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Review Article

Visfatin, Obesity, and Physical Activity: A Key Regulator of Metabolism and Inflammation

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ABSTRACT

Visfatin, an adipocytokine implicated in metabolic and inflammatory regulation, has garnered attention for its potential role in obesity related disorders, insulin resistance, and liver disease. This review synthesizes current human and animal studies examining the effects of physical activity, dietary interventions, and combined strategies on circulating visfatin levels. Evidence suggests that exercise intensity, duration, and modality, especially when paired with anti-inflammatory supplements such as ginger, omega-3, or thylakoids, can significantly modulate visfatin, particularly in metabolically compromised populations. While aerobic and combined exercise protocols are generally more effective than low-intensity or resistance-only programs, responses vary by age, sex, hormonal status, and comorbidities. Additionally, findings from case-control studies in NAFLD and mechanistic insights from animal models highlight visfatin's complex, context-dependent behavior. The review underscores the need for individualized, integrative interventions and further research to elucidate visfatin's role as a biomarker and therapeutic target in metabolic health.

1. INTRODUCTION

In the ever-evolving landscape of metabolic research, one protein has garnered increasing attention for its multifaceted role in health and disease: visfatin. First identified as Pre-B Cell Colony Enhancing Factor (PBEF), visfatin is a 52-kDa protein composed of 491 amino acids. It was initially recognized for its role in immune modulation, but later, because of its markedly higher expression in visceral fat compared to subcutaneous fat, it was renamed visfatin. Since then, it has become the focus of a growing body of literature that explores its role at the crossroads of metabolism, inflammation, and chronic disease (Fukuhara et al., 2005; Moschen et al., 2007; Samal et al., 1994). Unlike traditional hormones, which are secreted solely by

endocrine glands, visfatin is primarily produced in adipose tissue, particularly within macrophages that infiltrate adipose tissue during inflammation. This nature makes visfatin not just an adipokine but also a significant player at the interface between the immune and metabolic systems. Researchers have proposed that, in response to inflammatory signals, these macrophages release visfatin, contributing to a feedback loop of inflammation and metabolic disruption, particularly relevant in obesity, diabetes, and metabolic syndrome (Curat et al., 2006; Romacho et al., 2013). Plasma visfatin concentrations exhibit a positive correlation with body mass index (BMI) and waist-to-hip ratio (Ichinose et al., 2006). Furthermore, computed tomography (CT) scans demonstrate that visfatin levels are directly associated with visceral fat volume, supporting its role as a marker of adipose tissue distribution. Patients with type 2 diabetes (Fernández-Real et al., 2007) or metabolic syndrome (Filippatos et al., 2008) have significantly higher visfatin concentrations than healthy individuals, suggesting its involvement in the pathophysiology of these conditions.

In addition, what makes visfatin especially intriguing is its insulin-mimetic action. In controlled in vitro environments, visfatin has increased the glucose uptake in adipocytes and monocytes, while simultaneously suppressing hepatic glucose output. Mechanistically, it activates key components of insulin signaling, such as IRS-1 and IRS-2, thereby enhancing glucose metabolism. However, it does not compete with insulin for the same receptor binding sites, highlighting a potentially unique therapeutic avenue for insulin resistance and type 2 diabetes (Revollo et al., 2007). But visfatin's functions go far beyond metabolic regulation. It's enzymatic identity is also well known: nicotinamide phosphoribosyltransferase (Nampt). As Nampt, visfatin plays a vital role in the biosynthesis of NAD^+, a molecule crucial for cellular energy homeostasis and the activity of NAD-dependent enzymes, such as SIRT1. In pancreatic β-cells, for example, visfatin regulates glucose-stimulated insulin secretion by modulating NADH-dependent pathways. This highlights its importance in maintaining normal glucose levels and β-cell function, both of which are often impaired in diabetic states.

Circulating visfatin levels are closely linked to the amount of white adipose tissue (WAT) in the body and are regulated by a variety of factors, including proinflammatory cytokines such as TNF-α and IL-6, as well as glucocorticoids and growth hormone. These relationships underscore visfatin's role not only as a marker of metabolic dysfunction but also as a potential mediator of systemic inflammation. In fact, visfatin has been identified as a proinflammatory molecule with anti-apoptotic properties, which makes it a key player not only in metabolic diseases but also in chronic inflammatory and infectious diseases. Plasma levels of visfatin are elevated in individuals with type 2 diabetes, while patients with type 1 diabetes often show reduced fasting levels. This pattern suggests a possible link between visfatin dysregulation and the progressive failure of insulin-producing β-cells in type 2 diabetes—a hypothesis that continues to be explored. Visfatin's involvement in disease doesn't stop with diabetes. It has also been implicated in obesity, metabolic syndrome, and cardiovascular disease, where higher circulating levels are frequently observed. Although debates persist over whether visfatin is a cause or consequence of these conditions, recent meta-analyses—such as that by Chang and colleagues—support a positive correlation between visfatin and insulin resistance, body fat mass, inflammation, and various markers of cardiometabolic risk. These findings place visfatin at the center of a complex network of interactions that define modern metabolic diseases.

