THERAPEUTIC ADVANCES in
Endocrinology and Metabolism

Review

Therapeutic potential of adiponectin in prediabetes: strategies, challenges, and future directions

Ther Adv Endocrinol Metab

2024, Vol. 15: 1–19

DOI: 10.1177/20420188231222371

Mona Mohamed Ibrahim Abdalla

***Abstract*:** Adiponectin, an adipose-derived hormone, plays a pivotal role in glucose regulation and lipid metabolism, with a decrease in circulating adiponectin levels being linked to insulin resistance and prediabetes. This review examines the therapeutic potential of adiponectin in managing prediabetes, elucidating on multiple aspects including its role in glucose and lipid metabolism, influence on insulin sensitivity, and anti-inflammatory properties. Moreover, the paper highlights the latest strategies to augment adiponectin levels, such as gene therapy, pharmacological interventions, dietary modifications, and lifestyle changes. It also addresses the challenges encountered in translating preclinical findings into clinical practice, primarily related to drug delivery, safety, and efficacy. Lastly, the review proposes future directions, underlining the need for large-scale human trials, novel adiponectin analogs, and personalized treatment strategies to harness adiponectin's full therapeutic potential in preventing the transition from prediabetes to diabetes.

Keywords: adiponectin, anti-inflammatory, prediabetes, prophylactic, therapeutic

Received: 18 September 2023; revised manuscript accepted: 28 November 2023.

Correspondence to:
Mona Mohamed Ibrahim Abdalla
Human Biology Department, School of Medicine, International Medical University, 126, Jln Jalil Perkasa 19, Bukit Jalil, Kuala Lumpur, Federal Territory of Kuala Lumpur 57000, Malaysia
monamohamed@imu.edu.my

Introduction

Prediabetes, often considered the 'gray zone' between normal glucose homeostasis and overt type 2 diabetes mellitus (T2DM), is a condition marked by blood glucose levels that are higher than normal but not yet in the diabetic range.[1] Globally, the prevalence of prediabetes is on the rise, with an estimated 470 million people expected to be affected by 2030.[2] This surge is alarming, given that prediabetes increases the risk of progression to T2DM and elevates the chances of developing cardiovascular diseases.[3] The World Health Organization (WHO) and the International Diabetes Federation have recognized prediabetes as a critical global health challenge, given its strong association with the future onset of T2DM.[4] Recent epidemiological studies suggest that nearly one in three adults in developed countries may have prediabetes, with many being unaware of their condition.[5] The economic burden of prediabetes, considering its potential progression to diabetes and associated complications, is substantial.[6]

Adiponectin, a protein hormone predominantly synthesized by adipocytes, has been identified as a key player in the regulation of glucose and lipid metabolism.[7] Prediabetes, characterized by impaired glucose tolerance, fasting glucose, or glycated hemoglobin (HbA1c), is a critical stage in the progression toward type 2 diabetes.[8] Lower circulating levels of adiponectin have been associated with insulin resistance and prediabetes.[9,10]

Various *in vitro* and *in vivo* studies suggest that adiponectin enhances insulin sensitivity, exhibits anti-inflammatory properties, and may have a protective role against the progression from prediabetes to diabetes.[11,12] Although evidence demonstrates the significance of adiponectin in metabolic regulation, the therapeutic potential of adiponectin in prediabetes is yet to be fully exploited.

Novel strategies aiming to enhance adiponectin levels or activity include gene therapy, pharmacological interventions, and lifestyle changes.[13,14] However, these strategies face multiple challenges, including difficulties in drug delivery, potential side effects, and variability in individual responses.[15]

This review aims to elucidate the therapeutic potential of adiponectin in the management of prediabetes, detailing the various strategies employed, the challenges faced, and suggesting future directions to harness the full therapeutic potential of adiponectin.

Methodology: Search strategy

For the comprehensive review, a systematic search was executed across two predominant databases: PubMed and Google Scholar. These platforms were chosen due to their extensive collection of peer-reviewed articles, journals, and conference proceedings, providing a holistic view of the topic under investigation. Specific keywords and MeSH terms were employed to refine the search, ensuring the retrieval of the most relevant and recent studies related to the therapeutic potential of adiponectin in prediabetes. This rigorous search strategy ensured an in-depth understanding of the topic and ensured the quality and relevance of the sources referenced.

Biology and function of adiponectin

Adiponectin, a unique adipokine, has garnered significant attention in metabolic research due to its paradoxical increase in lean individuals and decrease in those with obesity and metabolic syndrome.[16] Unlike other adipokines, adiponectin appears to play a protective role against the development of insulin resistance and other metabolic complications.

Molecular structure and isoforms

Adiponectin, a 244-amino acid protein, is primarily secreted by adipocytes and is found in the bloodstream in three main isoforms: low-molecular-weight trimers, medium-molecular-weight hexamers, and high-molecular-weight (HMW) multimers.[17] The HMW form, which consists of 12–18 monomers, is believed to be the most biologically active isoform, particularly in terms of its insulin-sensitizing effects.[18] The varying molecular structures of these isoforms are attributed to the post-translational modifications, especially the formation of disulfide bonds, which influence their biological activities.[19]

Adiponectin receptors and signaling pathways

Two primary receptors mediate the effects of adiponectin: AdipoR1 and AdipoR2.[12] AdipoR1 is predominantly expressed in skeletal muscle, while AdipoR2 is mainly found in the liver. Upon binding to these receptors, adiponectin activates several intracellular signaling pathways. One of the most prominent is the AMP-activated protein kinase (AMPK) pathway, which plays a crucial role in energy homeostasis and metabolic regulation.[20] Another significant pathway is the peroxisome proliferator-activated receptor-alpha (PPAR-α) signaling, which is involved in fatty acid metabolism.[21]

Role of adiponectin in glucose and lipid metabolism

Studies have underscored the unique role of adiponectin in the activation of various biochemical pathways that regulate metabolic functions. A key mechanism involves the activation of 5′ AMPK a master regulator of cellular energy status.[11,22] Activation of AMPK results in increased glucose uptake in muscle cells and reduced gluconeogenesis in the liver, thereby contributing to better glycemic control.[22] In this context, AMPK activation leads to enhanced insulin sensitivity, crucial for optimal metabolic functioning.[9]

