The impact of dietary intervention on myokines: a narrative review

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Abstract

This review elucidates the role of dietary factors in influencing myokine secretion, complementing the recognized benefits of physical activity on metabolic health. While exercise is known to positively modulate myokines, contributing to their health-promoting effects, an exploration into how diet affects these critical cytokines remains sparse. Through analysis of the literature, this work identifies dietary patterns that markedly affect myokine levels, underscoring the complex relationship between nutrition and myokine activity. The investigation reveals that specific dietary approaches can profoundly alter myokine secretion, suggesting an essential avenue for combined dietary and exercise interventions to optimize health outcomes. These insights highlight the need for further detailed study into diet-induced myokine modulation.

Keywords

Dietary patterns, metabolic health, myokine secretion, nutritional impact, nutritional supplements

Introduction

Physical activity has undergone extensive study due to its well-established beneficial effects on various health conditions, including obesity, depression, and cardiovascular disease (Warburton 2006; Caranti et al. 2007; Metsios et al. 2009; Dinas et al. 2010). It is widely recognized that a sedentary lifestyle is associated with an increased risk of chronic diseases, reduced quality of life, and a shorter lifespan (Lee et al. 2012).

Conversely, regular physical activity is associated with a plethora of health benefits, ranging from the prevention of non-communicable diseases like cardiovascular disease and cancer to the enhancement of mental and emotional well-being (Reiner et al. 2013). Exercise plays a pivotal role in preventing and managing obesity by facilitating weight management and promoting metabolic health (Warburton 2006). The beneficial effects of exercise on depression symptoms, comparable to those of antidepressant treatments, underscore its potential as a health management strategy (Caranti et al. 2007). Substantial benefits have been observed in both primary and secondary prevention of cardiovascular disease, particularly through improvements in classical risk factors (Dinas et al. 2010).

Physical activity exerts its health effects through a multifaceted interplay of mechanisms, including the modulation of systemic inflammation and the promotion of metabolic and physiological adaptations (Wärnberg et al.
Assyov Y et al.: The Impact of dietary intervention on myokines

2010; Silverman and Deuster 2014). At the core of these benefits are myokines, cytokines produced and released by skeletal muscle fibers during contraction (Pedersen and Febbraio 2008). These molecules mediate their effects through autocrine, paracrine, and endocrine signaling pathways, contributing to the maintenance of energy balance, reduced inflammation, and overall metabolic health. Their release is influenced by exercise intensity, duration, and muscle mass (Wärnberg et al. 2010; Rinnov et al. 2014; Schnyder and Handschin 2015).

While ample evidence exists regarding the impact of physical activity on myokines, information in the literature about the influence of dietary interventions on their secretion is rather limited. This review aims to provide insight into the ways dietary factors influence myokine secretion.

Search strategy

For our narrative review, we searched the following databases: PubMed, MEDLINE, and Scopus, using both Mesh Terms ("Myokines", "Irisin", "BDNF", "Dietary interventions", "Supplements", "Diets") and free text terms ("Myokine Response to Dietary Factors", "Myokines and Nutrition", "Dietary Modulation of Myokines", "Effects of Macronutrients on Myokines Levels") and a combination of terms ("Irisin" OR "FNDCS") AND ("Diet" OR "Nutrition") AND ("Low-carb diet" OR "Keto-diet"); ("Dietary Changes" NOT "Exercise"), with date range up to 2023, written in English, publication types: reviews, original articles, communications, limited to human and animal studies and clinical trials. We retrieved approximately 250 relevant papers based on the specified search strategy. The selection process involved screening titles, abstracts, and full texts to ensure the inclusion of the most pertinent and recent literature on the impact of nutritional interventions on myokine levels and the regulation of myokines by dietary factors.

Dietary patterns and nutrients

Mediterranean diet

In a prospective study conducted by Sánchez-Villegas et al. (2013), participants with high cardiovascular risk were randomly assigned to follow a Mediterranean diet (MD) supplemented either with virgin olive oil, mixed nuts, or a low-fat control diet. The results indicate that among participants who had depression at the beginning of the study, those in the MD and nuts group showed significantly higher levels of the myokine brain-derived neurotrophic factor (BDNF).