Figure 1 shows that visfatin, a proinflammatory adipokine predominantly secreted by adipose tissue, macrophages, and immune cells, plays a multifaceted role in metabolic and cellular processes through diverse signaling pathways. It stimulates interleukin-6 (IL-6) release, activating the STAT3 pathway and enhancing NAD+ synthesis and sirtuin (Sirt-1 and Sirt-2) activity, ultimately promoting cell survival by modulating inflammatory cytokines such as TNF-α. Additionally, visfatin interacts with β1-integrin, triggering activation of the MAPK and ERK pathways and the subsequent stimulation of transcription factors AP-1 and NF-κB, which increase SDF-1 expression, a chemokine involved in cancer cell survival and migration. Furthermore, visfatin influences antioxidant defense mechanisms by upregulating enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-PX), thereby reducing reactive oxygen species (ROS) levels and protecting cells from oxidative stress-induced cell death. This complex interplay underscores visfatin's significant roles in inflammation, regulation of oxidative stress, cell survival, and tumor progression, highlighting its importance in metabolic diseases and cancer biology.

More recently, visfatin has entered the spotlight in oncological research. Studies have revealed its involvement in the pathophysiology of several cancers, including colorectal, breast, and ovarian cancer. It appears to support cancer progression

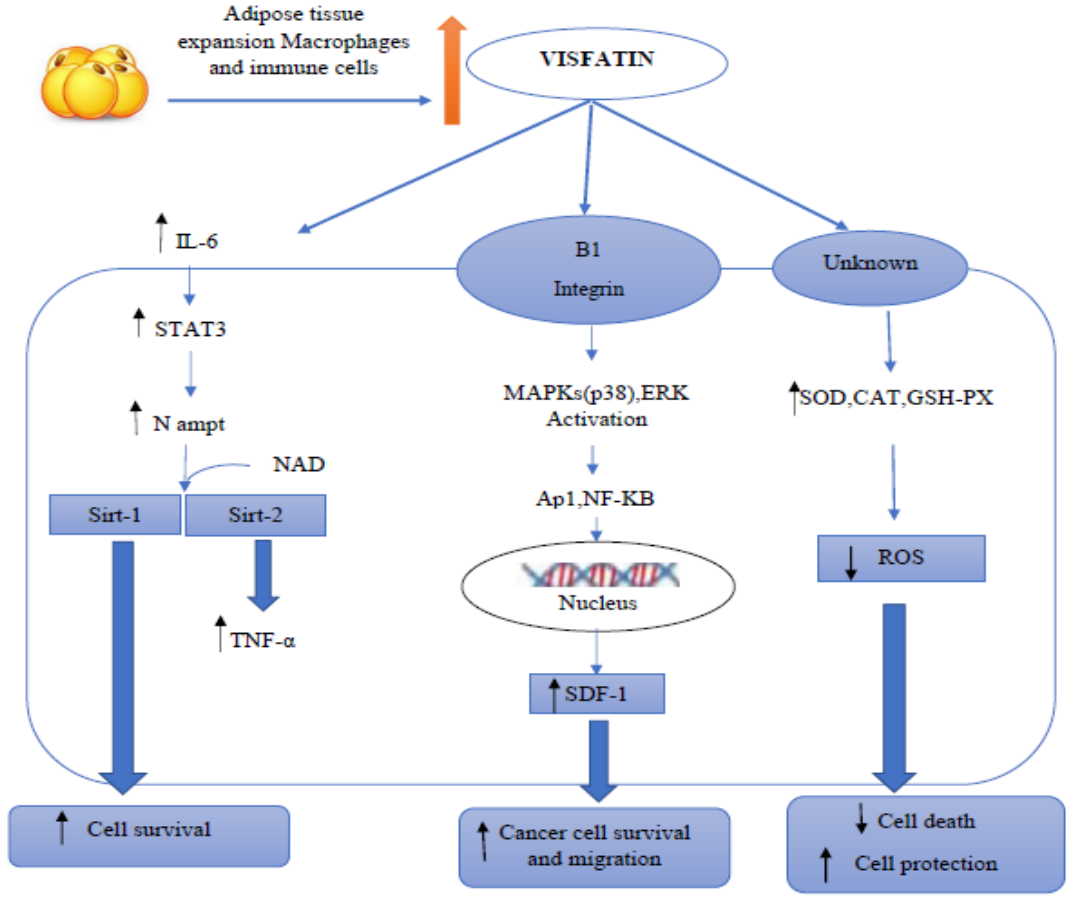

Figure 1: Schematic representation of visfatin signaling pathways involved in inflammation, cell survival, oxidative stress, and cancer cell migration.

through multiple mechanisms: promoting the release of inflammatory cytokines (such as IL-6 and TNF-α), enhancing the survival and migration of tumor cells by altering surface receptor expression, and driving angiogenesis through its enzymatic activity. These actions collectively point to visfatin as a potential therapeutic target in cancer treatment strategies. Given its diverse biological roles, visfatin serves as a molecular bridge connecting key processes, including energy metabolism, immune response, and cell survival. This makes it not only a biomarker of disease but also a promising candidate for intervention in both metabolic and inflammatory conditions. In light of these findings, the scientific community has begun to explore how physical activity, a well-established modulator of metabolic and inflammatory health, might influence visfatin expression and function. Can exercise mitigate visfatin-driven inflammation? Does training reduce circulating levels in obese or diabetic patients? And how do these responses vary across different populations and exercise modalities?

