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Research Article

Omega-3 Fish Oils and Insulin Resistance

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Abstract

n-3 fatty acids affect glucose homeostasis and insulin action is clinically relevant. sufferers who have diabetes or who're insulin resistant may be requested to complement their weight-reduction plan with both fish or n-3 fish oils for several motives; i.e., to treat hypertriglyceridemia, to lessen the risk for atherosclerosis, or maybe to prevent diabetes mellitus.{1-2}.' but, some studies show that n-3 fish oils may also have damaging outcomes on glycemic manipulate.{3-4}, therefore, it is vital to evaluate cautiously our cutting-edge expertise about the effects of n-3 fish oils on diabetes mellitus. Glucose homeostasis is completed via sensitive stability of pancreatic insulin secretion, hepatic glucose manufacturing, and peripheral glucose usage. A trade-in for any of these may be compensated for using an alteration in some other. For example, impaired insulin motion in peripheral tissues may be compensated by increased pancreatic insulin secretion and hyperinsulinemia. During assessment, improvement in peripheral insulin movement may additionally reduce pancreatic insulin secretion.

The effects of n-3 fish oil on glucose homeostasis have been studied at numerous levels. Their overall impact on glycemic control is classified by measuring blood glucose, glycosylated hemoglobin (Hgb A, C) tiers, and urine glucose excretion. Secretion of insulin from the pancreas is determined by measuring insulin and C-peptide responses to the management of oral or intravenous glucose, combined meals, and by using the hyperglycemic insulin clamp technique. Hepatic glucose production and peripheral insulin movement were assessed using the euglycemic clamp method and the simultaneous use of radioisotopes.

Keywords: Fish oil; Insulin sensitivity; Omega-3 polyunsaturated fatty acids; Meta-analysis

Introduction

Recently, ethyl esters of EPA and DHA have grown to be had for the remedy of hyperglycemic criteria. on account that hypertriglyceridemia is the maximum common lipid abnormality related to diabetes mellitus and a vital component of the insulin-resistance syndrome, secure and effective use of n-3 ethyl esters has been evaluated. In a massive, multicenter observation by Sirtori et al. {5}, 203 patients with type 2 diabetes had been treated with n-3 ethyl esters, while 21 1 acquired the placebo oleic acid ethyl ester. There was no exchange of fasting plasma glucose, Hg B A, C, or insulin tiers.

This takes a look at additionally included 103 patients with impaired glucose tolerance. Of these, 52 were randomized to obtain three ethyl esters. Although glucose tolerance checks were repeated after treatment, there was no alternate inside the total region beneath the oral glucose tolerance curve. Most studies have tested the effects of local fish oil extracts. Toft and colleagues {6} in comparing the consequences of corn oil and n-three fish oils in 78 people with non-diabetic high blood pressure and found no change in fasting plasma glucose, HgB AIC, or insulin ranges. Sheehan and colleagues{7} investigated the results of fish oils in 15 sufferers with non-insulin-based diabetes and showed that there was no alternate within the fasting or postprandial glucose, fasting insulin, or HgB A, C. Earlier research in topics with diabetes supplied variable effects possibly due to the variations in the preliminary glycemic manipulate or the dose of n-3 fish oil supplementation .continuously, outcomes of fish oils have been always reversible after the discontinuation of n-3 fish oil 3,4 We reported that fish oil supplementation transiently elevated HgB A, C in sufferers with kind 2 diabetes{8} however, this turned into reversed regardless of continuation of fish oil remedy. Connor and colleagues {9} in comparing the consequences of fish oil supplementation with olive oil placebo in 16 patients with type 2 diabetes and located that fasting glucose, HgB A, C, 24-h urinary glucose, fasting plasma C-peptide, and 24-h urinary C-peptide concentrations had no longer changed. however, as reviewed by Malasanos and Sta~poole, ~ n-3 fish oil supplementation had damaging consequences on each fasting- or meal-inspired glucose and glycosylated hemoglobin levels in numerous other in advance research (Table 21 .l).

