesion molecule-1 (ICAM-1) in endothelial cells (24, 25-29). Other authors have expressed that OA does not have any effect on endothelial cells or human leukocyte adhesion molecule (24, 30). In any case, it has been reported that OA does not have pro-inflammatory effect.

Furthermore, it was has been determined that OA is capable of reducing the inflammatory effects of long chain saturated fatty acids in human aortic endothelial cells, OA caused this situation by inhibiting both of stearic acid-induced ICAM-1 expression and nuclear factor kappa B (NF-KB) phosphorylation which is transcriptional regulator of ICAM-1 (24,31).

In contrast, it has been reported that OA increases the cell surface expression of CD11b and this leads to high affinity state of the integrin. It has been reported that oleic acid causes neutrophil accumulation and neutrophil-endothelial cell adhesion by virtue of a CD11b mediated mechanism (24, 32).

The effect of OA on leukocyte migration has been found only in a few studies. Ferrante et al. have shown that it is possible to inhibit the leukocyte migration, however, this effect has been reported to be far from the effect shown by PUFAs (24, 33).

Contradictory results can be found also in relation with other leukocyte functions. Although some researchers have reported that OA improves the neutrophils' phagocytic capacity and candidacidal activity (24,34,35) other researchers have shown that these fatty acids did not cause any change in the bactericidal activity and only led to a moderate decrease in phagocytosis and chemotaxis in very high concentrations (24,36).

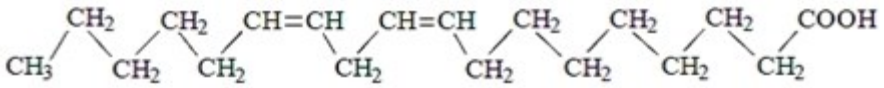
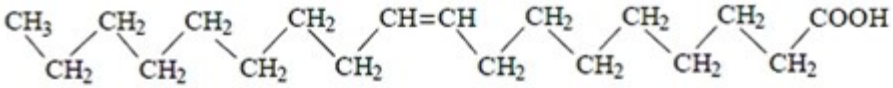
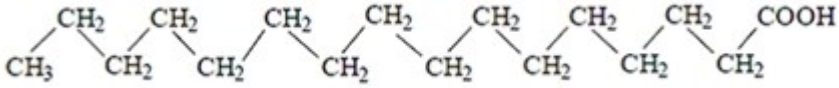
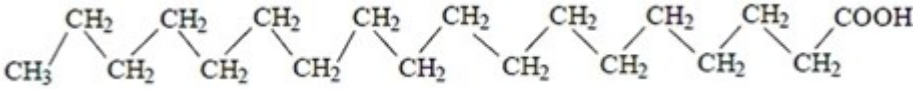
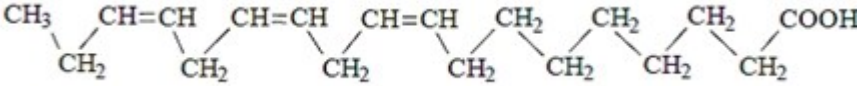
Production of reactive oxygen species (ROS)

Several studies have reported that unsaturated fatty acid effects the ROS production in neutrophils (24,34, 37-46). Nevertheless, fatty acids can develop or inhibit the development of neutrophil activation depending on the experimental conditions. For example, some studies have reported that of C18 fatty acids inhibit ROS production (24, 45). In contrast, it has shown a significant interaction between other fatty acids, and cytokines and it has been shown that superoxide have increased in neutrophils pretreated with TNF remarkably which is generated in response to fatty acids (24, 42). In any case, most of the studies in literature have reported increased ROS production in neutrophils stimulated by unsaturated fatty acids (24).

Some studies have reported that OA changes the Ca^{+2} homeostasis in different immune system cells (24, 47-52).

However, the relationship between OA-induced ROS production and Ca^{+2} mobilizations is complex and its mechanism of action is still not known clearly. Some authors have reported a Ca^{+2} independent mechanism in the background of ROS production (24, 43). In contrast, other studies have shown the connection between these two ways (24, 39, 53).

Table 1: Common Oleic Acid and Formulas.

Linoleic Acid $C_{18}H_{32}O_2$	
Oleic Acid $C_{18}H_{34}O_2$	
Palmitic Acid $C_{16}H_{32}O_2$	
Stearic Acid $C_{18}H_{36}O_2$	
Linolenic Acid $C_{18}H_{30}O_2$	

The effect of oleic acid on T cell proliferation

Verlengia et al. has reported that OA leads to reduction in production of IL-2 and IFN-gama and has in vitro inhibitory effect on proliferation of JurkatT cells (24, 54). It has been confirmed by these findings that minerval which is a synthetic analog of OA inhibits the proliferation of Jurkat cells (24, 55).

Animal studies have reported the inhibition of lymphocyte proliferation in response to T-cell mitogen. It has been shown that lymphocyte proliferation was inhibited in the spleen and the lymph nodes of rats fed on olive oil diet during the weeks inhibited (24, 56, 57). Similarly, it has been found that splenic lymphocyte proliferation was inhibited in rats fed with cashew kernel oil rich in OA compared to rats fed with coconut oil rich diet (24, 58). It has been shown that this effect is due to oleic acid more than the other components in olive oil (24,59). Another study showed that when the dietary levels of OA are increased, proliferation of spleen lymphocytes decrease (24, 60).

Inhibitory effects on NK (Natural Killer) cell proliferation of diet with olive oil have been caused by virtue of oleic acid (24, 61).

Jeffery et al. concluded that inhibitory effects on NK (Natural Killer) cell proliferation of olive oil diet has been arised from OA rather than other components of olive oil (24, 59). Human lymphocytes, jurkat (T lymphocytes) and raji (B lymphocytes) cells show morphological features of apoptosis after being exposed to OA (24, 61, 62). In addition to this Llado et al. have stated for the first time that minerval which is a synthetic OA analogue also induced apoptosis in jurkat T cells (24, 55).

Conclusion

Studies conducted revealed the fact that oleic acid which is present in large amounts in olive oil compositions, have positive effects on human health especially by reducing the systolic blood pressure on the cardiovascular system, inhibiting platelet aggregation, reducing TXA_2 secretion and decreasing serum LDL cholesterol, while some experimental studies reported the fact that some negative effects could also emerge due to increase in the ER stress depending on the dose. Further studies are needed to be carry out because of different results of oleic acid studies such as increased of tumorigenesis in some cancers, inhibited oncogene causing cancer in some cancer types; made anti-inflammatory effect on T cells by affecting the immune system by different ways, and didn't make any change in this activity and even led to decrease of high doses of phagocytosis function.

Financial Support: This research received no specific grant from any funding agency, commercial or not-for-profit sectors

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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