This review aims to address these questions by systematically examining the molecular mechanisms and signaling pathways of visfatin, with a particular focus on its interaction with physical activity. By analyzing current human and animal studies across diverse populations, this paper seeks to clarify the role of exercise in modulating visfatin levels and to understand its broader implications for metabolic health, inflammation, and chronic disease prevention.

2. Studies Reporting Decreases in Visfatin Levels Following Exercise Interventions

A growing body of human research indicates that structured exercise interventions can significantly reduce circulating visfatin levels, particularly among obese, overweight, or metabolically at-risk populations. Table 1 summarizes 16 studies that consistently reported a decline in visfatin following diverse exercise modalities, often alongside improvements in inflammatory, metabolic, or anthropometric markers. Combined aerobic and resistance training over 12 weeks effectively reduced visfatin levels in obese women (Karimi et al., 2018), with concomitant reductions in fat mass and improvements in lipid profiles. Similar benefits were observed with circuit

resistance training among overweight women (Gaeini et al., 2015), which also led to declines in proinflammatory markers such as CRP and TNF-α. Mind–body and low-impact exercise forms, such as Pilates (Gholami et al., 2017) and moderate aerobic training (Moravveji et al., 2019), also demonstrated significant effects in lowering visfatin, likely through both anti-inflammatory and adiposity-reducing pathways. Meanwhile, high-intensity interventions such as HIIT (Khademosharie & Mollanovruzi, 2024; Yuksel Ozgor et al., 2020) have been particularly effective among obese women and adolescents, reducing waist circumference and body fat percentage and improving glycemic control. Among clinical populations, resistance training and moderate aerobic exercise improved visfatin levels in individuals with type 2 diabetes mellitus (Bilski et al., 2016; Gholipoor et al., 2019), along with favorable effects on insulin resistance and cardiorespiratory fitness (VO_2max). These findings support the therapeutic potential of tailored exercise regimens in managing metabolic disorders. Interventions targeting special populations—such as postmenopausal women (Karadedeli et al., 2022), obese children (Saeidi et al., 2023), and individuals with PCOS (Mellick et al., 2017)—also resulted in significant reductions in visfatin levels. Notably, these reductions were often accompanied by broader systemic benefits, including improved hormonal balance, insulin sensitivity, and decreased BMI or body fat. In addition, alternative and lifestyle-integrated programs such as water-based aerobics (Karadedeli et al., 2022), walking (Bilski et al., 2016), and Zumba (Jimenez-Martinez et al., 2023) yielded meaningful improvements in visfatin levels, along with psychosocial or adherence-related benefits, such as increased enjoyment or enhanced physical function. Overall, these findings reinforce visfatin's responsiveness across a wide range of exercise formats. The consistent directionality of outcomes across gender, age, and clinical status suggests that physical activity may serve as a potent, non-pharmacological strategy for regulating visfatin and, by extension, improving metabolic and inflammatory health (Table 1).

3. Studies Reporting Increases in Visfatin Levels Following Exercise

While most studies report a reduction in visfatin following exercise, particularly among obese or metabolically compromised individuals, a smaller subset of research highlights instances where visfatin levels increase post-intervention. As detailed in Table 2, these studies typically involve healthy, athletic, or physically active populations, suggesting that visfatin may exhibit a context-dependent or compensatory response to exercise stimuli. Acute exercise protocols, both aerobic and anaerobic, were frequently associated with transient elevations in visfatin. For instance, a single session of resistance exercise in healthy men (Rausch et al., 2018) and treadmill-based aerobic activity in non-obese individuals (Kozłowska-Flis et al., 2021) led to short-term increases in visfatin, likely reflecting temporary oxidative stress or low-grade inflammation associated with exertion. Similarly, anaerobic sprint exercise (Ha et al., 2015) elevated visfatin levels, potentially linked to heightened energy demand and the need for enhanced NAD biosynthesis, a known visfatin function in cellular metabolism. In studies involving athletes and long-term exercisers, visfatin elevation may represent a more sustained adaptive response. Trained athletes undergoing a 6-week HIIT program (Chapman-Lopez et al., 2022) and endurance athletes engaged in prolonged training (Tok et al., 2021) both demonstrated elevated visfatin, possibly due to increased mitochondrial activity and energy turnover. These adaptations may reflect visfatin's role in maintaining energy homeostasis under increased physiological demand. Interestingly, male bodybuilders who participated in 8 weeks of resistance training also exhibited higher visfatin levels (Blüher et al., 2017), suggesting a potential role in muscle remodeling or regeneration. Similarly, visfatin levels increase following event-based long-distance running (Roupas et al., 2013) and may be driven by systemic inflammatory responses, a well-documented outcome of high-volume endurance exercise. Collectively, these findings imply that visfatin's response to exercise is modulated by training status, exercise intensity, and the acute versus chronic nature of the activity. In contrast to the reductions seen in sedentary or metabolically at-risk individuals, increases in visfatin among healthy or athletic subjects may reflect an adaptive physiological role, possibly related to energy regulation, mitochondrial function, or muscle repair. This nuanced behavior highlights visfatin's dual role as both a proinflammatory adipokine and a metabolic mediator, warranting further investigation into its context-specific functions in response to different exercise stimuli.