Another pertinent biochemical pathway influenced by adiponectin involves its interaction with peroxisome proliferator-activated receptors (PPARs), particularly PPARα. The activation of PPARα leads to increased fatty acid oxidation and a consequent reduction in triglyceride content, thereby protecting tissues like skeletal muscle and liver from lipid-induced insulin resistance.[21,23,24] Additionally, adiponectin potentiates the expression of genes involved in fatty acid oxidation while suppressing those associated with fatty acid synthesis, thereby maintaining a favorable lipid profile.[25]

The interplay between adiponectin and insulin sensitivity cannot be understated. Adiponectin enhances the sensitivity of liver and muscle cells to insulin through its impact on the insulin signaling pathway, primarily by stimulating tyrosine

phosphorylation of the insulin receptor and its downstream effector.[16,26] Adiponectin-induced improvements in insulin sensitivity are further facilitated through its anti-inflammatory effects. The hormone inhibits the secretion and action of pro-inflammatory cytokines such as tumor necrosis factor-alpha, which has been implicated in the development of insulin resistance.[27–29] This suggests a dual role for adiponectin in enhancing insulin sensitivity directly through intracellular signaling cascades and indirectly through its anti-inflammatory properties.

Moreover, adiponectin appears to have protective roles in atherosclerosis through its action on lipid metabolism. It enhances the uptake of high-density lipoprotein cholesterol by hepatocytes, contributing to reverse cholesterol transport.[30] This suggests that adiponectin might also have a role in mitigating the cardiovascular risks often accompanying metabolic disorders like diabetes.

In summary, adiponectin's versatile role in regulating glucose and lipid metabolism positions it as an intriguing therapeutic target for various metabolic disorders. Its involvement in key biochemical pathways like AMPK and PPARα activation provides multiple avenues for potential pharmacological intervention. The hormone's positive impact on insulin sensitivity, both directly through cellular signaling and indirectly through its anti-inflammatory effects, further adds to its therapeutic appeal. Continued research into the mechanisms underlying these beneficial effects will provide valuable insights for the development of targeted therapies.

Adiponectin and prediabetes: Connecting the dots

Correlation between adiponectin levels and prediabetes

Several studies have shown an inverse correlation between circulating adiponectin levels and prediabetes. Low adiponectin concentrations have been associated with elevated fasting glucose, increased insulin resistance, and impaired glucose tolerance, key hallmarks of prediabetes.[31–33] Moreover, epidemiological research has found that reduced adiponectin levels can predict the future development of prediabetes, even after controlling for age, sex, and body mass index.[10,34–36] The hormone's effects on lipid metabolism, particularly its capacity to lower triglyceride levels, further implicates its protective role against the onset of prediabetes.[37,38] Additionally, adiponectin levels have been inversely associated with visceral fat accumulation, a known risk factor for prediabetes.[39–41]

Moreover, gender-specific correlations have been noted, wherein low adiponectin levels appear to be a stronger predictor of prediabetes in women than in men.[36] Interestingly, there is also evidence that adiponectin can improve endothelial function, which might offer additional protective effects against the vascular complications often seen in prediabetic states.[9,42,43]

In addition to its role as a biomarker, adiponectin levels are also being investigated in the context of exercise and lifestyle interventions. Studies have shown that physical activity and dietary changes can lead to increased adiponectin levels, with subsequent improvements in markers of prediabetes.[44,45] Moreover, adiponectin levels may also be influenced by pharmacological interventions like metformin, which is commonly used in treating prediabetes.[46,47]

Potential mechanisms of adiponectin in prediabetes progression

Adiponectin is more than just a marker of metabolic health; emerging evidence indicates that it may actively participate in the pathogenesis of prediabetes through multiple mechanisms. Its well-documented role in enhancing insulin sensitivity is mediated through activation of AMPK, which results in increased glucose uptake by skeletal muscle and suppressed hepatic glucose production.[11,25] Additionally, adiponectin exerts anti-inflammatory effects by inhibiting the secretion of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α,) which have been implicated in insulin resistance.[31] It has been demonstrated that adiponectin suppresses the activation of NF-κB, a critical regulator of pro-inflammatory cytokines, and thus may mitigate inflammation-driven impairment in glucose tolerance.[42] Recent evidence has also shown that adiponectin may play a role in modulating oxidative stress, which contributes to insulin resistance. Adiponectin has been shown to induce the expression of antioxidants like heme oxygenase-1, which counteracts oxidative stress and may improve insulin sensitivity.[48] Another intriguing area of

investigation involves adiponectin's role in lipid partitioning. Evidence suggests that adiponectin promotes the clearance of triglycerides from the bloodstream and helps in partitioning lipids toward oxidation, reducing the lipotoxic effects that can contribute to insulin resistance.[49] Furthermore, adiponectin has been shown to have neuroprotective effects. While the primary focus has been on neurodegenerative diseases, there is speculation that the hormone could influence the central regulation of glucose metabolism, thereby affecting the risk of prediabetes.[50,51]

In a state of low adiponectin levels, these protective mechanisms are compromised, contributing to elevated blood glucose and lipid levels, and thereby, the progression to prediabetes.[31,32] Furthermore, adiponectin influences lipid metabolism, which in turn affects insulin sensitivity; reduced adiponectin levels can result in increased free fatty acid release, contributing to insulin resistance and hyperglycemia.[25,37]

Further mechanistic insights have revealed that adiponectin can improve mitochondrial function and biogenesis, mediated in part by PPAR coactivator 1-alpha, thereby improving overall cellular metabolism and reducing oxidative stress.[52,53] Additionally, it has been found to modulate autophagy in hepatic and pancreatic cells, which could protect against cell death and dysfunction, key contributors to prediabetes progression.[54] Adiponectin also interacts with other adipokines, such as leptin, and this interaction could offer synergistic effects in improving insulin sensitivity and glucose regulation.[55] The crosstalk between adiponectin and gut microbiota is a new and intriguing field, suggesting that adiponectin levels could be manipulated through dietary or probiotic interventions.[56–58] Some studies have started to explore the impact of adiponectin on gut microbiota, which is known to play a role in metabolic health. Higher adiponectin levels have been linked to a healthier gut microbiome composition, possibly offering another mechanism by which adiponectin could affect prediabetes.

