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The Effect of Omega-3 Fatty Acids on Hypertriglyceridemia: A Review

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Abbreviations: FHTG: Familial hypertriglyceridemia; FCH: Familial Combined Hyperlipidemia, systemic lupus erythematosus, CVD: Cardiovascular Disease, SRBP-1c: Sterol Receptor Binding Protein-1c; TRLP: Triglyceride-Rich-Lipoprotein; LDL-C: Low-Density Lipoprotein Cholesterol; LPL: Lipoprotein Lipase

ABSTRACT

Hypertriglyceridemia is a common problem in adults in the developed world. It is associated with increased levels of triglycerides within the blood, which subsequently promote the development of other diseases such as cardiovascular disease and pancreatitis. Triglycerides are mostly consumed through the diet and act as a source of energy in between meals. However, the levels of triglycerides increase proportionally with the number of calories consumed. This only leads to a problem if the total daily energy expenditure is exceeded. Additionally, the type of macronutrients taken in through the diet has a direct influence on having an increased level of triglycerides, as for instance, high carbohydrate intake has been associated with an increased plasma triglyceride level. If the levels of the triglycerides in the blood rise above 150 mg/dL, it is considered as hypertriglyceridemia. Increasing numbers of triglycerides can have multiple underlying causes, which can be divided into primary and secondary causes. Primary causes include genetic predispositions for such disorders as well as genetic syndromes like Familial hypertriglyceridemia (FHTG), Lipoprotein lipase (LPL) deficiency as well as apolipoprotein C-II (apoC2) deficiency.

Moreover, secondary causes include diseases like diabetes mellitus or Hypothyroidism, medications including corticosteroids and beta-blockers. Additionally, an unhealthy lifestyle is also considered a secondary cause of hypertriglyceridemia. By way of example, the American diet poses the highest risk for the development of the disease as it includes the highest consumption of fat compared to others. Treatment of hypertriglyceridemia consists of omega-3 fatty acids among other things. Omega-3 can be derived from oily fish and fish oil and has hypolipidemic effects on hypertriglyceridemic patients, however, the mechanism is not fully understood. Nevertheless, omega-3 can suppress hepatic lipogenesis, upregulate fatty acid oxidation in liver and skeletal muscle and inhibit enzymes involved in triglyceride synthesis. Therefore, it can decrease the number of triglycerides circulating in the body, thus having a positive effect on our overall health.

Introduction

Triglycerides (TGs) are lipids that consist of three fatty acid chains as well as one molecule of glycerol. They are normally stored in adipose tissue but can be transported in the blood with the help of certain lipoproteins, these lipoproteins are essential since TGs can't move around alone due to their hydrophobic nature [1]. Once they are needed, they can be released and act as a source of energy for various tissues [1]. However, if there is constantly an excess of calories consumed with regards to the calories expended, the triglyceride levels can rise above the normal value of 150 mg/dL [2]. High triglyceride levels are becoming an increasingly common problem in developed countries, like the United States of America, thus displaying a major global health problem since they are associated with an increased risk of cardiovascular disease and severe pancreatitis [3]. If these levels rise above 150ml/dL, it is described

as Hypertriglyceridemia. The disease affects approximately 25% of the population of the United States [4] and occurs in approximately 10% of men older than 30 and 10% of women older than 60 years [5]. The severity of the disease is characterized by the levels of TGs in the blood. Mild hypertriglyceridemia is described as ranging from 150-199mg/dL, moderate Hypertriglyceridemia ranges from 200-499mg/dL while severe Hypertriglyceridemia is described as ranging from 1000-1999 mg/dL.

Moreover, very severe hypertriglyceridemia is defined as having a Blood triglyceride concentration of above 2000mg/dL [1]. Primary causes for Hypertriglyceridemia include genetic syndromes, such as rare syndromes like Lipoprotein lipase (LPL) deficiency, Apolipoprotein C-II (apoC2) deficiency, and more common syndromes like Familial hypertriglyceridemia (FHTG), Familial combined hyperlipidemia (FCHL), and metabolic syndrome. Furthermore, Diet is another primary cause for Hypertriglyceridemia. Diets that put people at risk for Hypertriglyceridemia include an excess of alcohol and a positive-energy balanced diet with saturated fat or a high glycemic index [1]. Secondary causes include diseases such as hypothyroidism, diabetes mellitus, obesity, as well as Medications like Beta-blockers, Thiazides, Corticosteroids. The disease is treated through lifestyle changes, reduction of body weight or supplementation with omega 3 fatty acids [3]. Omega 3 fatty acids are essential fatty acids, which means that they can't be produced by the body. The three main omega 3s are Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) as well as Alpha-linolenic acid (ALA) [6]. However, only the long-chain omega-3 fatty acids, EPA and DHA can be used as a treatment for hypertriglyceridemia because they decrease the triglyceride levels in the blood by decreasing the synthesis & secretion of them [3].