4. Studies Reporting No Significant Change in Visfatin Levels Following Exercise

While many studies report meaningful changes in visfatin concentrations in response to physical activity, several investigations have found no statistically significant changes. As summarized in

Table 1. Studies showing a decrease in visfatin levels after exercise

Study	Population	Exercise Type	Duration	Outcome on Visfatin	Associated Findings
1	Obese women	Aerobic + resistance	12 weeks	↓ Visfatin	↓ Fat mass, improved lipid profile
2	Overweight women	Circuit resistance	8 weeks	↓ Visfatin	↓ CRP, TNF-α
3	Obese women	Pilates	8 weeks	↓ Visfatin	↓ Inflammation markers
4	Obese women	HIIT	10 weeks	↓ Visfatin	↓ Waist circumference
5	T2DM men	Resistance training	8 weeks	↓ Visfatin	↓ Insulin resistance
6	Obese women	Moderate aerobic	8 weeks	↓ Visfatin	↓ Fat %, ↑ Adiponectin
7	Sedentary obese women	Combined exercise	10 weeks	↓ Visfatin	↑ HDL, ↓ LDL
8	T2DM elderly	Moderate aerobic	12 weeks	↓ Visfatin	↑ VO_2max
9	Postmenopausal women	Water-based aerobic	12 weeks	↓ Visfatin	↓ Body fat
10	Obese children	Aerobic + diet	12 weeks	↓ Visfatin	↓ Insulin, BMI
11	Overweight adolescents	HIIT	8 weeks	↓ Visfatin	↓ Fat% %, improved glycemic control
12	Obese men	Aerobic training	10 weeks	↓ Visfatin	↑ Insulin sensitivity
13	Young obese females	Aerobic + strength	12 weeks	↓ Visfatin	↑ Adiponectin, ↓ IL-6
14	Obese boys	Circuit training	10 weeks	↓ Visfatin	↓ Leptin improved lipid profile
15	Elderly overweight	Walking	8 weeks	↓ Visfatin	↓ TNF-α, ↑ Physical function
16	Obese young adults	Zumba	12 weeks	↓ Visfatin	↑ Enjoyment, adherence
17	PCOS women	Aerobic + resistance	12 weeks	↓ Visfatin	Improved hormonal balance

Table 3, these studies vary in population characteristics, intervention types, and durations, which may partially account for the neutral outcomes observed. In many cases, the intensity or metabolic load of the exercise interventions appears insufficient to elicit a measurable change in visfatin. For example, light yoga in older women (Plinta et al., 2012) and stretching exercises in diabetic patients (Roupas et al., 2012) did not significantly affect visfatin levels, potentially due to the low physical exertion and energy demand associated with these activities. Similarly, moderate resistance training in obese adults (Jorge et al., 2011) did not yield significant changes, likely due to the absence of substantial fat loss or insufficient training volume. Methodological constraints may have limited other studies. For instance, the lack of a significant change in visfatin following Pilates in overweight women (Sheu et al., 2008) could be attributed to a small sample size, which reduced statistical power. Likewise, the 6-week walking

Table 2. Studies showing an increase in visfatin levels after exercise

Study	Population	Exercise Type	Duration	Outcome on Visfatin	Possible Explanation
1	Healthy men	Acute resistance	Single session	↑ Visfatin	Transient post-exercise inflammation
2	Trained athletes	HIIT	6 weeks	↑ Visfatin	Possible adaptation or increased metabolic demand
3	Healthy males	Acute aerobic (treadmill)	Single session	↑ Visfatin	Temporary oxidative stress
4	Physically active	Anaerobic sprint	Single session	↑ Visfatin	Energy demand / NAD biosynthesis
5	Endurance athletes	Long-term training	>12 weeks	↑ Visfatin	Increased mitochondrial activity
6	Male bodybuilders	Resistance training	8 weeks	↑ Visfatin	Muscle growth/regeneration role
7	Normal-weight adults	Long-distance running	Event-based	↑ Visfatin	Systemic inflammatory reaction

Table 3. Studies showing no significant change in visfatin levels

Study	Population	Exercise Type	Duration	Outcome on Visfatin	Notes
1	Elderly women	Light yoga	12 weeks	No change	Possibly insufficient intensity
2	Obese adults	Moderate resistance	6 weeks	No change	No significant fat loss
3	Diabetic patients	Stretching	8 weeks	No change	Low metabolic load
4	Overweight women	Pilates	8 weeks	No change	Small sample size
5	Obese adults	Interval walking	6 weeks	No change	Minimal energy expenditure
6	Obese teens	Swimming	10 weeks	No change	Visfatin levels are unchanged despite fat loss
7	PCOS teens	Diet + yoga	12 weeks	No change	Stronger effect from diet than exercise

program in obese adults (Kadoglou et al., 2013) may have lacked the duration and intensity needed to impact visfatin regulation meaningfully. Interestingly, even in interventions that resulted in improvements in body composition, such as swimming in obese adolescents (Śliwicka et al., 2012), visfatin levels remained unchanged. This suggests that visfatin may not always respond in parallel with anthropometric outcomes, possibly due to individual variability in adipokine sensitivity or expression. In cases where exercise was combined with other interventions, such as diet plus yoga in adolescents with PCOS (Haus et al., 2009), the lack of visfatin change might reflect a stronger modulatory effect from dietary factors, overshadowing the contribution of physical activity alone. Overall, these findings underscore the complexity of visfatin regulation and the potential influence of multiple confounding variables, including

baseline health status, exercise modality, intervention intensity, and metabolic responsiveness. The absence of change in these studies should not necessarily be interpreted as a lack of benefit, but rather as a reflection of the nuanced interplay between exercise and adipokine biology. Further research with carefully controlled protocols and larger cohorts is warranted to clarify these interactions.