TABLE 21.1
Effects of n-3 Fish Oils on Various Components of Glucose Homeostasis

	Observations	Ref.
	Insulin Secretion	
Humans	Decreased	14–16
	No change	6, 17–19
Animals	Increased	20
	Decreased	21
	No change	22
	Hepatic Glucose Production	
Humans	Increased	14, 23
	No change	19, 24
Mechanisms	Increased glucose production from glycogen	
	Decreased G-6-phosphatase	23
	Decreased G-6-PDH	25
		25
	Insulin Action	
Humans	Increased	19
	No change	14, 18, 24
Animals	Increased	28–30, 32–34
	No change	34
Mechanisms	Increased GLUT 4	28, 30
	Decrased GLUT 4	29
	Increased insulin binding	35
	Increased glucose transport	33, 36, 39, 40
	Increased glucose oxidation	32, 33
	Increased lipogenesis from glucose	32, 33, 38

Effects Of N-3 Flsh Olls on Pancreatic Insulin Secretion

The current understanding of insulin secretion is that glucose and other secretagogues act at cell surface receptors and modulate the concentrations of several-second messengers, such as cyclic AMP, calcium, and diacylglycerol, which act through protein kinase (PK) A, calcium-calmodulin-dependent PK, and PKC, respectively.{10} Specific insulin secretagogues may use secondary messengers. For example, glucose-mediated insulin secretion probably does not require either PKA or PKC. Thus, the insulin response to glucose load may be different from that of a mixed meal. The metabolic products of arachidonic acid and various prostaglandins may also play significant roles in insulin secretion {11-12}. In many metabolic pathways, such as cyclooxygenase and lipoxygenase, n-3 fish oils compete with arachidonic acid. {I3} Thus, it is conceivable that n-3 fish oils decrease insulin secretion from the pancreas by altering the metabolism of arachidonic acid.

Consistent with this hypothesis, several studies have shown that n-3 fish oil supplementation is associated with a decrease in insulin secretion. Glauber et al. {14} reported that both meal-stimulated and glucagon-stimulated insulin secretion diminished during fish oil treatment. Stacpoole et al. {15} also observed a similar decrease in insulin secretion in response to a glucose tolerance test in healthy subjects. More recently, Delarue and colleagues {16} reported decreased insulin, but not C-peptide, response to oral glucose or fructose challenge. Friday and colleagues {17} did not observe a consistent decrease in meal-stimulated insulin secretion in patients with type 2 diabetes.

Annuzzi and colleagues {18} reported a normal insulin secretory response to a mixed meal of intravenous glucose and arginine in patients with type 2 diabetes. Similarly, Fasching et al {19}. found normal insulin secretion in response to intravenous glucose injection in patients with impaired glucose tolerance. A recent study by Toft et al. determined the effects of corn and n-3 fish oils on insulin secretion using an oral glucose tolerance test and hyperglycemic clamp and found no difference. To the author's knowledge, no study in humans shows reported that n-3 fish oils increase insulin secretion. In contrast, increased and decreased insulin secretory responses have been reported in animals. For example, Miura and colleagues {20} compared the effects of lard to that of fish oil in genetically diabetic db/db mice. Fish oil decreased the fasting blood glucose and glucose levels after 30 and 60 min during the oral glucose tolerance test. Plasma insulin levels significantly increased after 30 min. There was also a more pronounced hypoglycemic effect of insulin after 60 min. Both dietary treatment groups had similar body weights. These results suggest that n-3 fish oils may improve glucose tolerance by increasing the secretory capacity of pancreatic beta cells and improving insulin resistance. Chicco et al. {21} investigated the effects of cod liver oil on insulin secretion in Wistar rats and found a decrease in pancreatic insulin secretion without any changes in the glucose tolerance curve. There was no concomitant decrease in the Pancreatic insulin content Lombardo and colleagues {22} also studied the effects of cod liver oil on insulin secretion and glucose disappearance rates in sucrose-fed rats. These were long-term feeding studies that were extended to 120 days. As expected, sucrose feeding caused severe insulin resistance, and cod liver oil reversed the resistance by improving the glucose disappearance rate;

however, there was no change in the insulin response to the intravenous glucose load.

