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# An Update on the Role of Omega-3 Fatty Acids in Metabolic Health and Insulin Resistance: A narrative review

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***Abstract***

*Insulin resistance and metabolic health are largely regulated by important pathways that omega-3 fatty acids influence. The molecular pathways by which Omega-3 fatty acids, specifically Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA), work is the main topic of concern in this narrative overview. Through modifying inflammatory responses, enhancing lipid metabolism, and impacting insulin signaling pathways, these fatty acids mainly increase insulin sensitivity. Studies have demonstrated that EPA and DHA can increase insulin sensitivity by downregulating the nuclear factor kappa B (NF-κB) pathway, reducing pro-inflammatory cytokines, and increasing the activation of peroxisome proliferator-activated receptors (PPARs). Furthermore, Omega-3s mitigate lipotoxicity and encourage the effective utilization of fatty acids as an energy source, all of which are critical for preserving insulin sensitivity. They also lessen ectopic fat accumulation. Additionally, the interaction between Omega-3s and membrane phospholipids enhances insulin receptor signaling and activity. Notwithstanding these advantages, further research is necessary to fully understand the unique impacts of certain Omega-3s, such as Alpha-Linolenic Acid (ALA), on these pathways as well as how they might interact with other dietary components and gut flora. We can more effectively utilize the therapeutic potential of omega-3 fatty acids to enhance metabolic health and combat insulin resistance by clarifying these pathways.*

**Keywords:** *Docosahexaenoic Acid (DHA), Eicosapentaenoic Acid (EPA), Insulin Resistance, Inflammatory Responses, Metabolic Health, Omega-3 Fatty Acid.*

## Introduction

Metabolic health is foundational to overall well-being, with disruptions potentially leading to insulin resistance and type 2 diabetes. Insulin resistance, characterized by diminished sensitivity to insulin in peripheral tissues, is central to these metabolic disorders [1, 2]. Research into the effects of dietary fats on insulin sensitivity has highlighted Omega-3 fatty acids as a significant focus due to their potential benefits in metabolic health. Omega-3s are vital nutrients with a wide range of health advantages. They are mostly found in marine sources like fish oil and plant sources like flaxseeds and walnuts. Their beneficial effects on metabolic health are mostly attributed to their noteworthy anti-inflammatory qualities. The impact of Omega-3 fatty acids on insulin resistance-related pathways, such as lipid metabolism, insulin signaling, and inflammation, has been clarified by recent research [3].

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The primary mechanism by which omega-3 fatty acids affect insulin sensitivity is through their anti-inflammatory properties. Insulin resistance is largely caused by chronic low-grade inflammation, and studies using omega-3 fatty acids have demonstrated their ability to lower inflammatory markers including C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α). Omega-3s have the potential to improve insulin sensitivity and reduce the incidence of metabolic diseases by reducing inflammation. Furthermore, the impact of Omega-3s on lipid metabolism is noteworthy, as it is closely associated with insulin sensitivity. By reducing triglycerides and raising high-density lipoprotein (HDL) cholesterol levels, they enhance lipid profiles [4]. These improvements in lipid profiles have the potential to improve insulin sensitivity and decrease the build-up of fat in the liver, a condition linked to insulin resistance. Additionally, omega-3s have a direct effect on insulin signaling pathways, which are necessary for preserving metabolic health by increasing insulin receptor sensitivity and boosting muscle cell uptake of glucose [5]. Additionally, peroxisome proliferator-activated receptor gamma (PPAR-γ), which controls lipid and glucose metabolism, is activated by omega-3 fatty acids [6].

An extensive and up-to-date summary of the role of omega-3 fatty acids in insulin resistance and metabolic health is given in this narrative review. The review seeks to shed light on the possible therapeutic benefits of Omega-3 fatty acids by synthesising current research on how 00these fats affect insulin sensitivity, with a particular emphasis on their effects on inflammation, lipid metabolism, and insulin signaling. In order to improve our comprehension of the role that omega-3 fatty acids play in metabolic health and to guide clinical practice, it also aims to highlight knowledge gaps and suggest subjects for further study.