However, overall differences in plasma BDNF levels among the intervention groups did not reach statistical significance. According to the research by Sandberg et al. (2018), eating whole-grain rye flour-based bread, frequently consumed in the MD, boosts the plasma BDNF concentrations in apparently healthy young people when compared to white wheat flour-based control bread. This highlights the potential benefits of dietary interventions as a prevention for cognitive decline (Sánchez-Villegas et al. 2013).

Nevertheless, to validate these findings and explore the possible therapeutic implications of a healthy diet for depression management, further research is required.

Ketogenic diet

Serum BDNF levels dramatically rose within the first two weeks of a 12-week-long ketogenic diet in an uncontrolled intervention trial with obese, inactive individuals (Mohorko et al. 2019). Likewise, a cross-over randomized controlled trial with two 4-week long phases and a 4-week long washout period on 12 adults with metabolic syndrome revealed positive changes in the serum BDNF levels after following a carbohydrate-restricted paleolithic-based diet that contains less than 50 g carbohydrates per day (Rabiee et al. 2020).

Sajoux et al. (2019) found that the very low-carbohydrate ketogenic (VLCK) diet had the strongest impact on myokine levels in individuals with obesity compared to low-carb diets or bariatric surgery. Specifically, levels of irisin and matrix metalloproteinase-2 increased notably with the VLCK diet, while IL-8 levels rose during active weight loss, particularly with the VLCK diet. However, IL-6 remained unchanged. These findings highlight the potential role of diet-induced myokine changes in managing obesity-related diseases (Sajoux et al. 2019).

Low-calorie diet

Admittedly, inconsistent and contradictory findings have been reported in the literature regarding the effects of hypocaloric dietary interventions on myokines levels. However, the impact of diverse types of low-calorie intake on BDNF levels was thoroughly examined (Guimarães et al. 2008; Glud et al. 2019; Kackley et al. 2022). Remarkably, across all these studies, no significant increase in BDNF levels was observed in response to variations in calorie intake. In a study involving participants with mental disorders, it was found that a hypocaloric diet significantly increased serum BDNF concentrations (Guimarães et al. 2008).

Furthermore, Glud et al. (2019) found that the BDNF levels decreased only in women on an exceptionally low-energy diet after 12 weeks. Contrary to the findings of previously mentioned research, Kackley et al. (2022) demonstrated that in overweight and obese individuals, a hypocaloric diet resulted in a consistent and significant decrease in BDNF regardless of diet composition and ketosis.

These findings highlight the complex nature of BDNF regulation and suggest that other factors beyond calorie intake might play a more substantial role in modulating BDNF concentrations. This outlines the need for addition-
al research to investigate any alternative factors or interventions that may have a greater impact on BDNF levels.

The impact of dietary interventions on irisin levels is not consistent across different studies and populations, as well (Park et al. 2014; Quiñones et al. 2015). Park et al. (2014) examined the relationship between circulating irisin levels and various dietary factors, including macronutrients, energy intake, and dietary scores, and evidenced that food intake fails to demonstrate an effect on irisin secretion. Furthermore, no association was found between dietary patterns and irisin regarding diet quality and quantity. Alzoughool et al. (2019) found decreased irisin levels after fasting as compared to pre-fasting values in a study involving individuals practicing Ramadan fasting, a type of religious fasting involving abstinence from food and drink from sunrise to sunset. According to de la Iglesia et al. (2014), individuals with metabolic syndrome on an energy-restricted dietary regime demonstrated a decrease in irisin levels and plasma lipid profile markers.

Similarly, both human and mouse studies revealed that a hypocaloric diet and calorie restriction result in a reduction in circulating irisin (Crujeiras et al. 2014; Varela-Rodriguez et al. 2016). Various studies indicate that muscle tissue is the main source of irisin secretion (Raibee et al. 2020; Yano et al. 2021). Hence, irisin emerges as a prospective biomarker to evaluate muscle dysfunction and contribute to the early identification of sarcopenia and age-related progressive loss of muscle mass (Chang et al. 2017).