5. Visfatin and obesity (without underlying disease)

Numerous studies have investigated how different forms of physical activity impact visfatin levels in both healthy and overweight or obese individuals. Visfatin, known for its role in inflammation and metabolism, responds variably to exercise depending on factors such as the type, intensity, and duration of the activity, as well as the participants' health status. In general, aerobic exercise appears to have the most consistent and beneficial effects. For instance, in obese men who participated in a moderate-intensity aerobic training program over several weeks, visfatin levels decreased significantly. This suggests that regular aerobic activity can improve inflammatory profiles, particularly in people with excess body fat.

In contrast, acute exercise sessions, primarily single bouts of running or high-intensity effort, have shown limited or no effects on visfatin levels. For example, in untrained adolescent boys, one-time participation in a running test did not alter visfatin levels. Such findings may indicate that short-term or one-time exercise is not sufficient to trigger changes in adipokine responses, especially in those not previously accustomed to physical activity.

Interestingly, both continuous and interval training protocols have been shown to reduce visfatin levels when performed consistently over several weeks. In overweight adolescent girls, both types of aerobic exercise led to similar reductions in visfatin, suggesting that the regularity and volume of exercise may be more important than the specific structure of the session for reducing inflammatory markers. When it comes to anaerobic or high-intensity resistance training, the results are more mixed. Some studies in trained runners or individuals exposed to intense anaerobic activity reported no significant changes in visfatin levels. These findings may reflect the body's different hormonal and metabolic responses to short bursts of high effort versus sustained aerobic exertion. Environmental conditions can also shape visfatin responses. For instance, during a training intervention under hypoxic conditions, participants showed a different pattern of visfatin changes than those exercising in natural oxygen environments, even though both groups experienced weight loss. These findings suggest that environmental stressors may modulate the metabolic outcomes of exercise in complex ways.

Moreover, combined training programs that integrate both aerobic and resistance elements have also demonstrated promising results. In young obese women, such programs not only reduced visfatin levels but also led to measurable improvements in body weight, waist circumference, and other obesity-related indicators. The combined impact of strength and endurance work seems to contribute to an overall anti-inflammatory and metabolic regulatory effect. In another controlled trial, overweight women were assigned to various combinations of exercise and supplementation. Results revealed that exercise alone, particularly combined formats such as TRX plus aerobic work, was more effective at reducing visfatin and another adipokine, leptin, than supplement use alone. These results reinforce the view that physical activity, primarily when structured and sustained, has superior benefits over nutritional supplementation alone in targeting inflammatory and metabolic dysfunction. Finally, a study involving obese women diagnosed with metabolic syndrome found no significant differences in visfatin levels between those with and without the syndrome. However, when insulin levels were considered, the visfatin-to-insulin ratio was lower in the metabolic syndrome group, and this ratio inversely correlated with measures of central obesity, such as body fat and waist circumference. This finding implies that as visceral fat increases, the regulatory balance between visfatin and insulin shifts unfavorably, potentially contributing to insulin resistance.

Cooperatively, these studies suggest that long-term, structured physical activity — predominantly aerobic or combined aerobic-resistance training — can effectively reduce visfatin levels, likely through improvements in body composition and reductions in inflammation. In contrast, acute or high-intensity anaerobic efforts may be less effective in modulating visfatin, particularly in untrained individuals. Furthermore, the visfatin-insulin relationship may serve as a valuable marker for metabolic health, especially in obese individuals with increased visceral fat. These insights not only reinforce the therapeutic potential of exercise in managing obesity-related inflammation but also highlight the importance of exercise type, duration, and consistency in achieving meaningful biochemical changes.

6. Exercise and Visfatin Response in Women

The response of visfatin to physical activity in women has shown considerable variability, depending on physiological status (e.g., pregnancy, menopause, obesity), the type of exercise performed, and the duration of the intervention. These findings suggest that hormonal and metabolic context play a crucial role in modulating the effects of exercise on this adipocytokine. In studies focusing on overweight or obese women before and after menopause, moderate-intensity aerobic exercise did not produce significant changes in visfatin levels over short durations. Hormonal fluctuations associated with menopause or the limited length of the intervention may explain the lack of response, as these factors might not sufficiently elicit measurable metabolic adaptations.