**Metabolic Health**

A variety of physiological functions that uphold the body's energy equilibrium and general well-being are included in metabolic health. Body maintenance, lipid metabolism, and glucose metabolism are important aspects of metabolic health. Maintaining homeostasis and preventing long-term conditions including type 2 diabetes, cardiovascular disease, and metabolic syndrome depends on proper metabolic function. The control of glucose levels is essential to metabolic health [7]. The pancreas secretes the hormone insulin, which is essential for the metabolism of glucose because it makes it easier for cells to absorb glucose and use it as fuel. Cells respond to insulin efficiently when their sensitivity to the hormone is at its peak, which keeps blood glucose levels within a normal range. However, the body's capacity to regulate glucose is hampered when insulin sensitivity is reduced, as shown in insulin resistance, which raises blood sugar levels and increases the risk of metabolic diseases [8].

A further crucial component of metabolic health is lipid metabolism. Fatty acids are broken down and used as fuel in the fat metabolism process. Dyslipidemia, which is defined by high levels of triglycerides and low-density lipoprotein (LDL) cholesterol risk factors for cardiovascular disease can come on by abnormalities in lipid metabolism. Reducing the risk of heart disease and promoting general metabolic function require maintaining a healthy lipid profile [9]. The management of body weight and metabolic health are tightly related. Excess body fat can aggravate inflammation and insulin resistance, especially visceral fat that is accumulated around internal organs. In order to support metabolic health and lower the risk of metabolic diseases, it is essential to achieve and maintain a healthy weight through a balanced diet and regular physical activity [10]. All things considered, hormonal balance, body weight regulation, and the metabolism of carbohydrates and fats interact intricately to form metabolic health. A multimodal strategy is needed to maintain optimal metabolic health, including regular exercise, a good diet, and efficient stress and other lifestyle management [11].

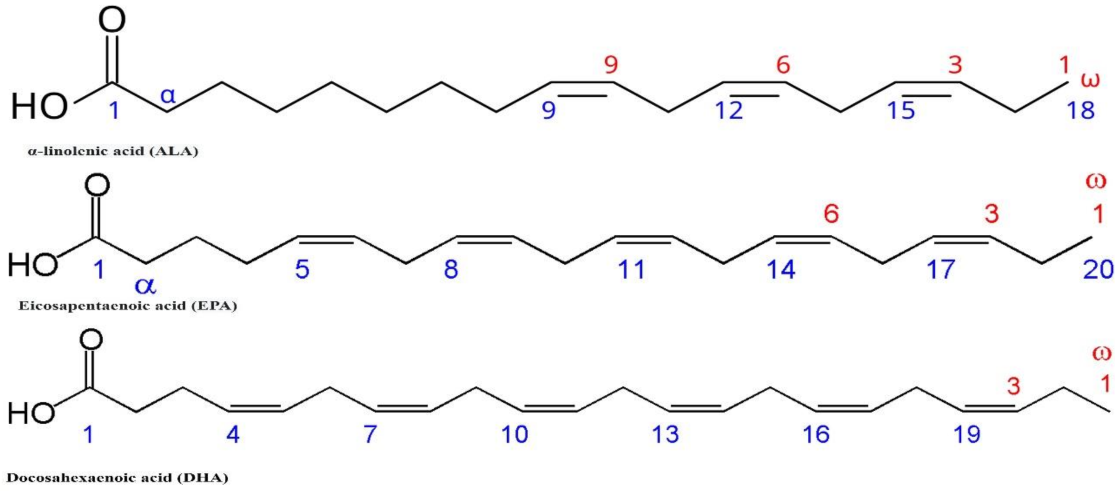


**Figure 1**. Structure of Omega 3 Fatty Acids (Alpha-Linolenic Acid (ALA), Eicosapentaenoic Acid (EPA), and Docosahexaenoic Acid (DHA))

