Dietary Supplementation With Omega-3 Polyunsaturated Fatty Acids: Can It Reduce Insulin Resistance?

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Learning Objectives:
After reading this article, the participant should be able to:

1. Describe insulin resistance and its clinical impact.
2. List the results of epidemiologic and intervention studies assessing the effects of omega-3 polyunsaturated fatty acids on insulin resistance.
3. Describe the mechanisms through which omega-3 polyunsaturated fatty acids may inhibit the inflammation that contributes to insulin resistance.

WHAT IS INSULIN RESISTANCE?
Insulin resistance (IR) is a condition in which normal amounts of insulin fail to maintain normal blood glucose because of decreased responsiveness of muscle, liver, and fat cells. Initially it leads to elevated circulating insulin and glucose and eventually to metabolic syndrome and non-insulin-dependent diabetes mellitus (NIDDM). About 35% of the adult U.S. population has IR, whereas only about 10% of U.S. adults have NIDDM. IR often is associated with non-alcoholic fatty liver disease, which is the most common liver disease in the Western world. Both IR and non-alcoholic fatty liver disease are found in people with abdominal obesity.

Many factors, including diet, inactivity, antibodies against insulin or its receptor, excess counter-regulatory hormones (e.g. glucocorticoids, catecholamines, growth hormone, and placental lactogens), stress, and inflammation may contribute to the development of IR. The dietary factors that induce IR include diets high in fat or sucrose and diets that are rich in saturated and trans fatty acids (SFA and TFA). By contrast, diets rich in omega (n)-3 polyunsaturated fatty acids (PUFAs) are believed to prevent and retard IR, primarily by limiting inflammation and its associated deleterious effects. In this article, we summarize results from human studies that examined associations between n-3 PUFA intake and IR. We focus on studies that showed

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The continuing education activity in Clinical Nutrition Insight is intended for physicians and health care professionals with an interest in nutrition-related disorders.
an inverse association between n-3 PUFAs and IR, with special attention to research highlighting differences in the effects of individual n-3 PUFAs (e.g. docosahexanoic acid [DHA] vs. eicosapentaenoic acid [EPA]). We also discuss the mechanisms through which n-3 PUFAs are thought to exert their benefits, and suggest priorities for future research to determine the clinical role, if any, of n-3 PUFAs in the management and prevention of NIDDM.

**HUMAN EPIDEMIOLOGICAL STUDIES**

Prior to the introduction of Western diets, which are characteristically high in omega-6 fatty acids, SFA, and TFA, the incidence of NIDDM was much lower among Greenland Inuits and natives of Alaska than among the Danes and residents of the United States. Similarly, Japanese Islanders had a lower prevalence of NIDDM compared with their mainland counterparts. The traditional diets in these regions are rich in oily fish, which is an excellent source of long-chain n-3 PUFAs. Although other lifestyle factors also may have contributed to the changing rate of NIDDM among these populations, results from these geographic comparisons suggest that long-chain n-3 PUFAs may play a protective role.

Despite the consistency of these geographic data, results from two large epidemiological studies conducted within the mainland U.S. population found no association between n-3 PUFA intake and NIDDM. Several potential explanations exist for this discrepancy, including differences in the specific type of n-3 PUFA consumed in mainland vs. traditional diets (EPA and DHA vs. alpha-linolenic acid [ALA]); the higher intake of SFA and TFA among mainland populations; and the differing ratios of n-3 to n-6 PUFAs in the traditional and mainland diets. The last issue may be important because n-3 and n-6 fatty acids compete for many of the same metabolic pathways that mediate inflammation. Therefore, the higher background intake of n-6-based vegetable oils in the Western diet may cancel out the beneficial effects that increased intake of n-3 PUFAs would be expected to produce.

**HUMAN INTERVENTION STUDIES**

Intervention studies of n-3 PUFAs with diabetic patients have reported conflicting results. However, most of these studies used fish oil rather than purified EPA and DHA as the source of n-3 PUFAs, and the studies varied widely both in the doses used (ranging from 1 to 18 g/d) and the duration of the intervention (ranging from one week to more than a year). Furthermore, most of these studies did not control the composition of the baseline diet or total caloric intake; had varying ratios of EPA to DHA concentrations; and did not provide information regarding the concentrations of n-6, SFA and TFA in the basal diet or in the supplement. Also, many of these studies examined only fasting plasma...
glucose or performed an oral glucose tolerance test (OGTT), which is not as sensitive an indicator of insulin sensitivity as the insulin clamp.

Given the significant variability in the methods used in these intervention studies, it is not surprising that they have reported wide variations in outcomes. In fact, results from these studies have ranged from deterioration to improvement of blood glucose levels. In some studies the deterioration occurred in the placebo group as well as in the experimental group, possibly due to increased caloric intake. Other factors that may have influenced the findings include relatively high concentration of SFAs in the basal diet or in the fish oil supplements, inadequate duration of treatment, insensitive methods, and differences in the health status of the NIDDM study subjects in different cohorts.