Research has also illuminated the role of adiponectin in improving the function of β-cells in the pancreas, which are crucial for insulin secretion.[59,60] Given that β-cell dysfunction is a critical factor in the progression from prediabetes to diabetes, the protective effects of adiponectin on these cells further underscore its potential as a therapeutic target.[61,62] More recent studies are focusing on the genetic polymorphisms associated with adiponectin levels, adding another layer to our understanding of its impact on prediabetes.[63,64]

Recent evidence has also pointed to the relationship between adiponectin and the renin-angiotensin-aldosterone system (RAAS). Adiponectin appears to antagonize RAAS, which is known to exacerbate insulin resistance and contribute to prediabetes.[65–67] Another intriguing aspect is adiponectin's effect on skeletal muscle composition. Studies have suggested that adiponectin can stimulate the transformation of white skeletal muscle fibers to more oxidative, metabolically efficient red muscle fibers.[53,68]

Adiponectin has also been implicated in the modulation of gut hormones like glucagon-like peptide-1 (GLP-1), which plays a vital role in postprandial insulin secretion and could offer additional pathways for managing prediabetes.[69,70] Furthermore, adiponectin appears to interact with nitric oxide signaling, improving endothelial function and contributing to vascular health, which is often compromised in prediabetic and diabetic states.[71]

Another emerging field of research is the involvement of adiponectin in circadian rhythm regulation.[72] Adiponectin levels have been shown to exhibit a circadian rhythm, which can be affected by sleep deprivation and shift work, both known risk factors for prediabetes.[73,74] This presents the possibility that targeting adiponectin could also help address some of the lifestyle factors contributing to prediabetes.

Moreover, adiponectin has been found to interact with other regulatory proteins like sirtuins. For instance, the co-regulation between SIRT1 and adiponectin could play an essential role in calorie restriction-induced improvements in insulin sensitivity.[75,76] Adiponectin has also been shown to inhibit angiogenesis, thereby affecting adipose tissue remodeling.[77] This mechanism could be relevant in prediabetes, given that adipose tissue dysfunction is a known contributor to metabolic disorders.[78]

Lastly, a new line of research is focusing on the impact of epigenetic modifications on adiponectin expression. Methylation patterns affecting

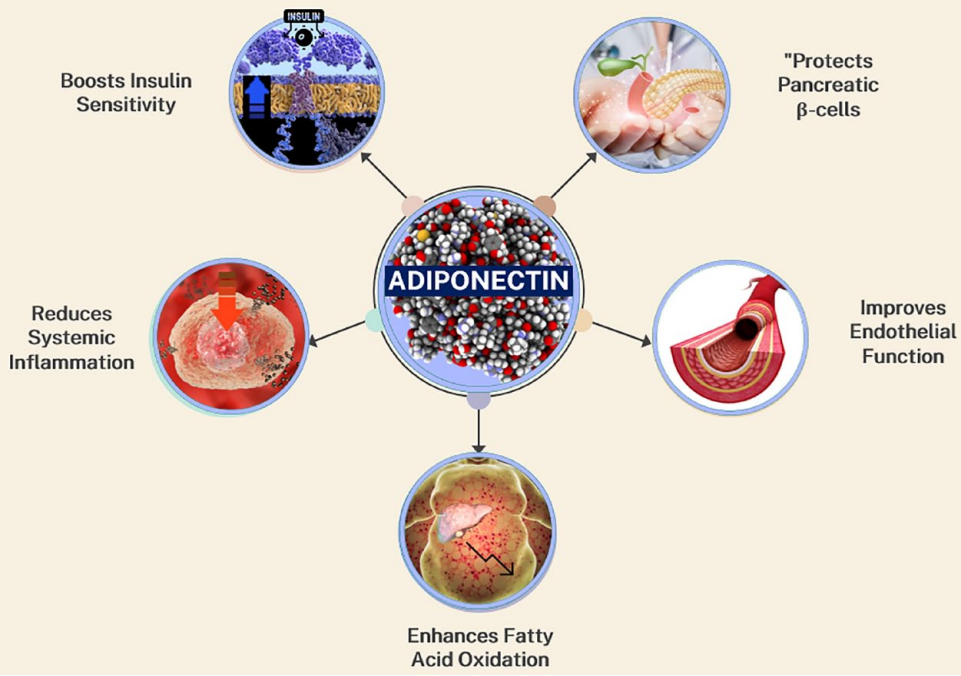

Figure 1. Adiponectin's role in mitigating the evolution from prediabetes to diabetes.

adiponectin gene expression have been associated with prediabetes, suggesting that epigenetic modulation could be a therapeutic avenue.[79,80]

As our understanding of adiponectin deepens, the complexity of its interactions with multiple physiological systems becomes more evident. This reinforces the need for a multidisciplinary approach to harness adiponectin's therapeutic potential for managing prediabetes. Given the multifaceted nature of its action, adiponectin may serve as a cornerstone for future therapies aimed at not just alleviating symptoms but potentially reversing the pathophysiological hallmarks of prediabetes.

These newly explored mechanisms further attest to the complexity of adiponectin's role in metabolic regulation and represent new frontiers for therapeutic interventions. While more studies are needed to fully understand these mechanisms and their clinical relevance, the data strongly suggest that adiponectin is a promising target for the management of prediabetes. The continuously emerging evidence underscores the multifunctional role of adiponectin in various metabolic processes and regulatory pathways. These pathways are not mutually exclusive but interact in a complex fashion, contributing to the overall metabolic profile and prediabetes risk. Consequently, adiponectin not only serves as a biomarker but also as a promising target for multifaceted therapeutic strategies in prediabetes management.

Figure 1 provides a comprehensive overview of the multi-faceted mechanisms underlying the therapeutic potential of adiponectin in the modulation and management of prediabetes.