## Overview of Omega-3 Fatty Acids

Omega-3 fatty acids are crucial polyunsaturated fats essential for maintaining overall health and well-being (Figure 1). These fatty acids are characterized by their chemical structure, featuring a double bond three carbon atoms from the end of the fatty acid chain. The primary types of Omega-3 fatty acids include Alpha-Linolenic Acid (ALA), Eicosapentaenoic Acid (EPA), and Docosahexaenoic Acid (DHA). ALA is predominantly found in plant sources such as flaxseeds, chia seeds, and walnuts. EPA and DHA are primarily derived from marine sources like fatty fish (e.g., salmon, mackerel, and sardines) and marine algae (Table 1) [12].

**Table 1**. Sources and Types of Omega-3 Fatty Acids. The Table Summarizes the Types of Omega-3 Fatty Acids, their Common Dietary Sources, Typical Amounts per Serving, and their Primary Health Benefits. It also Highlights the Role Each Omega-3 Type Plays in Improving Insulin Sensitivity and Reducing Insulin Resistance

| Omega-3 Type | Source | Typical Amount (per serving) | Main Benefits | Role in Insulin Resistance | Reference |
|---|---|---|---|---|---|
| Alpha-Linolenic Acid (ALA) | Flaxseeds, Chia seeds, Walnuts | ~2.5 grams per tablespoon of flaxseed oil | Cardiovascular health, anti-inflammatory | ALA can be converted to EPA and DHA; helps improve insulin sensitivity and reduce inflammation | 13 |
| Eicosapentaenoic Acid (EPA) | Fatty fish (e.g., Salmon, Mackerel) | ~1 gram per 3-ounce serving of salmon | Reduces inflammation, supports heart health | Directly improves insulin sensitivity; reduces inflammatory markers associated with insulin resistance | 14 |

| | | | | | |
|---|---|---|---|---|---|
| Docosahexaenoic Acid (DHA) | Fatty fish, Marine algae | ~1 gram per 3-ounce serving of salmon | Supports brain function, eye health | Enhances insulin receptor sensitivity; promotes better glucose uptake in muscle cells | 15 |

Omega-3s play a pivotal role in various physiological functions. They are integral to maintaining cell membrane integrity, regulating blood clotting, and modulating inflammatory responses. They influence the production of eicosanoids, which are signaling molecules that help control inflammation and immune responses. Additionally, Omega-3 fatty acids are involved in gene expression related to metabolic health and disease prevention. EPA is known for its anti-inflammatory effects, while DHA is a crucial component of the brain and retina, supporting cognitive function and visual health [16,17]. The health benefits of Omega-3 fatty acids are well-documented. They help lower triglyceride levels, reduce the risk of cardiovascular diseases, and support joint health. Incorporating Omega-3-rich foods or supplements into the diet can contribute to overall health and disease prevention.

**Affecting Mechanisms Insulin Sensitivity**

Insulin sensitivity is a critical factor in maintaining metabolic health, reflecting how effectively cells respond to insulin, a hormone essential for glucose regulation. Several mechanisms influence insulin sensitivity, including inflammation, lipid metabolism, and cellular signaling pathways. Chronic low-grade inflammation is a prominent factor contributing to insulin resistance. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) can impair the insulin signaling pathway, reducing the efficiency of insulin in facilitating glucose uptake into cells [18]. This impairment leads to elevated blood glucose levels and a higher risk of developing type 2 diabetes. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to exert anti-inflammatory effects that counteract this process. They modulate the production of inflammatory cytokines and eicosanoids, thus reducing chronic inflammation and improving insulin sensitivity. By decreasing inflammation, Omega-3s can help restore the efficiency of insulin signaling, thereby mitigating the risk of insulin resistance and related metabolic disorders [19].