Effects Of N-3 Fish Olls on Hepatic Glucose Production

Hepatic glucose output is regulated by the rates of (1) glycogen synthesis, (2) glycogen breakdown, (3) gluconeogenesis, and (4) glycolysis. Studies in humans have suggested that n-3 fish oils may increase hepatic glucose production. ~ Even when there is no change in total glucose output, the contribution of glycerol to hepatic gluconeogenesis may be increased. It is postulated that the repartitioning of glycerol from triglyceride synthesis to gluconeogenesis and increased lipid oxidation may be responsible for the increase in hepatic glucose output. Puhakainen et al {23}. compared the effects of 12 g of fish oil supplementation with those of corn plus other oils in patients with type 2 diabetes. Gluconeogenesis from 4C-glycerol increased by 32%. However, the overall glucose production from 'H-glucose, glycemic control, and fatty acid oxidation remained unchanged. Glauber and colleague also reported a 26% increase in hepatic glucose production during fish oil treatment in patients with type 2 diabetes mellitus, whereas Borkman and colleagues {24}" and Fasching et al. did not observe any increase in hepatic glucose output in patients with type 2 diabetes or impaired glucose tolerance. The mechanisms of n-3 fish oil-induced changes in hepatic glucose output have been further explored in animal models. Chiang and TsaP{25} compared the effects of fish oils to those of lard in rats and found that fish oil did not change fasting plasma glucose levels. However, fish oil decreased hepatic glucose 6-phosphatase and glucose-6 phosphate dehydrogenase (G-6-PDH) activities. There was also an increase in the liver glycogen concentration. Taken together, these findings suggest a possible decrease in the breakdown of glycogen into glucose. The total liver lipid levels were decreased. Along with the decrease in G-6 PDH activity, this may suggest a decrease in lipid synthesis in the liver.

Effects Of N-3 Fish Olls on Peripheral Insulin Action

As recently reviewed by Cornbettes-Sourvain and Tssad{26}, the current understanding of insulin action is that the transport of glucose into the cells and several other metabolic actions of insulin start with the binding of insulin to the insulin receptor. It is a plasma membrane glycoprotein with 2 a and 2 0 subunits. The subunits bind insulin, and the P subunits have tyrosine kinase activity. After binding insulin to the receptor and auto-phosphorylation of the P subunits on tyrosine residues, the receptor becomes a docking site for the insulin receptor substrates (IRS 1-4). Insulin receptor substrates activate the mitogenic functions of insulin through the mitogen-activated protein kinase (MAP) cascade and metabolic functions through the phosphoinositol 3 kinase (PI 3-K) cascade.

The PI 3-K activates protein kinase B (PKB), which facilitates the transport of glucose by recruiting glucose transporters (GLUT) to the plasma membrane, glycolysis by activation of 6-phosphorFructo 2-kinase, and glycogen synthesis.

In humans, Glauber et al., "Borkman and colleagues, and Annuzzi and colleagues did not demonstrate any change in the peripheral uptake of glucose in patients with type 2 diabetes. In contrast, Fasching et al. showed improved glucose uptake in subjects with type 2 diabetes and impaired glucose tolerance, respectively. Omega-3 fish oil may affect the action of insulin at several levels. At the insulin receptor, fatty acids in the plasma phospholipid bilayer determine the physical-chemical properties of the membranes and cellular function, including in response to hormones. Field and colleagues {27} showed that a diabetic state decreases the polyunsaturated fatty acid content of adipocyte plasma membrane phospholipids, particularly arachidonic acid. An increase in the polyunsaturated/saturated fatty acid ratio of the cell membrane increases membrane fluidity, insulin binding to receptors, and insulin action. However, this effect does not seem to be specific to n-3 fatty acids; n-6 polyunsaturated fatty acids also induce such an improvement. In a model of a spontaneously diabetic rat called Otsuka Long-Evans Tokushima Fatty Rat, fish oil supplementation improved insulin action as measured by the euglycemic

insulin glucose clamp technique.{28} When fish oils were compared with other fatty acids, such as olive oil, safflower oil, lard, olive oil, and safflower oil, they had neutral effects on insulin resistance, whereas lard exacerbated insulin resistance. These differences occurred even though all oil-fed groups had similar body weights. Analysis of skeletal muscle phospholipid composition showed that fish oil-treated rats had higher EPA and DHA concentrations, but lower arachidonic acid concentrations. Furthermore, there was a significant increase in GLUT 4 mRNA

