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Original Article

Anti-atherogenic and Synergistic Effect of Decosapentanoic Acid/Linoleic Acid Fatty Acids via Janus Kinase [JAK] Mediate Inhibition of HMG-CoA Reductase in Rats Fed High Fat Diet

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ABSTRACT

Introduction: Atherosclerosis is common CHD caused by accumulation of oxidized LDL-c forming foam cell with macrophage that narrowing blood vessels. It increased risk of CVD. Green vegetables rich with PUFA is important to maintain healthy status. This study investigated the mechanistic pathway mediate combination of Decosapentanoic acid (DPA) and linoleic acid (LA) as anti-atherothengic effect in rats fed high fat diet. **Materials and Methods:** Seventy-five male albino rats were divided into five groups (15 rats each) were fed high fat diet (40% Saturated fat) for 3 months: Group (I): Rats given 10 % DPA. Group (II): Rats given 10 % LA. Group (III): Rats given 10 % DPA+10% LA. Group (IV): Rats treated with atorvastatin (10 mg/kg BW) and Group (v) Untreated. In addition, Group (VI): 15 rats fed normal diet. **Results:** Data obtained showed that, plasma cholesterol and LDL-c levels were highly significant reduced in group III ($p < 0.001$) versus other groups compared with untreated. Level of triglycerides was reduced but still high than normal ($p=0.05$) and atherogenic index. The activity of HMG-CoA reductase was reduced while apo-A, apo-c elevated, JAK was upregulated in combination therapy ($p< 0.001$). The elevated Apo-A, apo-c activate clearing factor and decreased triglycerides. **Conclusion:** It was concluded that, upregulated of JAK by combination therapy mediate inhibition of HMG-CoA reductase that decreased endogenous synthesis of cholesterol and reduced its level in circulation.

Keywords: Omega fatty acids, Janus kinase, HMG-CoA reductase, Atherosclerosis.

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INTRODUCTION

The atherosclerosis being health problem worldwide that increased risk of morbidity and mortality.[1] The reasons may be due to life style, sedation, fast foods rich with saturated fatty acids, genetic or hormonal causes.[2] The key enzyme in cholesterol synthesis is hydroxymethylglutaryl CoA reductase (HMGCoA-R). The management of hypercholesterolemia depends on inhibition of this enzyme. The unsaturated fatty acids found to be less energetics than saturated fatty acids. There are two distinct groups of multi-unsaturated acids which are Decosapentanoic Acid (DPA) and Linoleic Acids (LA).[3] It has been shown that DPA have the ability to reduce the incidence of sudden death and cardiovascular disease. DPA fatty acids are available from fish such as salmon,[4] also linseed oils, nuts, rapeseed, soy are good sources of the fatty acids of the DPA type. These acids reduce the incidence of infections.[5] On the contrary, we find that Amino LA available in most vegetable oils, seeds and meat increase the rates of infections, and the use of DPA fats to address the increase in the blood and nervous tension arthritis Systems.[6] It was reported that, the fatty acid DPA derived from fish oils act though protection from heart disease and coronary arteries. Because of the impact to reduce total cholesterol and reduce the Low-Density Lipoprotein (LDL-c), increasing protein fatty high-density and on the contrary, the fatty acid LA reduces the triglycerides, which is protecting the heart.[7]

It is worth noting the importance of balance between accessible from the main two basic unsaturated acids and not according to the level of acid on each unit, because any deviation from the ratio between them could affect the quality and strength of Eicosanoids generated from them.[8] The resulting change in the kinds of meals to the change in the balance of affordable acid (n-3, n-6) tissue.

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Therefore, (WHO) has recommended meals rich in fish oils from 3-2 meal every week so that these foods reduce the level of blood triglycerides and reduce fatal heart diseases and thus highlights the importance to the health of the heart and vascular system.[9]

Previous study[10] indicated that fat diet had varying effects on serum triglycerides in the serum where the highest level of tri-Glycerides when rich in saturated fat in the diet,[10] the lowest level in containing non-saturated fats and also referred to elevated in the level of cholesterol in the diet increased the content of saturated fatty acids.[11] There is a link between the atherogenic index and blood cholesterol. The preventive role of the multi-unsaturated fatty acids in the protection from heart disease.[12] The rational of current study was to investigate the role of DPA or LA alone or combined together in inhibition of HMGOA reductase and modulation of apo-proteins as a target for antiatherogenic activity.