Current Status of Knowledge

Hypertriglyceridemia

HYPERTRIGLYCERIDEMIA refers to an elevated level of triglycerides in the blood plasma, a condition that increases the risk of coronary artery disease (the narrowing or blockage of the coronary arteries, usually caused by atherosclerosis a result of the buildup of fatty deposits and cholesterol ultimately forming plaques that compromise the available diameter of the arteries lumen resulting in a blockage of blood supply to a region of the heart and this will result in myocardial infarction) [7]. The triglycerides found in our bloodstream are a mixture of triglycerides that have been obtained from the diet and those produced in the body to provide an energy source. Hypertriglyceridemia is habitually caused or worsened by factors such as obesity, unwell controlled diabetes, and an inactive lifestyle [8]. However, triglycerides are a vital part of the blood as they are required in the blood to serve as a source of energy, only in excess, they increase the risk of heart disease, stroke, and other health issues [9].

Triglycerides and their Effect on Cardiovascular Disease

Triglycerides themselves do not directly cause the fatty deposits that accumulate in atherosclerosis, but the cholesterol inside triglyceride-rich particles called very-low-density lipoproteins may add to the formation of plaques. In many cases, people with hypertriglyceridemia have other lipid disorders or risk factors associated with heart disease and stroke, including obesity and metabolic syndrome [9]. After consumption and absorption of excess carbohydrates and fat, they are stored in the body in the form of triglycerides within the adipose tissue. In between meals, certain hormones can release triglycerides for energy. If regularly more calories are consumed than needed for everyday life, a high blood triglyceride level will be developed. Whether or not a person's triglyceride level falls within a healthy range can be ascertained using a simple blood test. The levels of triglyceride that is considered normal, is below a specific value (the lower quartile) (150 mg/dL). Whereas, middle quartile ranges from (150 to 199 mg/dL), upper quartile from (200 to 499 mg/dL) and the uppermost quartile is (500 mg/dL or above). All levels above 150mg/dL are associated with the development of hypertriglyceridemia [10,11].

Reasons for the Development of Hypertriglyceridemia

Hypertriglyceridemia can have a variety of causes, including genetic predispositions, obesity as well as certain medications. These causes can be divided into primary and secondary causes [1]. However, most frequently a primary cause is present in combination with one or more secondary factors, which determine the severity of the disease [12]. Primary factors include Genetic syndromes that present as Chylomicronemia [1]. These syndromes are characterized by their lack of the ability to break down lipids correctly, leading to their build-up in the blood [13]. Examples include Lipoprotein lipase (LPL) deficiency, Apolipoprotein C-II (apoC2) deficiency as well as Dysbetalipoproteinemia. Other genetic syndromes that contribute to high TG levels in the blood include Familial Hypertriglyceridemia (FHTG), characterized by the overproduction of hepatic VLDL as well as Familial combined hyperlipidemia (FCHL) and genetic susceptibility for the Metabolic syndrome [1]. Furthermore, a primary cause is an unhealthy diet like excess consumption of alcohol, and overconsumption of calories in relation to calories expended. Secondary causes include diseases like Hypothyroidism, poorly controlled Diabetes mellitus, central obesity as well as autoimmune disorders like systemic lupus erythematosus (SLE). Medications are additionally considered to be a secondary cause of hypertriglyceridemia. High triglyceride promoting medications include Beta-blockers, thiazides, corticosteroids as well as many others [1]. Additionally, pregnancy can also cause an increase in TG levels [1].

The Symptoms of Hypertriglyceridemia

Hypertriglyceridemia doesn't typically present with symptoms

and until it is considered as severe Hypertriglyceridemia with values above 1000 mg/dL. However, if symptoms are present, they include gastrointestinal pain, difficulty breathing, memory loss and Dementia. If the patient has already developed diseases associated with Hypertriglyceridemia, like pancreatitis, symptoms include severe abdominal pain, nausea, vomiting, fever as well as a loss of appetite. Most notably is the increased incidence of cardiovascular disease with patients of increased lipid levels in the plasma [14].