However, it has also been reported that visceral adipose tissue can secrete irisin Furino et al. (2021). In support of the preceding hypothesis, a decrease in fat-free mass might affect the secretion of irisin, which is predominantly released by the muscle tissue (Arhire et al. 2019). The positive association between irisin and fat-free mass has been further supported in the literature (Stengel et al. 2013; Liu et al. 2021).

Nevertheless, another study suggests that a rise in caloric intake is associated with a decrease in irisin levels (Schlögl et al. 2015). In a 12-week follow-up study conducted by Tok et al. (2021), participants went through an energy-restricted diet with a caloric restriction of about 750 kcal per day. Serum irisin and FGF21 levels decreased in overweight subjects with prediabetes after the intervention. The concentrations of FGF21 appeared to be significantly reduced in people who followed hypocaloric diets with relatively high protein contents (≥ 30% of diet calories from protein) compared to their pre-diet FGF21 levels (Crujeiras et al. 2017).

Vegetarian diet

Irisin levels are inversely associated with meat consumption and positively correlated with fruit and vegetable intake (Ko et al. 2016). Indeed, it has been shown that irisin significantly increases with the DASH diet (Ko et al. 2016). Admittedly, in a study comparing vegetarian and omnivorous diets in prepubertal children, Ambroskiewicz et al. (2021) did not find any significant statistical differences in serum myokine levels. However, their findings indicated a tendency for vegetarians to have higher levels of myostatin, omentin, Visfatin/NAMPT, and irisin as compared to omnivores. These differences were observed to be approximately 30% higher for myostatin and omentin, 20% higher for Visfatin/NAMPT, and 10% higher for irisin.

High-fat diet

There are discrepancies in the findings related to the interrelationship between high-fat diet (HFD) and irisin (de Macêdo et al. 2017; Rodriguez Lanzi et al. 2020). Kang et al. (2019) demonstrated that Sprague-Dawley mice following a high-fat diet for 16 weeks exhibited a decrease in irisin levels at the conclusion of the experiment. Lu et al. (2016) reported similar results after 24 weeks of HFD, and Yang et al. (2015) found comparable outcomes in C57BL/6 rodents after 12 weeks of HFD. The sedentary mice on a HFD from another study demonstrated a marked reduction in plasma irisin levels (Mazur-Bialy et al. 2017).

However, in a study led by Guilford et al. (2017), an increase in irisin secretion was observed 8 weeks after the introduction of a HFD. These findings provide evidence in favor of the theory that irisin serves a compensatory function in metabolic disorders, including obesity, impaired glucose homeostasis, and insulin resistance. It has been demonstrated that there is a positive correlation between irisin and obesity, as evidenced by considerably higher FNDC5 mRNA expression in adipose tissue in the high-fat diet group as compared to their counterparts (Li et al. 2021). In another study, after 10 weeks of a HFD with concomitant 4-week garlic supplementation, Seo et al. (2014) observed an increase in the circulating irisin. In their study, Furino et al. (2021) observed a significant increase in FNDC5 expression in mice fed chow, which was positively correlated with leptin levels. These results support previous findings that have demonstrated the ability of leptin to positively regulate FNDC5 expression in murine C2C12 myocytes, promote baseline myogenesis, and reduce mRNA expression of factors associated with muscle atrophy (Rodriguez et al. 2017).

However, no significant increase in FNDC5/irisin expression has been observed in mice on a HFD (Guo et al. 2023). Despite several effects being noted in rodents, Quiñones et al’s (2015) research found that Sprague-Dawley mice following a high-fat diet for 10 weeks did not exhibit any significant variations in their irisin levels as compared to the control group. In another study, Rocha-Rodrigues et al. (2016) observed no significant changes in FNDC5 or circulating irisin levels in rats after a 17-week high-fat diet.

Admittedly, in these studies, irisin levels were assessed only after the conclusion of the nutritional intervention, therefore changes in irisin levels may represent an acute response to nutrient absorption rather than a long-lasting effect.
Functional foods and supplements

Omega-3 Polyunsaturated fatty acids

Multiple studies have evaluated the effects of supplementation with various vitamins, minerals, and omega-3 fatty acids on myokine levels. Admittedly, there is limited research on the associations between the endocrine activity of skeletal muscle and stimuli other than exercise (Agh et al. 2017; Ansari et al. 2017).