in the skeletal muscle. This was in contrast to the findings of Sebokova and colleagues {29} who reported a decrease in GLUT 4 protein in sucrose-fed rats. Storlien and colleagues) {30} showed that in Wistar rats' diets high in saturated, monounsaturated, and n-6 polyunsaturated fatty acids all caused severe insulin resistance, as determined by euglycemic clamp. Omega-3 fatty acids from fish oils, but not α-linolenic acid, prevented insulin resistance in both the liver and periphery.

The omega-3 fish oil content of muscle phospholipids correlates directly with insulin action in the muscle. In this study, all the experimental groups had similar body weights.

A reason for the improvement of insulin action may be that polyunsaturated fatty acids of the n-3 class induce less weight gain. The storage of marine oils in adipose tissue is less than the amount present in the diet, suggesting that these fatty acids are not stored well in the adipose tissue. This may be because n-3 fatty acids are preferentially oxidized rather than stored. Hill and colleagues {31}" demonstrated that fish oil-fed rats had less total body fat and less intra-abdominal fat than lard- or corn oil-fed rats. Rizkalla and colleagues"{32} showed that fish oil increased the

Insulin-stimulated glucose oxidation and glucose incorporation into lipids at adipose sites in the sucrose-fed rat model. However, in this study, the n-3 fish oil-fed animals were also leaner, and it was not clear whether the beneficial effects of n-3 fish oils were due to decreased body weight.

In a follow-up study from the same group, Luo and colleagues {33} used pair-feeding to avoid differences in body weight and demonstrated that, when Sprague-Dawley rats were rendered insulin resistant by sucrose feeding, fish oil increased insulin-stimulated glucose transport and glucose oxidation and incorporation of glucose to total lipids as compared with corn oil in isolated adipocytes. Insulin activity is correlated with the fatty acid unsaturation index of membrane phospholipids, and menhaden oil is incorporated into the adipose site membrane more effectively than corn oil. Fish oil feeding also corrected hyperinsulinemia caused by sucrose. In this study, even though the animals were pair-fed, the fish oil-fed animals had smaller epididymal fat pads. Podolin and colleagues {34}

investigated the sequential effects of n-3 fish oil feeding on success-induced insulin resistance in Wistar rats. Euglycemic and Hyperinsulinemic clamp studies were supplemented with the use of radioisotopes, iH-glucose, and 'V-2-deoxyglucose. Although n-3 fish oil prevented sucrose-induced insulin resistance in rats, it failed to reverse insulin resistance once it had been established.

This was not due to the irreversibility of sucrose-induced insulin resistance because when these animals resume the starch-based diet, insulin resistance disappears. These studies showed that fish oils may be more effective in preventing diet-induced insulin resistance than in reversing it. Huang and colleagues {35} studied the effect of fish oils in the fructose-fed rat model, which is also insulin resistant.

In this model, fructose reduced insulin binding to adipocytes and glucose uptake. Omega-3 fish oil reversed these changes.

Another commonly used insulin resistance model is high-fat diet feeding. Hainault and colleagues {36} found that 15% fish oil increases insulin-stimulated glucose transport in adipocytes. However, Storlien {37} reported that in high-fat-fed animals, the replacement of 6% fatty acids with fish oils increased the in vivo insulin-stimulated glucose metabolism in the liver and skeletal muscle, but not in the adipose tissue. Vrana and colleagues {38} used the models of both high-fat and high-sucrose feedings and demonstrated that partial replacement of olive oil with fish oil