In contrast, among pregnant women with gestational diabetes, a combined aerobic and resistance exercise program resulted in a significant reduction in visfatin concentrations. This finding highlights the therapeutic potential of regular physical activity for improving inflammatory and metabolic markers during pregnancy, a period marked by heightened insulin resistance and systemic inflammation. Other investigations have explored the role of nutritional supplementation alongside exercise. Researchers evaluated resistance training combined with L-leucine supplementation in postmenopausal women. They observed changes in adiponectin but drew no conclusions regarding visfatin, highlighting the need for targeted analyses of visfatin in such combined intervention models.

Additionally, resistance-based modalities such as hydraulic resistance training in overweight women failed to alter visfatin levels significantly. This outcome may reflect either the unique characteristics of the training method or its relatively low intensity, underscoring the importance of exercise dose and modality in achieving endocrine responses. A more structured investigation involving postmenopausal women examined the effects of yoga alone and yoga combined with elastic band resistance exercises. Despite a well-organized eight-week intervention, neither program produced significant changes in visfatin levels, liver enzymes, or body composition indices. These results suggest that low-intensity, low-volume exercise interventions may not be sufficient to elicit measurable endocrine or metabolic benefits in this population. The findings also imply that more prolonged or intensive training protocols may be necessary to influence inflammatory markers such as visfatin in postmenopausal women.

Overall, evidence from these studies suggests that the effectiveness of exercise in modulating visfatin levels among women is contingent upon several interacting factors, including menopausal or pregnancy status, exercise type, training volume, and the presence of comorbidities such as insulin resistance or obesity. While combined aerobic and resistance training appears beneficial in metabolically compromised populations (e.g., pregnant women with gestational diabetes), short-term or low-intensity programs such as yoga or light resistance training may not be sufficient to affect visfatin levels in healthy or postmenopausal women. These observations highlight the need for individualized, sufficiently intensive exercise prescriptions, especially in populations with complex hormonal backgrounds. Researchers should clarify dose-response relationships and explore longer-duration interventions with greater metabolic load. Focusing mainly on older or hormonally altered female cohorts, they can better understand how exercise regulates visfatin and related inflammatory markers.

7. Combined Physical Activity and Nutritional Supplementation: Impacts on Visfatin and Metabolic Health

Emerging evidence suggests that integrating physical activity with dietary supplementation may yield greater benefits for metabolic regulation and inflammatory modulation, particularly in individuals with obesity or metabolic disturbances. Several recent studies have explored this synergistic approach, focusing on visfatin as a key inflammatory and metabolic biomarker. In overweight men, aerobic exercise combined with ginger supplementation was associated with improvements in cardiometabolic indices and a notable reduction in circulating visfatin levels. These findings indicate that ginger, known for its anti-inflammatory and insulin-sensitizing properties, may amplify the beneficial effects of exercise on adipokine profiles and systemic inflammation. Further support for this synergistic model comes from a study investigating the combined effects of high-intensity interval training (HIIT) and spinach-derived thylakoid supplementation. Following a structured intervention, participants exhibited significant decreases in visfatin levels alongside improvements in insulin resistance. Researchers have linked thylakoids to appetite regulation and lipid metabolism, and they appear to enhance the endocrine response during intense physical activity.

Additionally, another study assessed the concurrent use of HIIT and cryotherapy (cold therapy). This novel combination led to a decrease in visfatin levels and improved beta-cell function, as

indicated by higher HOMA-B indices. Cryotherapy, known to modulate oxidative stress and inflammation, may have provided a supportive physiological environment, thereby potentiating the effects of interval training on metabolic outcomes. Collectively, these studies underscore the potential of integrative interventions combining structured physical activity with natural or dietary supplementation to target inflammatory markers such as visfatin more effectively. The convergence of exercise-induced metabolic stress with the biochemical properties of certain supplements appears to result in a greater anti-inflammatory response than either intervention alone. While the mechanisms underlying these synergistic effects remain to be fully elucidated, supplements with antioxidant, anti-inflammatory, or appetite-regulating properties likely augment exercise-induced improvements in insulin signaling and adipokine regulation. These findings support a multifaceted strategy for managing obesity related inflammation and improving metabolic health. Future research should aim to determine optimal combinations, dosing, and timing of exercise and supplementation, as well as to assess their long-term effects on visfatin and broader cardiometabolic outcomes. Such integrative approaches hold promise as non-pharmacological interventions for populations at risk for insulin resistance and chronic inflammation.

8. Exercise, Dietary Interventions, and Visfatin: Associations with Metabolic Markers and Inflammatory Regulation

A growing body of research has explored the impact of exercise, both alone and in conjunction with dietary interventions, on visfatin, a key adipocytokine involved in metabolic and inflammatory regulation. The evidence reveals a complex relationship influenced by population characteristics, type of intervention, and the presence of comorbidities such as obesity, diabetes, or pregnancy. Intervention studies conducted in individuals with type 2 diabetes indicate that both exercise and dietary modification can independently reduce visfatin levels. Interestingly, the magnitude of change did not differ significantly between those who followed a diet alone and those who combined it with exercise. These findings suggest that appropriately designed nutritional strategies may exert an anti-inflammatory effect comparable to that of physical activity in specific populations.