Strategies to enhance adiponectin levels

The regulation of adiponectin, a hormone with anti-inflammatory and insulin-sensitizing properties, has gained considerable attention for its potential in managing prediabetes and mitigating the progression to type 2 diabetes. Given its role in enhancing insulin sensitivity, regulating lipid metabolism, and modulating inflammatory responses, strategies to boost adiponectin levels could offer therapeutic benefits. This section will delve into various emerging strategies aimed at enhancing adiponectin levels, focusing on innovative approaches such as gene therapy, pharmacological interventions, and combinatory treatments. The aim is to provide a comprehensive overview of the current state of research, the

challenges, and the future prospects in this exciting and rapidly evolving field.

Gene therapy

Gene therapy has emerged as a groundbreaking strategy for treating a variety of disorders, and its application in modulating adiponectin levels has gained a growing interest in recent years. One of the primary methods focuses on using viral vectors, particularly adeno-associated viruses (AAVs), to deliver adiponectin genes into targeted cells or tissues. Rodent models subjected to AAV-mediated adiponectin gene therapy have depicted improved insulin sensitivity and glucose tolerance, making them potent candidates for prediabetes management.[81–83]

Concurrently, nanoparticle-assisted delivery platforms for gene therapy have been probed to augment adiponectin concentrations. Nanoparticles allow for targeted delivery and lower risks of immunogenicity compared to viral vectors. Such nanoparticle-based approaches have shown promise in preclinical studies, increasing adiponectin levels and consequently improving metabolic markers that are particularly relevant for prediabetes.[84,85] Novel methodologies are also considering the concurrent delivery of adiponectin with other therapeutic molecules like antioxidants or anti-inflammatory agents.

Cutting-edge gene-editing tools, such as CRISPR-Cas9, have been investigated to potentially alter the adiponectin gene or its regulators, aiming for enhanced expression. This technique provides the advantage of precision and durability but also comes with challenges related to off-target effects and long-term safety.[86–88] Despite the promise, these techniques harbor challenges, primarily related to off-target effects and safety concerns. Ongoing research endeavors to harness advancements in machine learning and computational biology to refine these gene-editing strategies.[89]

Another intriguing avenue for gene therapy involves the use of small interfering RNA (siRNA) or short hairpin RNA (shRNA) to silence genes that inhibit adiponectin production. Such RNA interference (RNAi) techniques have demonstrated the capacity to enhance adiponectin levels *in vitro*.[90–92] Additionally, epigenetic interventions that modify the adiponectin gene or its regulatory regions are under exploration, potentially offering an upregulation of adiponectin levels.[93–95]

A holistic approach contemplates the synergistic potential of combining gene therapy with established pharmacological agents, such as PPAR-γ agonists, known to elevate adiponectin expression.[96–98] Such integrative approaches aim to understand how gene therapy interacts with other treatment modalities and metabolic pathways, allowing for more personalized and effective interventions.[99] Advanced gene therapy techniques, however, confront obstacles ranging from ethical quandaries to stringent regulatory frameworks and the demand for robust safety and efficacy data[100]

Pharmacological interventions

Advancements in drug discovery and research have opened up a range of pharmacological interventions aimed at enhancing adiponectin levels, a pivotal component in metabolic health. This section offers an overview of these promising agents, shedding light on their mechanisms of action and clinical relevance.

Thiazolidinediones (TZDs), Recognized for their role as peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists, TZDs, particularly pioglitazone and rosiglitazone, dualistically enhance adiponectin expression and foster its secretion within adipose tissues.[97] Clinical trials consistently report elevated circulating adiponectin levels post-TZDs treatment, often accompanied by improved insulin sensitivity.[101,102]

In tandem with TZDs, metformin, a mainstay antidiabetic biguanide, has shown the capacity to increase adiponectin levels irrespective of diabetic status. Although the exact mechanism remains under scrutiny, a plausible route suggests the involvement of AMP-AMPK activation, promoting adiponectin synthesis in adipocytes.[47,103]

Complementing these drug-based approaches are dietary supplements, with omega-3 fatty acids. Clinical trials have spotlighted the positive effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on adiponectin synthesis and release, enriching the therapeutic panorama of these fatty acids.[104–106]

Additionally, the lipid-modulating domain, represented by statins, offers another intriguing perspective. While primarily championed for cholesterol modulation, certain statins, notably atorvastatin and simvastatin, have been linked to increased adiponectin concentrations. The underlying mechanisms remain a subject of exploration but may hinge on their anti-inflammatory properties or direct adipocyte interactions.[107,108]

Rounding off this gamut of interventions is the promise shown by green tea extracts. Epigallocatechin gallate (EGCG), a potent polyphenol, has demonstrated adiponectin-enhancing potential in preliminary studies. The mechanistic roots of this effect likely reside in the antioxidative and anti-inflammatory prowess of EGCG.[109]

In addition, berberine, an alkaloid derived from various plants used in traditional medicine, has demonstrated potential in managing diabetes and dyslipidemia. There is emerging evidence suggesting that berberine can upregulate adiponectin expression, thereby modulating glucose metabolism and improving insulin sensitivity.[110]

Furthermore, medications like liraglutide and exenatide, under the GLP-1 receptor agonists umbrella, have been associated with amplified adiponectin concentrations, contributing to their repertoire of metabolic benefits.[111]

In addition, salsalate, the non-acetylated salicylate has been explored for its potential anti-diabetic properties. Clinical trials have suggested that salsalate treatment could increase adiponectin concentrations in individuals with T2DM, possibly linked to its anti-inflammatory effects.[112,113]

Resveratrol, a polyphenol predominantly found in red grapes, garners interest due to its cardioprotective and anti-diabetic prospects. Research postulates that resveratrol might enhance adiponectin secretion, presenting a novel avenue for metabolic regulation.[114]

Fenofibrate, while primarily employed for dyslipidemia management, showcases potential in amplifying adiponectin expression, hinting at a broader metabolic significance implications.[115]

A noteworthy addition to this pharmacological repertoire is AdipoRon, emerging as a unique pharmacological contender, AdipoRon mimics adiponectin's actions. By activating the AdipoR1 and AdipoR2 receptors, this small molecule holds promise in ameliorating insulin resistance and stimulating fatty acid oxidation in muscles, thereby replicating the benefits of adiponectin sans direct modulation of its levels.[116]

In summation, the pharmacological landscape is rich with agents displaying potential in adiponectin modulation. Spanning conventional medications to novel molecules, this array offers therapeutic avenues that can be harnessed for optimal metabolic health outcomes.