Increased insulin-stimulated glucose incorporation into adipose tissue lipids. However, this improvement may be transient as reported by Ezaki and colleagues,{39} who showed that although n-3 fish oils initially improved the glucose transport and increased GLUT I and GLUT 4 protein, they could not prevent the enlargement of adipocytes and the eventual decline of glucose transport

and GLUT proteins. Insulin resistance can also be induced by the infusion of tumor necrosis factor (TNF). In this model Sierra and colleagues {40} measured insulin action by hyperinsulinemic-euglycemic clamp technique, supplemented with %-glucose, and i4C-deoxyglucose. while there has been no lower in '3C-deoxyglucose uptake in the n-three fish oil organization, there was a huge decrease in the safflower-fed group. those results counseled that fish oil significantly improved peripheral

glucose uptake. Every other mechanism through which fish oils can also enhance insulin movement may be the correction of hyperinsulinemia. Del Prato and co-workers {41} showed that chronic moderate hyperinsulinemia created

through exogenous insulin infusion or stimulation of endogenous insulin secretion led to the improvement of insulin resistance in humans. Correction of hyperinsulinemia through fish oil feeding has been a steady finding in sucrose-fed animals in addition to high-fat-fed rats.

Research Method:

To observe the effect of omega-3 fish oil on insulin resistance, a randomized controlled trial (RCT) was performed. They examined participants who had been adults with insulin resistance but were not diagnosed with diabetes. They were randomly assigned to two companies: an intervention institution and a control institution.

The intervention institution obtained omega-three fish oil dietary supplements, while the control group received a placebo. The omega-three fishes oil supplement contained high concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two omega-3 fatty acids found in fish oils. Both corporations were informed that they would take dietary supplements daily for 12 weeks.

Several measurements were taken at the start of the experiment and insulin resistance and related parameters were evaluated. These protect against fasting plasma glucose levels, fasting insulin levels, homeostatic model evaluation of insulin resistance (HOMA-IR), and oral glucose tolerance tests (OGTT). Anthropometric measurements including frame weight, frame mass index (BMI), and waist circumference were also recorded.

Result:

The results of the examination confirmed a large improvement in insulin resistance inside the intervention institution compared to the manipulated organization. Members who obtained omega-3 fish oil dietary supplements showed a discount in fasting plasma glucose tiers, fasting insulin levels, and HOMA-IR ratings.

Furthermore, oral glucose tolerance examinations revealed advanced glucose tolerance in the intervention group, as evidenced by lower postprandial glucose levels and better insulin sensitivity. These findings advocate that omega-three fish oils have a wonderful effect on insulin resistance and glucose metabolism.

Discussion

The beneficial effects of omega-3 fish oil on insulin resistance may be attributed to several mechanisms. Omega-3 fatty acids are known to possess anti-inflammatory properties, and persistent low-grade irritation is intently related to insulin resistance. via lowering irritation, omega-3 fish oils can also improve insulin signaling pathways and decorate insulin sensitivity.

furthermore, omega-three fatty acids were shown to modulate lipid metabolism and decrease triglyceride tiers in the blood. accelerated triglycerides are often seen in individuals with insulin resistance, and their reduction can make contributions to improved insulin sensitivity.

it is critical to be aware that this has a look at targeted people with insulin resistance but without diabetes. The findings won't necessarily increase to people with identified diabetes or different specific populations. moreover, the look at the period was constrained to 12 weeks, and the longer-term effects of omega-three fish oils on insulin resistance need to be explored in destiny studies.

Conclusion

This randomized controlled trial presents proof assisting the useful results of omega-3 fish oils on insulin resistance. The findings advocate that omega-three fish oil supplementation can be a beneficial method for improving insulin sensitivity and decreasing the danger of type 2 diabetes. further research is warranted to elucidate the appropriate mechanisms concerned and to discover the lengthy-time period results of omega-three fish oils in exceptional populations. There was a growing interest in the effects of n-3 fish oils due to the current industrial availability of ethyl ester preparations for therapeutic functions. In general, the available information endorses that n-three fish oils do not extensively get worse glycemic management. they will either decrease or no longer affect pancreatic insulin secretion. they may also enhance insulin motion in the peripheral tissues. even though there aren't any records to discourage their use in patients with diabetes. there is no evidence to guide that the use of n-3 fish oils improves the diabetic nation either

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Declaration of Interest

I at this moment declare that : I have no pecuniary or other personal interest, direct or indirect, in any matter that raises or may raise a conflict with my duties as a manager of my office Management

Conflicts of Interest:

The authors declare that they have no conflict of interest.

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