Different Types of Diets and Risk of Hypertriglyceridemia

The diet has a direct effect on the levels of cholesterol and triglyceride found in the bloodstream. Subsequently, the amount of fat consumed through the diet is proportional to the risk of developing Hypertriglyceridemia. Some examples of common diets are the American, Mediterranean, and Asian diets [15]. The American diet has the highest percentage of fat consumed. The typical American diet is about 2,200 calories per day, with 30% of calories from carbohydrates, 15% protein, and 55% fat. In comparison, the Mediterranean diet consists of 1500-1800 calories with about 50% of the calories coming from protein and 25% from carbohydrates and 25% from fat. The typical Asian diet has about 1200-1500 calories with about 40% of the calories from protein and 55% carbohydrates and 5% fat. Considering the above-mentioned diets, it can be concluded that the diet that presents the least risk of the development of hypertriglyceridemia when considering the fat intake, is the Asian because of the low percentage of fat. Since the American diet has the highest amount of fat consumed, it can be presumed that it is associated with the highest risk of the development of Hypertriglyceridemia, and therefore associated with a high incidence rate of cardiovascular disease. However, another important value to consider is the amount of carbohydrates consumed in the diet as an increased intake has been shown to be associated with an increased triglyceride level in the blood [16]. Taking this into consideration shows that the Asian diet also presents an increased risk of the development of hypertriglyceridemia as it has a carbohydrate consumption of 55%. When considering both the fat and carbohydrate intake, it can be concluded that the Mediterranean diet is associated with the lowest risk of developing hypertriglyceridemia as it has a moderate intake of both fat and carbohydrates compared to the high intakes in the Asian and American diet [16].

Clinical Relevance

In severe hypertriglyceridemia, the administration of TG-lowering drugs to reduce the risk of chylomicronemia is necessary to avoid the development of pancreatitis. When levels exceed (1000 mg/dL) patients are at a high risk of developing complications related to cardiovascular disease (CVD) [17]. In these patients, the chylomicrons are now chylomicron remnants (a TG rich lipoprotein that is extremely small), or other atherogenic particles that will result in heart disease, myocardial infarction and mortality in both men and women [18]. These particles can enter the arterial wall and become trapped [19]. These ultra-low-density lipoproteins are more readily taken up by macrophages resulting in the formation of foam cells, a type of cell that can form plaques leading to atherosclerosis causing a stroke or a heart attack [20]. Foam cells also trigger an inflammatory response and necrosis through TG hydrolysis that results in the release of free fatty acids (FFA) and monoacylglycerols [20].

Effect of Omega-3-Fatty Acids on Hypertriglyceridemia

The Supplementation of omega-3 fatty acids and its long-chain fatty acids called Docosahexaenoic acid as well as Eicosapentaenoic acid have been shown to have hypolipidemic effects in hypertriglyceridemia patients. However, the mechanism of the effects of omega-3-fatty acids in humans on hypertriglyceridemia has not yet been clarified [21].

Effect of Omega-3 Fatty Acids in the Human Body

Studies have shown, that a sterol receptor binding protein-1c (SREBP-1c) functions as a main genetic switch that controls lipogenesis and also regulates ≥ 4 metabolic nuclear receptors such as the liver X receptor, the hepatocyte nuclear factor-4a (HNF-4a), the farnesol X receptor and the peroxisome proliferator-activated receptors (PPARs) [22].The effects of omega-3 fatty acids (O3FA) on Triglyceride levels are hypotriglyceridemic. Several mechanisms have been proposed. O3FA can reduce levels of SREBP-1c and therefore can suppress hepatic lipogenesis resulting in less cholesterol-, fatty acids-, Triglyceride- synthesizing enzymes being expressed [22]. In addition to that, it activates Peroxisome-Proliferator-Activated-Receptor (PPAR) which is followed by an upregulation of fatty oxidation in the liver and skeletal muscle which in turn leads to a less available substrate for TG (triglyceride) and VLDL (very-low-density-lipoproteins) synthesis [22]. Correlated to that, another effect of O3FA is the inhibition of key enzymes like phosphatidic acid phosphatase and diacylglycerol acyltransferase which are involved in hepatic TG Synthesis [22]. Furthermore, it down-regulates Hepatocyte-Nuclear-Factor 4a (HNF-4a) which then is followed by an enhanced flux of glucose to glycogen. Lastly, they increase the expression of Lipoprotein Lipase which is a key component in Triglyceride-Rich-Lipoprotein (TRL) biosynthetic pathways resulting in increased TG removal from circulating VLDL and chylomicron particles [22]. Research has also shown that the components of O3FA, EPA (Eicosapentaenoic acid) and DHA (Docosahexaenoic acid), both reduce TG. However, DHA reduction of TG is greater as well as the increase in low-density lipoprotein cholesterol (LDL-C) compared to EPA. Additionally, DHA raises high-density lipoprotein cholesterol (HDL-C) which isn't the case for EPA [23-25].