MATERIALS AND METHODS

Animals

This research was conducted n in the Unit of the animal house at King Fahad Center for Medical Research, King Abdul Aziz University in Jeddah according to ethical committee of King Abdulaziz University. Ninety male albino rats ranging weigh of between 70±5 gm were used in this study, housed in plastic cages at 24ºC, relative humidity is 50-60% with the following observation lighting between darkness and light, has been adapting for a period of one weeks before the start of experiment. Seventy-five rats were fed high fat diet (40% fats) for 3 months and divided into five groups (15 rats each); Group (I): Rats treated with 10% LA. Group (II): Rats treated with 10% DPA. Group (III): Rats treated with 10% DPA+10% LA. Group (IV): Rats treated with atorvastatin (10 mg/kg orally). Group (V): Rats not treated. The other 15 rats were fed normal diet as normal control. These rats were fed for 3 months. Fasting rats for 14 hr, blood will be withdrawn on Lithium heparin, then liver separated and stored at -80ºC.

Methods

Plasma was subjected for assay of t. cholesterol, LDL-c, HDL-c, LDL-c triglyceride and atherogenic index. The activity of HMGOA reductase, by ELISA kit from ABCam # ab204701. (Apo-A, Apo-c) from ELAbScience (E-EL-R3029), Lipoprotein lipase activity and *Janus* kinase [JAK] were determined by ELISA kit from My BioSource cat # MBS3808124.

Statistical Analysis

The data will be statistically analyzed using SPSS version 20. A $p<0.05$ was considered as statistically significant.

RESULTS

Data analysis and statistically compared between treated and untreated with unsaturated FA, the changes in overall lipid profile (T. cholesterol, LDL-c, HDL-c, TG). Rats fed high fat diet for 3 months showed a significant elevation in the levels of TG, T. cholesterol, LDL-c and a significant reduction in HDL-c compared with control (Figure 1). Decline at level of ($p<0.001$) for each of cholesterol and LDL-c and increased HDL-c when compared with the rest of groups experimental. However, level of triglycerides was reduced but not significant at the level of ($p=0.05$) only in the group, which fed combined DPA and LA when compared with other groups. Data in (Figure 2) referred the levels of JAK that upregulated in rats fed combined DPA and LA compared with other studied groups ($p<0.05$). The combined effect is effective than individual ones DPA but not significant, however individual is effective compared with untreated group.

The levels of Apo-A, Apo-c and HMGCo-A reductase levels were presented in (Figure 3) showed that, rats fed high diet downregulated ApoA and C and upregulation of HMGCo-Rase ($p<0.05$). Treatment with DPA or LA or combined reversed the expression, upregulation of APoA and ApoC and downregulation of HMGCo-Rase ($p<0.05$) compared with untreated.

DISCUSSION

Cardiac and vascular diseases are the most important causes of death at the global level they constitute about 44% of the deaths in the United States of America.[13] It was reported that, an increase of the death rate from cardiovascular disease, vascular arteries, heart attacks and stroke.[14] The reason for the increasing incidence of diseases of the heart and vascular is due to the change in the pattern and quantity of food, in addition to doubling the fats quadrupled during this time period.[15] Knowing the family history, age and also gender (male or female) can be predicted for a way to the spread of diseases of the heart and arteries. It has been found spreading in more men than women in addition to the pattern of life. But to maintain normal weight, exercise and stay away from the increase in the consumption of fats could prevent cardiovascular diseases. The nutritional factors most closely increase risk as increased consumption of high amounts of fat.[16]

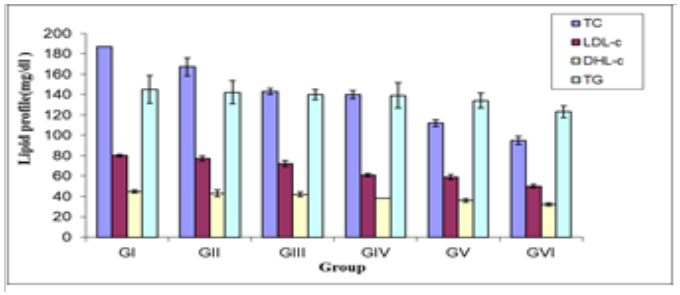

Figure 1: Comparison of the change in the level of total cholesterol, HDL-c, LDL-c and triglycerides in all groups (Mean±SE).

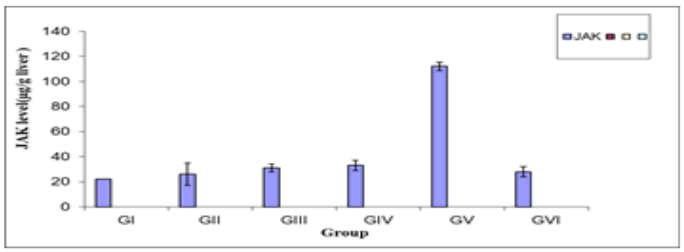

Figure 2: Level of JAK in all studied groups (Mean±SE).