Dietary modifications

The interplay between diet and metabolic health is unequivocal, with mounting evidence underscoring the modulatory influence of specific dietary components on adiponectin, a salient adipokine implicated in glucose regulation and fatty acid oxidation.[44,117–121] Importantly, dietary interventions can act as pivotal modulators of adiponectin levels, presenting an opportunity for non-invasive intervention in prediabetes management.

Whole grains and dietary fiber. High intake of whole grains is positively correlated with elevated adiponectin levels. Notably, individuals consuming higher amounts of whole grains often exhibit greater plasma adiponectin concentrations, irrespective of their body composition. The bioactive compounds in whole grains, such as lignans and phenolic acids, could be responsible for these beneficial effects.[118,122,123] Similarly, the benefits of dietary fiber, especially soluble fibers like β-glucans found in oats, barley, and fruits, have been noted.[124,125] These fibers not only enhance gut health but also modulate gut hormone release. Moreover, their fermentation by gut microbiota produces short-chain fatty acids, which may stimulate adipose tissue receptors, fostering adiponectin synthesis and release.[125]

Gut health and microbiota. The gut microbiota plays a pivotal role in metabolic health. Specific strains of probiotics, such as Lactobacillus and Bifidobacterium, have been shown to potentially elevate adiponectin levels. It is speculated that probiotics might improve gut health and integrity, reduce low-grade inflammation, and modulate the release of gut peptides, indirectly influencing adiponectin synthesis and secretion.[121,126,127] Fermented foods, rich in these probiotics, further

underscore the importance of gut health. For instance, regular yogurt consumption is linked to higher adiponectin secretion, potentially due to gut microbiome shifts favoring anti-inflammatory pathways[121,128]

Antioxidants and fat. Beyond gut health, the diet's broader components play roles too. Antioxidant-rich foods like berries, dark chocolate, and spinach are associated with increased adiponectin levels.[129,130] Their antioxidant properties might counter the inhibitory impacts of oxidative stressors on adiponectin expression and affect intracellular signaling pathways in adipocytes. Another critical dietary aspect is fats. Specifically, monounsaturated and polyunsaturated fats seem to elevate adiponectin concentrations. This connection is evident in diets like the Mediterranean diet, known for its richness in these beneficial fats and its association with higher adiponectin levels.[131–133]

Bioactive compounds. Dietary compounds also play an influential role. Omega-3 fatty acids, particularly EPA and DHA, have piqued interest due to their potential anti-inflammatory properties and their possible effects on adiponectin levels. Polyphenols, prevalent in green tea and berries, alongside other compounds such as resveratrol and curcumin, have been linked to adiponectin synthesis enhancement given their antioxidative and anti-inflammatory effects.[134–136] Other noteworthy compounds include soy isoflavones, flavonoids, and bioactive peptides – all of which have been researched for their potential modulatory effects on adiponectin synthesis.[137–141]

Vitamins and minerals. Lastly, the role of specific vitamins and minerals should not be overlooked. Vitamin D, for instance, is being explored for its relationship with adiponectin, with preliminary research suggesting its supplementation might benefit those with metabolic disturbances.[130] Vitamin D can influence intracellular calcium levels. Changes in intracellular calcium are known to influence several cellular processes, including protein synthesis. Elevated calcium levels might promote the synthesis and release of adiponectin from adipocytes.[142,143] Furthermore, the supplementation of minerals like zinc and magnesium has garnered attention due to their potential roles in insulin signaling, inflammation modulation, and enzyme activities crucial for glucose and fat metabolism.[144–148]

Lifestyle changes

The complex interrelationship between lifestyle habits and adiponectin levels has become increasingly apparent. Beyond dietary considerations, numerous daily practices influence adiponectin synthesis, as underscored by emerging research. This section delves into these lifestyle elements, elucidates their mechanistic interplay with adiponectin, and provides a comprehensive roadmap for potential interventions.

Exercise and physical activity. Exercise, regardless of weight loss, positively influences adiponectin concentrations. Mechanistically, exercise stimulates the secretion of muscle-derived interleukin-6, which in turn upregulates adiponectin production. Regular physical activity also modulates adipose tissue inflammation, potentially creating an environment conducive for adiponectin synthesis.[149,150] Notably, aerobic exercises have been linked with augmented adiponectin release compared to resistance training, suggesting a differential response based on exercise modality.[45,151,152]

Weight management. The inverse association between visceral adiposity and adiponectin is well-documented.[39] Weight loss, particularly when visceral fat is reduced, can amplify adiponectin synthesis.[153,154] This effect is further accentuated by the reduction in pro-inflammatory cytokines like TNF-α, which inhibit adiponectin production.[154]

Sleep and its metabolic ramifications. Chronic sleep deprivation impacts various metabolic hormones, including adiponectin.[155,156] Studies have connected short sleep durations with metabolic syndrome,[157] while conversely, longer, quality sleep has been linked with elevated adiponectin, independent of body fat changes.[158] Disrupted sleep might heighten nocturnal noradrenaline, which could suppress adiponectin. Optimizing sleep could mitigate this suppressive effect.[159,160]

Mental well-being and stress. Chronic psychological stress, often reflected in elevated cortisol levels, appears to inhibit adiponectin synthesis.[116,161,162] Practices such as yoga, meditation, and relaxation exercises could counteract this by lowering cortisol levels, thus potentially reversing this inhibition.[163,164]

Smoking and its implications. Chronic nicotine exposure has been shown to suppress adiponectin production in adipocytes.[165,166] On the other hand, smoking cessation appears to restore and even enhance adiponectin release.[167–169]

Alcohol: A double-edged sword. The role of alcohol in adiponectin modulation is debated. Some research suggests moderate wine consumption might elevate adiponectin levels,[170,171] possibly due to ethanol and wine polyphenols, though the exact mechanism remains elusive.[172,173]. However, excessive alcohol consumption can counteract this potential benefit and further perturb metabolic homeostasis.[174]