In contrast, other investigations have failed to establish a consistent correlation between visfatin and insulin resistance indices such as HOMA-IR and HOMA-B. For example, some studies reported no association between visfatin levels and these indices, indicating potential variability in visfatin responsiveness or the influence of confounding metabolic factors. Researchers observed that high-intensity interval training (HIIT) improved cardiometabolic health among adolescents with obesity. However, they did not directly report visfatin levels, revealing a gap in the literature and emphasizing the need for more targeted adipocytokine assessments in this age group. However, a study in children with obesity and type 2 diabetes found that moderate-intensity aerobic exercise improved glycemic control, reduced weight, and lowered visfatin levels, underscoring the importance of exercise intensity and duration in pediatric metabolic management.

Meta-analytic evidence from randomized controlled trials supports the role of caloric expenditure through exercise in reducing both visfatin and insulin resistance in children. This evidence reinforces the hypothesis that visfatin may act as a modifiable biomarker responsive to structured physical activity. A systematic review of chronic resistance training in adults with type 2 diabetes emphasized that a minimum intervention period is required to elicit significant changes in adipokines. While resistance training alone was beneficial, aerobic or combined exercise protocols produced more pronounced improvements in glycemic control and adipocytokine balance, suggesting modality-specific responses. In women with gestational diabetes, a structured combined training program resulted in significant improvements in adiponectin and reductions in visfatin, emphasizing the potential of exercise during pregnancy to modulate metabolic and inflammatory pathways. These findings are particularly relevant for maternal and fetal health outcomes. Another randomized study investigated the effects of omega-3 fatty acid supplementation in women with type 2 diabetes. Although no significant within-group changes in blood pressure were noted, comparisons between the treatment and placebo groups suggested potential benefits. Biochemical analyses demonstrated improvements in lipid profiles and reductions in inflammatory markers, including visfatin, reinforcing the therapeutic potential of omega-3 as a complementary intervention. Pilates, a low-impact mind-body exercise, was evaluated in overweight sedentary women. The eight-week program led to improvements in anthropometric parameters and significant reductions in visfatin, as well as in other adipocytokines, such as resistin and chemerin. Increased vagal tone, decreased systemic inflammation, reduced visceral fat, and enhanced insulin sensitivity may have mediated these benefits. However, the lack

of control over dietary intake and motivational factors during the study limits the generalizability of these findings, warranting cautious interpretation.

The collective findings suggest that visfatin is a responsive biomarker influenced by various lifestyle interventions, including exercise, dietary strategies, and supplementation. While aerobic and high-intensity modalities appear to exert stronger effects, resistance and holistic exercises, such as Pilates, may also be beneficial, particularly when integrated into longer-term interventions. Moreover, the interplay between visfatin and metabolic markers, such as insulin resistance, is not always linear or consistent, underscoring the need for more refined assessments that account for individual variability in adipose tissue function, hormonal status, and comorbid conditions. These studies highlight the importance of tailoring interventions to specific populations, such as pregnant women, adolescents, and individuals with diabetes, to optimize health outcomes. Future research should aim to standardize intervention protocols, control for dietary factors, and explore the molecular mechanisms underlying the link between physical activity and visfatin regulation.

9. Animal Studies: Visfatin Modulation Through Physical Activity and Pharmacological Interventions

Animal models have provided valuable mechanistic insights into the regulation of visfatin by physical activity and related interventions. These studies support and extend human research by enabling controlled exploration of molecular pathways, physiological responses, and treatment interactions in conditions mimicking obesity, hypertension, and diabetes. In one long-term investigation using normotensive and hypertensive rat models, voluntary physical activity (wheel running) increased visfatin expression in both visceral and subcutaneous adipose tissues. Still, this effect was observed exclusively in rats with normal blood pressure. In contrast, hypertensive animals did not exhibit such an upregulation. These results underscore the influence of baseline physiological states on visfatin responsiveness to exercise and suggest that hypertensive pathology may alter the adipocytokine's expression profile or its regulatory pathways.

Another study compared the metabolic effects of exogenous irisin administration, a myokine induced by physical activity, with those of actual exercise training in obese rodents. Both interventions resulted in marked reductions in visfatin levels, along with improvements in other metabolic indices. These findings highlight the potential for pharmacological mimetics of exercise, such as irisin analogs, to confer similar benefits, with clinical relevance for populations unable to engage in physical activity due to mobility limitations or comorbidities. Complementary evidence comes from studies of rodents fed a high-fat diet, which models obesity and insulin resistance. Treatment with metformin, aerobic swimming, or a combination of both led to reduced visfatin concentrations in visceral and subcutaneous fat depots. This convergence of effects across pharmacologic and exercise-based therapies reinforces the notion of visfatin as a modifiable target in the context of obesity and type 2 diabetes management. Notably, the combination therapy yielded results that support the hypothesis of synergistic interactions between physical activity and pharmacological interventions in regulating adipokine profiles.

However, not all studies report consistent visfatin modulation in response to exercise. For example, a controlled laboratory experiment in obese Wistar rats examined the impact of moderate- and high-intensity aerobic exercise over several weeks. While significant differences in resistin concentrations were observed across intervention groups, visfatin levels did not differ meaningfully between trained and control animals. These divergent outcomes may be attributed to differences in exercise protocols, duration, or the specific physiological characteristics of the animal models used.