Omega 3 - carboxylic acids (O3CA) which are found in the form of polyunsaturated free fatty acids, have been shown to have en-

hanced bioavailability in the treatment of dyslipidemia [26]. Several notable effects of O3CA have been found. For instance, O3CA can reduce apolipoprotein CIII levels (ApoCIII). The uptake of the plasma proteins VLDL, IDL and LDL is influenced by an inhibiting receptor-mediated uptake into the liver. This mechanism is regulated by ApoC-III.Furthermore, ApoC-III enhances hepatic assembly as well as the secretion of VLDL. A VLDL containing ApoC-III is broken down to LDL which has a slower clearance from plasma [27]. Moreover, ApoC-III inhibits the uptake of triglyceride-rich lipoproteins. Additionally, ApoC-III inhibits LPL which hydrolyzes TRL, VLDL, and Chylomicrons [28]. People suffering from hypertriglyceridemia usually have an overproduction of ApoC-III [28].

Supplementation of Omega-3 Fatty Acids on Hypertriglyceridemia

Based on the approval of the United States Food and Drug Administration omega-3 fatty acids can be used as a treatment for very high triglyceride levels. It has been suggested that 2-4 g/day of the total EPA and DHA dose recommended to lower triglyceride levels. If triglyceride levels above 500 mg/dl it is suggested to take in 4 g/day which leads to a reduction of triglyceride levels of ≥30% [29]. In addition to that, VLDL-C levels have been reduced by more than 50% whereas LDL-C, dependent on the baseline triglyceride level, may rise. Therapy with EPA and DHA on hypertriglyceridemia should be under a physician's care as stated by the American Heart Association. It has been shown that supplementation with omega-3 fatty acids and O3FA taken from marine or EPA/DHA-enriched food sources both have an effect in lowering TG-levels [30].

Sources of Omega-3 Fatty Acids

Diet

In a clinical study that tested the hypothesis that oil-rich fish can improve cardiovascular health. 48 non-obese and relatively healthy individuals, 16 men and 32 females, were instructed to maintain their usual dietary habits and physical activities over a time span of 4 weeks. The diet was then altered to include 125g of salmon (5.4g of n-3 PUFA) for another duration of 4 weeks. Fasting blood samples and Blood pressure, as well as body composition, were collected to compare the results. The results obtained before the dietary intervention: TGs - 83, Total-C - 167, LDL-C - 92) [30]. Blood pressure reduced by 4%, TGs were reduced by 15%, LDL-C reduced by 7%, and HDL-C was elevated by 5% [31].

Supplementation

A substitute for omega-3 intake besides dietary consumption is supplementation. Omega-3 is used in the treatment of patients with hypertriglyceridemia. These supplements must be paired with Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) to improve endothelial function and reduce biomarkers that cause platelet activation [32]. Although supplementation has shown to improve cardiovascular health a controlled study using a supplement containing DHA and no EPA was found to increase plasma levels of LDL and HDL in the plasma [33]. EPA has been shown to reduce hypertriglyceridemia in CVD patients although further research must be presented [34].

Conclusion

Hypertriglyceridemia, as well as its related disorders, are a big issue our developed world is facing. Genetic causes, like Lipoprotein lipase (LPL) deficiency as well as other factors such as an unhealthy diet, hypothyroidism and diabetes mellitus can ultimately lead to the development of hypertriglyceridemia. The disease is categorized according to the amounts of triglycerides in the blood. An increased number of TGs is associated with worsening of the disease and increased likelihood of developing diseases associated with hypertriglyceridemia, such as cardiovascular disease or acute pancreatitis. Diet is a risk factor for the development of the disease. Certain diets, such as the Asian and the American can be disease-promoting while others, like the Mediterranean, are not associated with an increased risk of developing hypertriglyceridemia. An omega-3 rich diet can decrease the potential risk and can be administered as a complementary drug in combination with other TG-lowering drugs. The importance of the consumption of omega-3 fatty acids, should therefore be conveyed to everyone. People must also be educated about the dangers of obesity. Understanding these consequences is critical in the prevention of obesity-related diseases in the developed world. Furthermore, the importance of a well-balanced diet should be emphasized to everyone in order to further promote overall well-being.

Conflict of Interest

The authors declare that they have no conflict of interest.

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