Hydration and metabolic function. Sufficient water intake is fundamental for optimal metabolic functioning. There is emerging evidence suggesting that chronic mild dehydration can impact adipocyte functioning, possibly hampering adiponectin secretion. Adequate hydration may support the optimal physiological environment for adiponectin synthesis and release.[175]

Harnessing thermogenesis. Activities like saunas and cold exposure are being examined for their metabolic implications. Cold exposure, for instance, activates brown adipose tissue, correlating with increased adiponectin levels.[176,177] The precise mechanism may involve the activation of thermogenic genes and the subsequent effect on white adipose tissue, promoting a 'browning' effect, thereby enhancing adiponectin secretion.[178]

Caffeine: A balancing act. There is a complex relationship between caffeine and adiponectin. While short-term consumption may reduce adiponectin levels, long-term intake, particularly from sources like green tea, might be beneficial.[179,180]The positive effects might be attributed to green tea catechins that potentially elevate adiponectin synthesis.[181]

Environmental considerations. Chronic exposure to environmental toxins, like endocrine disruptors found in plastics, can reduce adiponectin release. Avoiding these toxins and adopting a lifestyle that emphasizes natural, organic living can potentially enhance adiponectin synthesis.[182–184]

To encapsulate, the myriad interconnections between lifestyle factors and adiponectin synthesis transcend just dietary influences. A comprehensive, holistic approach – one that integrates physical activity, mental well-being practices, and environmentally conscious choices – forms the foundation of strategies aimed at bolstering adiponectin levels. Such integrative interventions, grounded in robust mechanistic insights, are poised to redefine metabolic health paradigms. Figure 2 provides a comprehensive overview of the multi-faceted strategies employed to augment adiponectin levels, encompassing gene therapy techniques, pharmacological interventions, and lifestyle modifications.

Challenges in translating adiponectin therapeutics from bench to bedside

While both *in vitro* and *in vivo* studies have underscored the potential of adiponectin therapeutics, their seamless transition from the bench to bedside remains encumbered by multifaceted challenges. These challenges are delineated as follows:

Drug delivery challenges

- Protein stability: The inherent stability challenges posed by adiponectin's multimeric forms, notably its HMW multimers – believed to be the most biologically active – necessitate stringent post-production and storage conditions to preserve therapeutic efficacy.[9]
- Short half-life: The transient half-life of native adiponectin in circulation implies the potential need for frequent dosing, compromising patient convenience and possibly compliance.[185] To ameliorate this, strategies such as liposomal encapsulation and polymer conjugation are under investigation.
- Delivery route: Given the questionable bioavailability of orally administered adiponectin – attributable to its vulnerability to digestive enzymes – alternatives like intravenous delivery are considered. However, the invasiveness and impracticality of such routes for chronic conditions pose constraints.[186]

Safety and efficacy concerns

- Off-target effects: Adiponectin's diverse physiological roles might precipitate unforeseen adverse effects. Its anti-inflammatory properties, although beneficial, when exaggerated, could inadvertently quell crucial inflammatory defense mechanisms.[187]

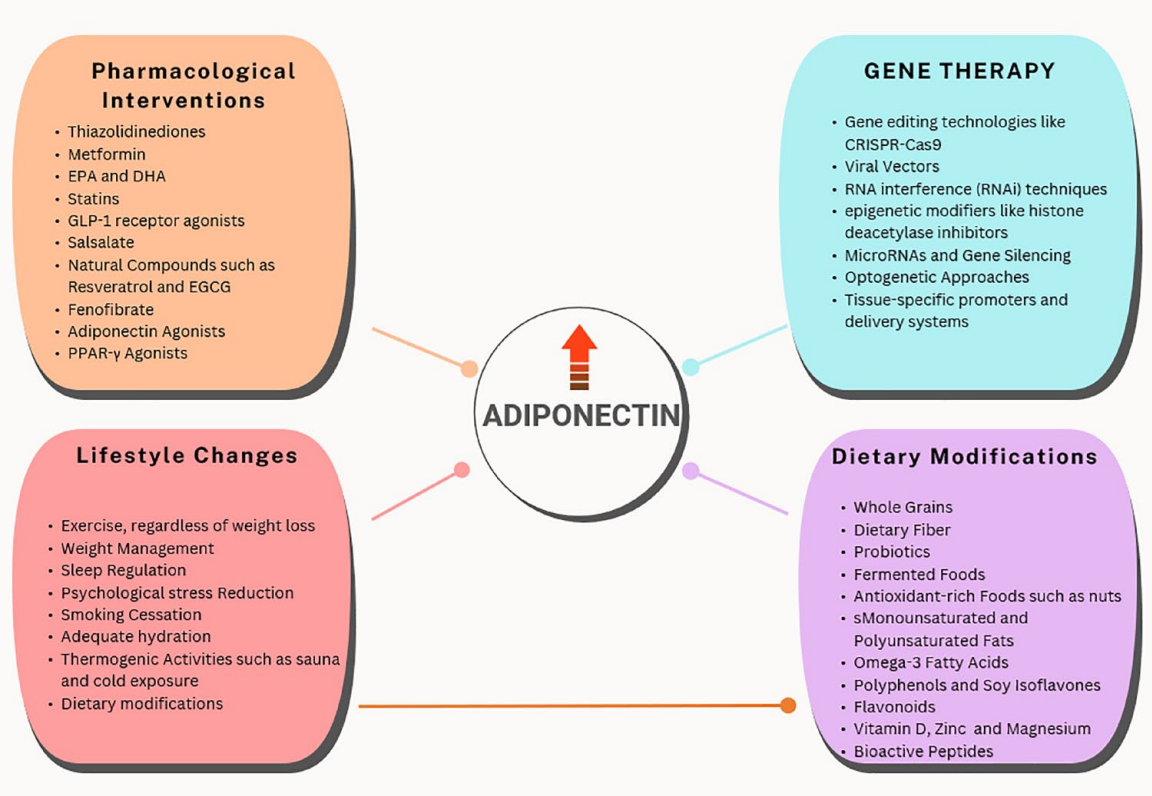

Figure 2. Strategies and approaches for adiponectin modulation: from gene therapy to lifestyle interventions. DHA, docosahexaenoic acid; EGCG, Epigallocatechin gallate; EPA, Eicosapentaenoic acid; GLP-1, Glucagon-like peptide-1; PPAR-γ, Peroxisome proliferator-activated receptor gamma.