However, the supplementation with omega-3 polyunsaturated fatty acids in patients with coronary heart disease (Agh et al. 2017) and type 2 diabetes (Ansari et al. 2017) was associated with a significant increase in irisin concentrations as compared to the placebo groups. These experimental findings evidence that DHA/EPA can effectively modulate the expression of irisin through the AMPK/PGC-1α pathway. Based on the aforementioned findings from clinical trials, it is evident that omega-3 polyunsaturated fatty acids could potentially enhance the production and release of irisin in skeletal muscle. This, in turn, may induce the browning of white adipose tissue, leading to improved insulin resistance and glucose tolerance (Rodriguez Lanzi et al. 2020). Wu et al. (2004) discovered that dietary omega-3 polyunsaturated fatty acids were able to normalize BDNF levels in a rat model of traumatic brain injury, which is crucial for neuronal survival, differentiation, and function. The interventions investigating the impact of various long-chain omega-3 polyunsaturated fatty acids in individuals with diabetes and depression (Bot et al. 2011) and overweight subjects (Sedláček et al. 2018) did not reveal any statistically significant differences in the serum BDNF concentrations.

An 8-week study conducted by Jafari Salim et al. (2017) explored the potential impact of omega-3 polyunsaturated fatty acids supplementation on FSTL-1 protein expression. Their findings in a limited cohort of coronary artery disease patients indicated that treatment with 1,200 mg of omega-3 polyunsaturated fatty acids per day led to an elevation in FSTL-1 levels and a concurrent reduction in inflammation.

Zinc

Zinc supplementation was found to lead to a significant rise in BDNF concentrations (Solati et al. 2015; Jafari et al. 2020). This effect has been observed specifically among individuals with premenstrual syndrome Jafari et al. (2020) and individuals diagnosed with obesity (Solati et al. 2015). Findings from a clinical study revealed that in overweight or obese individuals, a 12-week regimen of zinc monotherapy at a dosage of 30 mg not only raised serum BDNF levels but also alleviated depressive symptoms, as demonstrated by Solati et al. (2014).

In contrast, the response to zinc supplementation among individuals with type 2 diabetes (Kheirouri et al. 2019) and subjects with depression (Ranjbar et al. 2014) did not show any significant increase in serum BDNF concentrations. These results indicate that zinc may not have a substantial effect on BDNF levels in these specific populations.

Vitamin D3

Studies that examine the impact of vitamin D3 on BDNF in apparently healthy subjects imply contradictory results. Pirotta et al. (2015) reported no significant differences between the intervention and control groups in BDNF levels. However, the study by Walentukiewicz et al. (2018) observed a significant decrease in serum BDNF concentrations in the supplemented group, indicating a clinically relevant decline. Consistent with the latter findings, the study by Yosaei et al. (2020) demonstrated that both the zinc intervention group and the combined zinc and vitamin D3 intervention group exhibited a noticeable trend toward reduced serum BDNF concentrations. In a recent 8-week randomized, double-blind, placebo-controlled clinical trial on obese women with mild to moderate depressive symptoms, Abiri et al. (2022) found that co-supplementation with vitamin D (50,000 IU per week) and magnesium (250 mg per day) resulted in a significant increase in BDNF and a substantial reduction in depression score among the experimental group.

Furthermore, several studies have shown an association between vitamin D and irisin expression. Vitamin D was shown to upregulate irisin expression in diabetic animal models (Nadimi et al. 2019). In a randomized, double-blind, placebo-controlled clinical trial with type 2 diabetes patients with vitamin D insufficiency, supplementation with vitamin D (50,000 IU per week) for eight weeks improved insulin resistance and significantly elevated irisin as compared to placebo (Safarpour et al. 2020). Six months of vitamin D treatment in patients with primary hyperparathyroidism significantly increased irisin serum levels compared to baseline (Sanesi et al. 2023).

Faienza et al. (2021) conducted a study that revealed a decrease in irisin serum levels among adult patients with Prader-Willi syndrome (PWS) who did not receive any vitamin D supplementation. This finding suggests that the administration of vitamin D has a significant role in the regulation of irisin levels in adult individuals with PWS.