Another significant mechanism affecting insulin sensitivity is lipid metabolism. Elevated levels of free fatty acids in the bloodstream, often resulting from excessive dietary fat intake or impaired fat metabolism, can lead to the accumulation of lipid metabolites in non-adipose tissues such as the liver and muscle. These metabolites interfere with insulin receptor function and promote inflammation, further impairing insulin sensitivity. Omega-3 fatty acids play a vital role in improving lipid profiles by lowering triglyceride levels and reducing the levels of circulating free fatty acids. This improvement in lipid metabolism helps prevent the accumulation of harmful lipid metabolites, thereby enhancing insulin sensitivity [20]. Additionally, Omega-3s influence insulin signaling pathways directly. They activate peroxisome proliferator-activated receptor gamma (PPAR-γ), which is crucial for regulating glucose and lipid metabolism. Omega-3 fatty acids also help maintain cellular membrane fluidity, which supports proper insulin receptor function and signaling. By enhancing the activation of key signaling molecules such as insulin receptor substrates (IRS), phosphoinositide 3-kinase (PI3K), and protein kinase B (AKT), Omega-3s improve glucose uptake in muscle cells. Omega-3 fatty acids contribute to better insulin sensitivity through their anti-inflammatory effects, improvements in lipid metabolism, and enhancement of insulin signaling pathways, ultimately supporting overall metabolic health [21].

**Anti-Inflammatory Effects of Omega-3s**

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are renowned for their potent anti-inflammatory effects, which play a crucial role in maintaining overall health and mitigating chronic diseases. These effects are primarily mediated through their impact on inflammatory pathways and cellular mechanisms. One of the primary ways Omega-3s exert their anti-inflammatory effects is by modulating the production of inflammatory cytokines. Omega-3 fatty acids influence the synthesis of eicosanoids, which are signaling molecules derived from fatty acids [22, 23]. EPA and DHA compete with arachidonic acid, an Omega-6 fatty acid, for incorporation into cell membranes and subsequent eicosanoid production. This competition results in the production of less inflammatory eicosanoids, such as resolvins and protectins, which actively promote the resolution of inflammation. By reducing the levels of pro-inflammatory eicosanoids like prostaglandin E2 (PGE2) and leukotrienes, Omega-3s help lower systemic inflammation [24].

Additionally, Omega-3 fatty acids impact the expression of various inflammatory markers. They can downregulate the expression of genes associated with inflammation, including those encoding tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines are pivotal in the inflammatory response and are often elevated in chronic inflammatory conditions such as cardiovascular disease, diabetes, and arthritis. By reducing the production and activity of these cytokines, Omega-3s help mitigate chronic inflammation and its associated health risks [25]. Furthermore, Omega-3 fatty acids influence cellular processes that contribute to inflammation. They improve cellular membrane fluidity, enhancing the function of membrane-bound receptors and reducing the activation of inflammatory signaling pathways. Omega-3s also enhance the function of regulatory T cells, which play a key role in controlling inflammation and maintaining immune system balance [26]. Omega-3 fatty acids exert significant anti-inflammatory effects by modulating eicosanoid production, downregulating inflammatory cytokines, and improving cellular function. These effects contribute to reduced inflammation and a lower risk of chronic inflammatory diseases.

**Clinical and Preclinical Evidence**

Clinical and preclinical research has robustly supported the anti-inflammatory effects of Omega-3 fatty acids, underscoring their therapeutic potential in managing chronic inflammatory conditions. Clinical trials have consistently demonstrated the efficacy of EPA and DHA in reducing inflammation and associated health issues [27]. For example, supplementation with Omega-3 fatty acids has been shown to significantly lower levels of inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) in patients with rheumatoid arthritis, cardiovascular disease, and inflammatory bowel disease. Notably, a prominent study published in the New England Journal of Medicine reported that Omega-3 supplementation reduced the frequency of cardiovascular events in high-risk patients, highlighting its role in mitigating inflammation-related cardiovascular risks. Additionally, clinical evidence suggests that Omega-3s can alleviate symptoms and decrease the need for anti-inflammatory medications in individuals with chronic inflammatory conditions [28].