- Dose determination: Identifying the optimal therapeutic dose is challenging. Too little might be ineffective, while excessive amounts could instigate adverse effects, given adiponectin's role in pathways beyond metabolism.[188]
- Long-term impact: The long-term effects of adiponectin supplementation or modulation remain unclear, especially concerning its roles in inflammation and vascular health.[189]

Variability in individual responses

- Genetic polymorphisms: Variants in the ADIPOQ gene, which encodes adiponectin, could influence individual responses to therapeutics, making a one-size-fits-all approach impractical.[190,191] Tailoring therapy based on genetic makeup might be a future direction.
- Personalized medicine paradigm: Given the inter-individual variability in adiponectin levels and its effects, personalized medicine approaches may be required, tailoring treatments based on individual adiponectin profiles and genetics.[12,192]
- Drug interactions: The polypharmacy often associated with metabolic syndromes raises concerns about potential drug–drug interactions, underscoring the significance of exhaustive pharmacodynamic and pharmacokinetic evaluations.[193]
- Comorbid health conditions: Diseases like renal impairment or liver diseases can alter adiponectin's metabolism and action. This further complicates therapeutic strategies and underscores the need for individualized treatments.[194]

In summation, while adiponectin's therapeutic potential is undeniable, the translation of this promise into clinical treatments requires overcoming substantial challenges. Multidisciplinary collaboration between basic researchers, clinicians, and pharmacologists is essential to navigate

these complexities and bring adiponectin therapies to the patient's bedside.

Future directions and conclusion

While pre-clinical research has robustly elucidated the metabolic, anti-inflammatory, and cardioprotective properties of adiponectin, the clinical translation of these findings has been met with considerable challenges, primarily due to the heterogeneous presentation of metabolic syndromes in the human populace. This highlights the urgent requirement for expansive multicentric trials to rigorously assess adiponectin's therapeutic landscape in diverse patient cohorts. Complicating this scenario, inherent limitations tied to the stability and delivery of native adiponectin have accentuated the scientific push toward the development of advanced adiponectin analogs. Of particular interest are adiponectin agonists, which, by mimicking or amplifying the biological effects of adiponectin, present a promising frontier for enhancing therapeutic outcomes, potentially addressing issues of stability and variability inherent to the native protein. Such innovations, combined with emergent trends in personalized medicine leveraging advanced genomics and metabolomics, forecast an evolving paradigm of therapy: one that is precision-driven, catering to the intricate nuances of individual metabolic and genetic profiles.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Mona Mohamed Ibrahim Abdalla: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing.

Acknowledgements

None.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The author declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

ORCID iD

Mona Mohamed Ibrahim Abdalla https://orcid.org/0000-0002-4987-9517

References

1. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2022. *Diabetes Care* 2022; 45: S17–S38.
2. Tabák AG, Herder C, Rathmann W, *et al*. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012; 379: 2279–2290.
3. Huang Y, Cai X, Mai W, *et al*. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ* 2016; 355: i5953.
4. Roglic G. WHO Global report on diabetes: a summary. *Int J Noncommun Dis* 2016; 1: 3–8.
5. Gao HX, Regier EE and Close KL. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *J Diabetes* 2016; 8: 8–9.
6. Andellini M, Manco M, Esposito MT, *et al*. A simulation model estimates lifetime health and economic outcomes of screening prediabetes using the 1-h plasma glucose. *Acta Diabetol* 2023; 60: 9–17.
7. Kadowaki T and Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005; 26: 439–451.
8. American Diabetes Association; Professional Practice Committee Care in diabetes—2022. *Diabetes Care* 2022; 45: S17.
9. Achari AE and Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int J Mol Sci* 2017; 18: 1321.
10. Spranger J, Kroke A, Möhlig M, *et al*. Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 2003; 361: 226–228.
11. Yamauchi T, Kamon J, Minokoshi Y, *et al*. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002; 8: 1288–1295.

12. Yamauchi T, Nio Y, Maki T, *et al*. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 2007; 13: 332–339.

13. Stern JH, Rutkowski JM and Scherer PE. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. *Cell Metab* 2016; 23: 770–784.

14. Ohashi K, Ouchi N and Matsuzawa Y. Anti-inflammatory and anti-atherogenic properties of adiponectin. *Biochimie* 2012; 94: 2137–2142.

15. Wang ZV and Scherer PE. Adiponectin, the past two decades. *J Mol Cell Biol* 2016; 8: 93–100.

16. Yamauchi T, Kamon J, Waki H, *et al*. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; 7: 941–946.

17. Waki H, Yamauchi T, Kamon J, *et al*. Impaired multimerization of human adiponectin mutants associated with diabetes: molecular structure and multimer formation of adiponectin. *J Biol Chem* 2003; 278: 40352–40363.

18. Pajvani UB, Du X, Combs TP, *et al*. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications fpr metabolic regulation and bioactivity. *J Biol Chem* 2003; 278: 9073–9085.

19. Tsao T-S, Tomas E, Murrey HE, *et al*. Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity: different oligomers activate different signal transduction pathways. *J Biol Chem* 2003; 278: 50810–50817.

20. Iwabu M, Yamauchi T, Okada-Iwabu M, *et al*. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and ampk/sirt1. *Nature* 2010; 464: 1313–1319.

21. Tsuchida A, Yamauchi T, Takekawa S, *et al*. Peroxisome proliferator-activated receptor (PPAR)alpha activation increases adiponectin receptors and reduces obesity-related inflammation in adipose tissue: comparison of activation of PPARalpha, PPARgamma, and their combination. *Diabetes* 2005; 54: 3358–3370.

22. Jung D, Bucher F, Ryu S, *et al*. An adiponectin receptor agonist antibody stimulates glucose uptake and fatty-acid oxidation by activating AMP-activated protein kinase. *Cytokine* 2020; 126: 154863–154870.

23. Okamoto Y, Folco EJ, Minami M, *et al*. Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. *Circ Res* 2008; 102: 218–225.