Proteins, Amino Acids, and Derivatives

In a randomized control trial, a combination of high-purity caviar-derived DNA, collagen elastin, and sturgeon protein extracts increased the serum BDNF levels in individuals subjected to work-induced stress as compared to placebo (Chuai et al. 2014). The serum levels of BDNF of frail elderly adults who consumed milk fat globule membrane supplements did not reach any statistically significant change as compared to the control group (Kim et al. 2015). Additionally, recent studies indicate that the administration of royal jelly did not substantially increase serum BDNF concentrations in obese subjects (Petelin et al. 2019).
Another study investigated the effects of 14-day ingestion of 12 grams of beta-alanine per day on cognitive function, mood, and plasma BDNF in healthy men with limited oxidative stress and inflammation before simulating a 24-hour military deployment (Ostfeld and Hoffman 2023). The consumption of beta-alanine reduced the symptoms of depression, yet did not affect either cognitive function or BDNF concentrations (Ostfeld and Hoffman 2023).

**Herbal extracts**

In a randomized, double-blind, placebo-controlled clinical trial with major depressive disorder patients and healthy controls, a single dose of ayahuasca increased the serum BDNF levels in both groups (de Almeida et al. 2019). Therefore, BDNF may function as an indicator of the neuroplastic and therapeutic potential of psychedelics. Nevertheless, further research is needed to evaluate these findings.

**Polyphenols**

Polyphenols are among the nutraceuticals that have been investigated the most as regulators of irisin expression. Palacios-González et al. (2019) found that the increase in irisin concentration speeds up the browning process in mice given genistein, an isoflavone. Moreover, as green cardamom is high in polyphenols, it raises irisin levels, reduces fat build-up in NAFLD patients, improves insulin signaling, and has a beneficial effect on lipid profile (Daneshi-Maskooni et al. 2018). Consistent with these findings, two randomized, controlled trials led by Neshatdoust et al. (2016) have demonstrated simultaneous alterations in blood BDNF levels and global cognition scores after the ingestion of high polyphenol content. This finding suggests a potential involvement of BDNF in the cognitive enhancements generated by polyphenols. In a study involving 44 trained endurance athletes participating in a 10-week endurance training program, the daily intake of 5 grams of cocoa powder rich in flavonoids (providing a total of 425 mg) did not have a significant impact on serum myostatin levels throughout the study period (García-Merino et al. 2020).

Overall, polyphenols hold promise for impacting irisin and BDNF levels, potentially influencing metabolic and cognitive health. However, the specific effects can vary depending on the polyphenol source and individual characteristics.

**Probiotics supplementation**

The idea that dietary changes could affect BDNF by modulating microbiota composition is intriguing, yet the currently available literature is inconsistent. Pinto-Sanchez et al. (2017) and Riezzo et al. (2019) found that supplementation with a single-strain probiotic, specifically Bifidobacterium longum NCC3001 or Lactobacillus reuteri DSM-17938, did not have a significant impact on serum BDNF concentrations in individuals diagnosed with irritable bowel syndrome or constipation. In a study conducted by West et al. (2014), an investigation encompassing both a single-strain probiotic approach (Bifidobacterium animalis subsp. lactis BI-04) and a double-strain approach (Lactobacillus acidophilus NCFM and Bifidobacterium animalis subsp. lactis BI-07) in ostensibly healthy participants did not lead to statistically significant alterations in plasma BDNF.

Haghighat et al. (2019) examined both synbiotics (prebiotics and probiotics) and probiotics in hemodialysis patients with clinical depression. However, the results have shown a significant increase in serum BDNF levels only in the group, supplemented with synbiotics. In a 12-week, multi-center, randomized, double-blind, placebo-controlled clinical trial with cognitively impaired subjects, supplementation with Lactobacillus Plantarum C29-Fermented Soybean increased the serum BDNF concentrations and led to an enhanced cognitive performance (Hwang et al. 2019). Probiotic supplementation with Lactobacillus helveticus IDCC3801-fermented milk did not affect plasma BDNF concentrations in healthy subjects (Chung et al. 2014).