Preclinical studies further elucidate the mechanisms by which Omega-3 fatty acids exert their anti-inflammatory effects. Research using animal models and cell cultures has demonstrated that EPA and DHA reduce the production of pro-inflammatory cytokines and eicosanoids [29]. For instance, Omega-3 supplementation has been shown to decrease levels of inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and IL-6 in various tissues, including adipose tissue and the liver. Cellular studies have revealed that Omega-3s influence key inflammatory pathways by modulating transcription factors like nuclear factor-kappa B (NF-κB), which is central to the regulation of inflammation. Collectively, these findings from clinical and preclinical studies underscore the effectiveness of Omega-3 fatty acids in reducing inflammation, providing a solid basis for their use as therapeutic agents in managing chronic inflammatory diseases and improving overall health [30].

**Table 2**: Dietary Sources and Supplements of Omega-3 Fatty Acids. The Table Illustrates Dietary Sources and Common Supplements of Omega-3 Fatty Acids, Detailing their Types (Alpha-Linolenic Acid (ALA), Eicosapentaenoic Acid (EPA), and Docosahexaenoic Acid (DHA)), Typical Content per Serving, and Associated Health Benefits. The Data was Extracted from the Dietary Guidelines for Indians, Published by the Indian Council of Medical Research and National Institute of Nutrition (ICMR-NIN, 2024) [31] and Office of Dietary Supplements. (n.d.). Omega-3 Fatty Acids - Health Professional. National Institutes of Health [32]

| **Food Source** | **Type of Omega-3** | **Typical Amount (per serving)** | **Omega-3 Content (per serving)** |
|---|---|---|---|
| Salmon | EPA, DHA | 3 ounces (85 grams) | ~1.5 grams EPA + DHA |
| Mackerel | EPA, DHA | 3 ounces (85 grams) | ~1.0 grams EPA + DHA |
| Sardines | EPA, DHA | 3 ounces (85 grams) | ~1.0 grams EPA + DHA |
| Trout | EPA, DHA | 3 ounces (85 grams) | ~0.9 grams EPA + DHA |
| Algal Oil | DHA | 1 capsule (500 mg) | ~0.5 grams DHA |
| Flaxseeds | ALA | 1 tablespoon (10 grams) | ~2.4 grams ALA |
| Chia Seeds | ALA | 1 ounce (28 grams) | ~5.0 grams ALA |
| Walnuts | ALA | 1 ounce (28 grams) | ~2.5 grams ALA |
| Hemp Seeds | ALA | 1 ounce (28 grams) | ~0.6 grams ALA |
| Flaxseed Oil | ALA | 1 tablespoon (15 ml) | ~7.0 grams ALA |
| Chia Seed Oil | ALA | 1 tablespoon (15 ml) | ~8.0 grams ALA |
| Fish Oil (supplement) | EPA, DHA | 1 capsule (1000 mg) | ~0.3 grams EPA + DHA |
| Cod Liver Oil | EPA, DHA | 1 tablespoon (15 ml) | ~2.0 grams EPA + DHA |
| Krill Oil (supplement) | EPA, DHA | 1 capsule (500 mg) | ~0.3 grams EPA + DHA |
| Seaweed (nori) | DHA | 1 sheet (5 grams) | ~0.2 grams DHA |

**Sources and Supplementation**

Omega-3 fatty acids are found in various dietary sources and supplements, providing options for individuals to incorporate these beneficial fats into their diet [31]. The primary sources of Omega-3s include both marine and plant-based foods. Marine sources, particularly fatty fish, are the richest sources of EPA and DHA, the two most biologically active forms of

Omega-3s (Table 2). Fish such as salmon, mackerel, sardines, and trout are excellent sources, with a single serving often providing substantial amounts of these essential fatty acids. Algal oil is another valuable marine source, especially for those who do not consume fish, as it provides DHA and is suitable for vegetarians and vegans. Plant-based sources primarily contain Alpha-Linolenic Acid (ALA), which the body can convert into EPA and DHA, though the conversion rate is relatively low. Key plant sources of ALA include flaxseeds, chia seeds, walnuts, and hemp seeds. Flaxseed oil and chia seeds are particularly rich in ALA and can be easily incorporated into smoothies, salads, and baked goods [23].