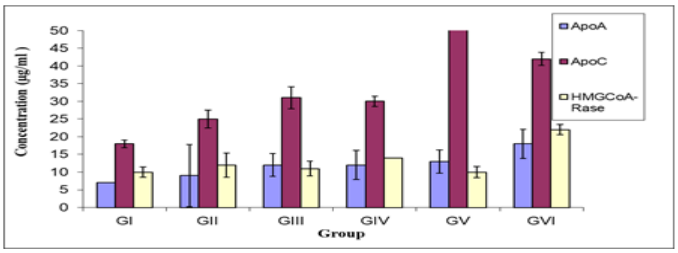

Figure 3: levels of ApoA, ApoC and HMGCo-Rase in all studied groups (Mean±SE).

There are two distinct groups of PUFA which are Omega-3 (n-3) and Omega-6 (n-6). These fatty acids cannot be converted into each other, the group of Omega-6 produces acid from Linoleic Acid, which contains two of the bilateral bonds, and a group omega-3 include Alpha-Linolenic Acid, which contains three of the bilateral bonds, which could not be formed human body, and must be supplied the body out through meals, and called on those two acids, basic acids.[17] It was reported that, omega-3 derived from fish oils protect from heart disease and coronary arteries by elevation HDL-c and reduced LDL-c. In addition it reduced the proportion of total cholesterol and reduce the proportion of fatty protein low-density, increasing protein fatty high-density and on the contrary, the fatty acid Omega-6 works reversely to fatty acids Omega-3.The action is mediated by elevation of Apo –a that a component of lipoproteins to avoid accumulation in blood. Apo-C activate lipoprotein lipase that degrade TG of chylomicron v-LDL to avoid hyperlipidemia.

Hence, we can deduce that the most effective types of oils used in the prevention of high cholesterol was fish oil-rich Omega-3 fatty acids This is consistent with the study of,[18] that depends basically on the fish oils which contains the fatty acids n-3 lead to the prevention of cholesterol from developing inside the blood serum, promoting human health for reducing the risk of heart and circulatory system disease incidence, which comes second in the prevention of a rise in the rate of cholesterol from developing in the blood serum of a mixture of n-3 and n-6 has a moderate impact in reducing the proportion of cholesterol and this is what referred to as the study of Wang *et al*,[19] who reported that, new lipid-lowering drugs, which are more effective in the prevention and therapeutic intervention of CHD that is the major cause of human death and disability worldwide The current study confirmed that the best result in the prevention and protection of the rise in LDL was the use of n-3.

HMGCo-Rase are the rate limiting enzyme in cholesterol synthesis. It was found that, combination of n2/n6 upregulate JAK protein that mediates inhibition of HMGCo-Rase and reduced cholesterol level. It was indicated that, the fatty acid n-3 reduces fat in the blood serum by reducing the oxidation of fatty acids and reducing the internal production in the liver and on the contrary, fatty acids n-6 of sesame oil was only in the most high internal affairs, while the balance between the fatty acid n-6 and n-3 to occupy the second rank in reducing LDL. The preventive role of the PUFA in the protection from heart disease, via prevention of blood platelets and the formation of a blood clot associated with vigor and vitality of the heart muscle fibers that have been severely affected by the regulations of food containing fats It is concluded and supports and strengthens that the fatty acid n-6, LA, n-3, EPA and DHA, LNA collectively protect the body from the risk of heart disease and find that the fatty acid LA, which regulates LDL-c and thus reduces the production, so it is important to address all these fatty acids combined.

CONCLUSION

It was concluded that, upregulated of JAK by combination therapy mediate inhibition of HMG-CoA reductase that decreased endogenous synthesis of cholesterol and reduced its level in circulation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

JAK: Janus kinase; **CHD:** Coronary heart disease; **DPA:** Decosapentanoic acid; **CVD:** Cardiovascular disease; **PUFA:** Polyunsaturated fatty acids; **LA:** Linoleic acid; **HMGCoA-R:** Hydroxymethylglutaryl CoA reductase.

SUMMARY

It was found that, combination of n2/n6 upregulate JAK protein that mediate inhibition of HMGCo-Rase and reduced cholesterol level. It was indicated that, the fatty acid n-3 reduces fat in the blood serum by reducing the oxidation of fatty acids and reducing the internal production in the liver and on the contrary, fatty

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