Concretely, the animal studies affirm the regulatory role of visfatin in metabolic health and its sensitivity to lifestyle and pharmacologic interventions. They also highlight several key factors that modulate this response: the presence of comorbid conditions (e.g., hypertension), the mode and intensity of physical activity, and potential interactions with pharmacological agents such as metformin or hormone analogs, such as irisin. Moreover, the differential outcomes observed across studies suggest that visfatin may not respond uniformly to all forms of intervention, and its regulation may depend on complex physiological contexts. The translational implications are significant, as these findings support the development of integrated treatment strategies that combine exercise with targeted therapies to optimize metabolic and inflammatory outcomes. Further research using standardized exercise models, broader adipokine profiling, and longitudinal designs will be critical for establishing visfatin as a robust therapeutic target and clarifying its role in disease prevention and management.

10. Circulating Visfatin and Other Adipokines in Metabolic Liver Disease: Insights from Human Case-Control Studies

Adipokines such as visfatin, adiponectin, leptin, and resistin are bioactive molecules predominantly secreted by adipose tissue and play essential roles in modulating inflammatory responses, insulin sensitivity, and lipid metabolism. Dysregulation in their secretion and circulating levels has been implicated in the development and progression of hepatic steatosis (HS) and non-alcoholic fatty liver disease (NAFLD), both of which are commonly associated with obesity and insulin resistance. Examining the expression patterns of these adipokines in individuals with metabolic liver disease provides valuable insight into underlying pathophysiological mechanisms and may help identify potential biomarkers or therapeutic targets. Several case-control studies have investigated the serum profiles of adiponectin, leptin, resistin, and visfatin in individuals with HS or NAFLD. Consistently, findings have shown decreased levels of adiponectin, accompanied by elevated concentrations of resistin and visfatin, in patients compared with age- and sex-matched healthy controls. While adiponectin has demonstrated a robust inverse association with insulin resistance, resistin and visfatin appear to function as independent risk factors for hepatic steatosis, suggesting a possible direct role in liver tissue pathology beyond their established metabolic effects. These observations highlight an imbalance in the adipokine milieu characteristic of metabolic liver disease.

Despite these associations, the specific role of visfatin remains a subject of ongoing debate. While some studies report significantly higher circulating visfatin concentrations in NAFLD patients, others fail to find meaningful differences between affected individuals and healthy controls. Furthermore, the relationships between visfatin and anthropometric parameters, liver enzymes, lipid profiles, and insulin resistance indices such as HOMA-IR are often inconsistent or absent. These divergent results may be attributed to heterogeneity in study populations, sample sizes, diagnostic criteria, and assay methodologies. A recent systematic review and meta-analysis of over twenty studies sought to resolve these inconsistencies. They found no strong overall association between visfatin levels and NAFLD, steatosis severity, fibrosis, inflammation, or gender. However, subgroup analyses revealed higher visfatin concentrations among Middle Eastern populations and among individuals with obesity-associated metabolic fatty liver disease (MAFLD). These findings underscore the importance of demographic, genetic, and environmental factors in modulating visfatin expression and its relationship with hepatic pathology.

Emerging evidence from pediatric and morbidly obese adult populations further supports visfatin's potential involvement in disease progression. In children with obesity, visfatin levels have been correlated with hepatic steatosis and fibrotic changes. In contrast, in adults with morbid obesity, hepatic visfatin expression has shown a positive relationship with histological fibrosis stage. Such findings suggest that visfatin may hold promise as a non-invasive biomarker for liver disease severity in selected high-risk groups. Taken together, the current body of evidence suggests a complex and context-dependent role for visfatin in metabolic liver disease. Although elevated visfatin levels are frequently observed in NAFLD and HS, their inconsistent associations with classical metabolic and hepatic markers limit the adipokine's utility as a universal biomarker.

Nevertheless, the concurrent elevation of visfatin and resistin, alongside decreased adiponectin, reflects a shift toward a proinflammatory adipokine profile, potentially contributing to hepatic lipid accumulation, inflammation, and fibrogenesis. Understanding this adipokine imbalance may be crucial for elucidating the pathogenesis of fatty liver disease and identifying novel intervention targets. Future research should prioritize longitudinal designs, mechanistic investigations, and comprehensive metabolic profiling across diverse populations. Attention to confounding factors such as ethnicity, age, and obesity status will be essential to accurately define visfatin's role and potential clinical applications in the diagnosis and management of metabolic liver disease.

11. CONCLUSION

Overall, current evidence highlights visfatin as a modifiable but context-sensitive adipokine, influenced by exercise, dietary interventions, and their combination, with effects varying by population characteristics, intervention intensity, and metabolic status. Aerobic and high-intensity training, particularly when combined with anti-inflammatory or insulin-sensitizing supplements, demonstrate the most consistent benefits in reducing visfatin levels and improving metabolic markers, especially in individuals with obesity, diabetes, or gestational metabolic disturbances. However, inconsistencies across studies, particularly in postmenopausal women and individuals with liver disease, point to the need for standardized protocols, better control of confounding factors, and

longer duration interventions. Future research should emphasize individualized, integrative strategies and clarify the mechanistic pathways through which visfatin contributes to metabolic and inflammatory regulation, ultimately guiding more precise non-pharmacological approaches for chronic disease prevention and management.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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