For individuals who may not consume sufficient amounts of these foods, Omega-3 supplements are a practical alternative. Fish oil supplements are widely available and provide both EPA and DHA. They come in various forms, including capsules, liquid, and chewable tablets. Algal oil supplements are an excellent option for those following a plant-based diet, providing DHA without the need for fish. Additionally, flaxseed oil and chia seed oil supplements offer ALA and can be used to complement a plant-based diet. When choosing supplements, it is important to consider the quality and purity of the product to avoid contaminants such as heavy metals and to ensure that it contains adequate amounts of EPA and DHA [32]. Consulting with a healthcare provider can help determine the appropriate dosage and type of Omega-3 supplement based on individual health needs and dietary preferences [33].

**Future Research Directions**

Future research on Omega-3 fatty acids and their role in metabolic health and insulin resistance holds significant promise for advancing our understanding and treatment of related conditions. One promising direction is exploring the differential effects of various Omega-3 fatty acids—EPA, DHA, and ALA—on insulin sensitivity and metabolic pathways. While much research has focused on EPA and DHA, understanding how ALA contributes to these processes could provide a more comprehensive view of Omega-3s' effects. Studies could investigate how different ratios and combinations of these fatty acids influence insulin resistance and overall metabolic health. Another critical area for future research is the impact of Omega-3 supplementation on specific populations, such as those with genetic predispositions to insulin resistance or metabolic disorders [34]. Personalized approaches based on genetic, metabolic, and lifestyle factors could help tailor Omega-3 interventions for more effective outcomes. For instance, research could explore how genetic variations in Omega-3 metabolism affect individual responses to supplementation.

Additionally, there is a need for long-term clinical trials to evaluate the sustained effects of Omega-3 supplementation on metabolic health. Most current studies are of limited duration, and longer-term research could provide insights into the chronic benefits and potential risks associated with prolonged Omega-3 intake. The interplay between Omega-3s and other dietary components also warrants further investigation. Research could examine how Omega-3s interact with various macronutrients, such as carbohydrates and proteins, and their combined effect on insulin resistance and metabolic health. Finally, exploring the mechanisms underlying Omega-3s' effects on gut microbiota could reveal new insights into their role in metabolic health. Understanding how Omega-3s influence gut bacteria and the subsequent impact on inflammation and insulin sensitivity could open up new therapeutic avenues. Overall, these research directions could significantly enhance our knowledge of Omega-3 fatty acids and their potential to improve metabolic health and manage insulin resistance.

## Conclusion

This review underscores the critical role of Omega-3 fatty acids in metabolic health and insulin resistance. Omega-3s, particularly EPA and DHA, demonstrate significant anti-inflammatory and metabolic benefits, contributing to improved insulin sensitivity and reduced risk of chronic diseases. Clinical and preclinical evidence supports their efficacy, highlighting the need for targeted supplementation and dietary strategies. Future research should focus on understanding the differential effects of various Omega-3s, personalizing interventions based on genetic and metabolic profiles and exploring long-term impacts. Additionally, investigating the interactions between Omega-3s and other dietary factors, as well as their influence on gut microbiota, could provide deeper insights into their mechanisms and therapeutic potential. By addressing these research gaps, we can better harness the benefits of Omega-3 fatty acids to enhance metabolic health and manage insulin resistance effectively.

## Conflict of Interest

The authors hereby declare that there is no conflict of interest.

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