Despite a wealth of laboratory and epidemiological data suggesting that n-3 PUFAs are protective, only a few intervention studies have shown improvement in insulin sensitivity with fish oil supplementation. In one such study—a randomized crossover trial involving overweight and obese women—supplementation with fish oil for 12 weeks improved insulin sensitivity of subjects with elevated markers of inflammation. No changes were seen in the group of women who were in the bottom quartile for inflammation. In another parallel, placebo-controlled study with patients with non-alcoholic fatty liver disease, long-term (i.e. 12 months) supplementation with a relatively small amount (1 g/d) of n-3 PUFAs caused a significant reduction in fasting blood glucose. Similarly, a trial involving patients with the metabolic syndrome found that only 200 µg/d of EPA plus DHA for three months significantly reduced fasting glucose levels. However, it is unclear whether it was the n-3 PUFAs or other additives in the supplement (e.g. folate, vitamin E) that reduced fasting glucose.

Finally, in a group of patients with NIDDM or those with impaired glucose tolerance, supplementation with fish oil increased the metabolic clearance rate of glucose and insulin sensitivity.

In contrast to these studies, two meta-analyses based on 18 and 26 studies, respectively, with diabetic patients found no improvement or deterioration of glucose control with fish oils. The lack of effect in these meta-analyses most likely was caused by the positive and negative studies canceling each other out.

**THE ROLE OF DHA**

Some preliminary research suggests that DHA may be a more important factor than its PUFA cousin, EPA, in the prevention of IR. In the mouse model, for example, DHA but not EPA prevented IR that was induced by a diet rich in conjugated linoleic acid. In addition, an in vitro study showed that 4-OH DHA was a more potent activator of peroxisome proliferator-activated receptor gamma (a protein critical for regulating glucose oxidation) than the diabetes drug pioglitazone. Moreover, DHA was nearly as effective as pioglitazone in preventing diabetes in mice and rats.

Similarly, at equivalent low concentrations, DHA, but not EPA, altered the activity of proteins that regulate cell proliferation, apoptosis, and insulin signaling pathways. These findings underscore the importance of establishing the individual effects of EPA and DHA on insulin resistance. The fish oil preparations used in most interventions contain EPA and DHA in varying concentrations. However, the studies just discussed suggest that it may be DHA, not EPA, that is primarily responsible for the protective effects of n-3 PUFAs on IR. Thus, although the fish oil interventions performed to date contained a dose many would consider adequate for cardiovascular protection, they may have contained insufficient DHA to yield a discernible clinical benefit on IR.

**MECHANISMS**

Increased inflammation is a contributing factor to the development of IR, NIDDM, and non-alcoholic fatty liver disease. These conditions often are associated with dyslipidemia (characterized by increased levels of triglycerides, free fatty acids, and other blood lipids) and increased levels of fat in the non-adipose tissues (e.g. the liver, skeletal muscle, and pancreas—otherwise known as “ectopic” fat). There is no consensus as to why certain individuals accumulate fat in these non-adipose tissues while others do not, but recent studies indicate that this pattern of fat storage is highly correlated with IR. Some researchers hypothesize that when the storage capacity of existing adipose tissue is exceeded, excess fatty acids are diverted to insulin-sensitive tissues such as the liver, where they trigger inflammation and other toxic effects. Other data suggest that changes in hormonal
balance may promote fat storage in ectopic tissue even when there is sufficient capacity in the existing adipose tissue.

Regardless of their source, saturated and some trans fatty acids induce inflammation by promoting the synthesis of inflammatory cytokines. The inflammation process starts in liver and adipose tissue and eventually spreads to skeletal muscle, either via the infiltration of inflammatory cells or through the circulating inflammatory cytokines.

DHA may counteract this process by reducing circulating triglycerides and free fatty acids, and inhibiting the production of inflammatory cytokines. In addition, n-3 PUFAs reduce the production of inflammatory eicosanoids from arachidonic acid. They also serve as substrates for the production of anti-inflammatory products called resolvins and protectins. Overall, n-3 PUFAs reduce IR by enhancing insulin signaling, increasing expression and activity of glucose transport and metabolizing enzymes, increasing fatty acid oxidation, and decreasing fatty acid synthesis.

**CONCLUSIONS AND FUTURE RESEARCH PRIORITIES**

A number of epidemiological studies have suggested improved insulin sensitivity by increased consumption of n-3 PUFAs. Results of intervention studies have been variable. Two meta-analyses did not show any adverse effects of taking fish oil supplements on IR, and a few studies reported improved insulin sensitivity. Other health benefits of n-3 PUFAs include reductions in triglycerides and remnant chylomicron particles, and a decrease in the number of total and small dense LDL particles. In addition, n-3 PUFAs also have been shown to reduce inflammation and platelet aggregation, as well as to stabilize atherosclerotic plaques and reduce the risk that they will rupture. All of these changes are considered beneficial and will reduce the risk for cardiovascular disease.

Recognizing the numerous health benefits of n-3 PUFAs, many experts believe that almost everyone should take at least 0.5 to 1 g/d of long-chain n-3 PUFAs or about 5 g/d of ALA. Health benefits at these levels of n-3 PUFA intake will be limited, unless the intake is sustained and there is a concurrent reduction in the intake of n-6, saturated, and trans fatty acids. Further studies are needed with individual n-3 PUFAs to determine their effects in isolation (i.e. when provided as a purified single supplement instead of as fish oil), the optimal therapeutic dose, and any synergism or antagonism between the effects of individual n-3 PUFAs. Also required are more studies into their interaction with other dietary fatty acids and the mechanisms involved. In addition, more controlled studies with appropriate placebos at moderate amounts of n-3 PUFA supplementation are needed to determine whether n-3 PUFAs will improve glucose control in subjects with NIDDM and with prediabetic patients to determine whether n-3 PUFAs will delay their progression to diabetes.

**REFERENCES**