However, probiotic supplementation with Bifidobacterium bifidum BGN4 and Bifidobacterium longum BORI exhibited a substantial increase in serum BDNF concentrations (Kim et al. 2021). Lactobacillus and Bifidobacterium appear to be more effective in boosting BDNF levels in patients with depression and neurological disorders than a supplement containing only one genus (Kim et al. 2021). Dietary supplements with 10 grams of probiotic camel milk powder for four weeks increased irisin levels in type 2 diabetic patients (Fang et al. 2020). Nevertheless, due to the relatively short trials, one might argue that additional large-scale, high-quality randomized controlled trials would be required for more robust conclusions regarding the effects of probiotics supplementation on myokines.

**Conclusion**

In brief, the findings from all the aforementioned studies indicate that the influence of dietary interventions and lifestyle modifications on myokine concentration is a complex phenomenon, with varying outcomes based on specific nutrients, health conditions, and individual responses. A summary of the discussed dietary modifications and their impact on myokine levels is listed in Table 1. Further research is also needed to elucidate the mechanisms underlying these effects and to optimize dietary strategies for promoting muscle health and neurological well-being. A proposed mechanism for the effects of dietary interventions on circulating myokine levels is presented in Fig. 1.
Table 1. Overview of different dietary modifications and their impact on myokine levels.

<table>
<thead>
<tr>
<th>Lifestyle modification</th>
<th>Overall outcome</th>
<th>Impact on Circulating Levels of Myokines (Publications)</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Fat Diet</td>
<td>Decrease</td>
<td>Seo et al. (2014); Guilford et al. (2017)</td>
<td>Lu et al. (2016); Mazur-Bialy et al. (2017); Yang et al. (2018); Kang et al. (2019) Quínones et al. (2015); Rocha-Rodrigues et al. (2016); Guo et al. (2023)</td>
</tr>
<tr>
<td>Energy-restricted diet</td>
<td>Decrease</td>
<td>Guimarães et al. (2008); Schlögl et al. (2015)</td>
<td>de la Iglesia et al. (2014); Crujeiras et al. (2017); Ghad et al. (2019); Kackley et al. (2022); Palacios-González et al. (2019) Park et al. (2014)</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>Neutral</td>
<td>Safarpour et al. (2020); Faienza et al. (2021); Abiri et al. (2022)</td>
<td>Walentukiewicz et al. (2018); Yosae et al. (2020) Pirotta et al. (2015)</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td>Increase</td>
<td>Sánchez-Villegas et al. (2013)</td>
<td>/</td>
</tr>
<tr>
<td>Omega-3 PUFAs</td>
<td>Increase</td>
<td>Wu et al. (2004); Agh et al. (2017); Ansari et al. (2017); Jafari Salim et al. (2017)</td>
<td>/</td>
</tr>
<tr>
<td>Ketogenic diet</td>
<td>Increase</td>
<td>Mohorko et al. (2019); Gyorkos et al. (2019); Sajoux et al. (2019)</td>
<td>/</td>
</tr>
<tr>
<td>Zinc</td>
<td>Increase</td>
<td>Solati et al. (2015); Jafari et al. (2020); Yosae et al. (2020)</td>
<td>/</td>
</tr>
<tr>
<td>Polyphenols</td>
<td>Increase</td>
<td>Yu et al. (2015); Neshatdoust et al. (2016); Choi et al. (2016); Liu et al. (2018); Palacios-González et al. (2019); Daneshi-Maskoomi et al. (2019); Rodríguez Lanzi et al. (2020); Osal (2020); Jin et al. (2022)</td>
<td>/</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Increase</td>
<td>Hwang et al. (2019); Haghjat et al. (2021); Kim et al. (2021)</td>
<td>/</td>
</tr>
<tr>
<td>Vegetarian diet</td>
<td>Increase</td>
<td>Ko et al. (2016); Ambroszkiewicz et al. (2021)</td>
<td>/</td>
</tr>
<tr>
<td>Protein</td>
<td>Neutral</td>
<td>/</td>
<td>/</td>
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</table>

Figure 1. The impact of various dietary interventions on myokine secretion as well as proposed mechanisms for the observed associations.

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