24. Zheng S, Shen M, Qian Y, *et al*. Growth differentiation factor-15/adiponectin ratio as a potential biomarker for metabolic syndrome in Han Chinese. *Front Endocrinol* 2023; 14: 1146376.

25. Guan Y, Zuo F, Zhao J, *et al*. Relationships of adiponectin to regional adiposity, insulin sensitivity, serum lipids, and inflammatory markers in sedentary and endurance-trained Japanese young women. *Front Endocrinol* 2023; 14: 1146376.

26. Eckstein SS, Weigert C and Lehmann R. Divergent roles of IRS (insulin receptor substrate) 1 and 2 in liver and skeletal muscle. *Curr Med Chem* 2017; 24: 1827–1852.

27. Takemura Y, Walsh K and Ouchi N. Adiponectin and cardiovascular inflammatory responses. *Curr Atheroscler Rep* 2007; 9: 238–243.

28. Gao M, Cui D and Xie J. The role of adiponectin for immune cell function in metabolic diseases. *Diabetes Obes Metab* 2023; 25: 2427–2438.

29. Eskut N, Cetiner M, Akdag G, *et al*. Effect of adiponectin on acute experimental cerebral ischemia/reperfusion injury. *Turk Neurosurg* 2023; 33: 296–301.

30. Hafiane A, Gasbarrino K and Daskalopoulou SS. The role of adiponectin in cholesterol efflux and HDL biogenesis and metabolism. *Metabolism* 2019; 100: 153953.

31. Lai H, Lin N, Xing Z, *et al*. Association between the level of circulating adiponectin and prediabetes: a meta-analysis. *J Diabetes Invest* 2015; 6: 416–429.

32. Jiang Y, Owei I, Wan J, *et al*. Adiponectin levels predict prediabetes risk: the pathobiology of prediabetes in A biracial cohort (POP-ABC) study. *BMJ Open Diabetes Res Care* 2016; 4: e000194.

33. Alfaqih MA, Al-Mughales F, Al-Shboul O, *et al*. Association of adiponectin and rs1501299 of the ADIPOQ gene with Prediabetes in Jordan. *Biomolecules* 2018; 8: 117.

34. Nakashima R, Kamei N, Yamane K, *et al*. Decreased total and high molecular weight adiponectin are independent risk factors for the development of type 2 diabetes in Japanese-Americans. *J Clin Endocrinol Metab* 2006; 91: 3873–3877.

35. Kim H-S, Jo J, Lim JE, *et al*. Adiponectin as predictor for diabetes among pre-diabetic groups. *Endocrine* 2013; 44: 411–418.

36. Brismar K, Hilding A, Ansurudeen I, *et al*. Adiponectin, IGFBP-1 and -2 are independent predictors in forecasting prediabetes and type 2 diabetes. *Front Endocrinol* 2022; 13: 109307.

37. Qiao L, Zou C, van der Westhuyzen DR, *et al*. Adiponectin reduces plasma triglyceride by increasing VLDL triglyceride catabolism. *Diabetes* 2008; 57: 1824–1833.

38. Potapov V, Chistiakov D, Dubinina A, *et al*. Adiponectin and adiponectin receptor gene variants in relation to type 2 diabetes and insulin resistance-related phenotypes. *Rev Diabet Stud* 2008; 5: 28.

39. Asayama K, Hayashibe H, Dobashi K, *et al*. Decrease in serum adiponectin level due to obesity and visceral fat accumulation in children. *Obes Res* 2003; 11: 1072–1079.

40. Moon HU, Ha KH, Han SJ, *et al*. The association of adiponectin and visceral fat with insulin resistance and β-cell dysfunction. *J Korean Med Sci* 2019; 34: e7.

41. Wang D, Fang R, Han H, *et al*. Association between visceral adiposity index and risk of prediabetes: a meta-analysis of observational studies. *J Diabetes Invest* 2022; 13: 543–551.

42. Ouchi N, Kihara S, Arita Y, *et al*. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a camp-dependent pathway. *Circulation* 2000; 102: 1296–1301.

43. Del Turco S, Navarra T, Gastaldelli A, *et al*. Protective role of adiponectin on endothelial dysfunction induced by AGEs: a clinical and experimental approach. *Microvasc Res* 2011; 82: 73–76.

44. Niramitmahapanya S, Chattieng P, Nasomphan T, *et al*. Effects of dietary supplementation on progression to type 2 diabetes in subjects with prediabetes: a single center randomized double-blind placebo-controlled trial. *Studies* 2023; 11: 18.

45. Jadhav RA, Maiya GA, Hombali A, *et al*. Effect of physical activity promotion on adiponectin, leptin and other inflammatory markers in prediabetes: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol* 2021; 58: 419–429.

46. Su JR, Lu ZH, Su Y, *et al*. Relationship of serum adiponectin levels and metformin therapy in patients with type 2 diabetes. *Horm Metab Res* 2016; 48: 92–98.

47. Duan X, Zhou M, Zhou G, *et al*. Effect of metformin on adiponectin in PCOS: a meta-analysis and a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2021; 267: 61–67.

48. Mandal P, Pritchard MT and Nagy LE. Anti-inflammatory pathways and alcoholic liver disease: role of an adiponectin/interleukin-10/heme oxygenase-1 pathway. *World J Gastroenterol* 2010; 16: 1330–1336.

49. Ye R, Holland WL, Gordillo R, *et al*. Adiponectin is essential for lipid homeostasis and survival under insulin deficiency and promotes β-cell regeneration. *eLife* 2014; 3: e03851.

50. Koch CE, Lowe C, Legler K, *et al*. Central adiponectin acutely improves glucose tolerance in male mice. *Endocrinology* 2014; 155: 1806–1816.

51. Coope A, Milanski M, Araújo EP, *et al*. AdipoR1 mediates the anorexigenic and insulin/leptin-like actions of adiponectin in the hypothalamus. *FEBS Lett* 2008; 582: 1471–1476.

52. Liu Y, Palanivel R, Rai E, *et al*. Adiponectin stimulates autophagy and reduces oxidative stress to enhance insulin sensitivity during high-fat diet feeding in mice. *Diabetes* 2015; 64: 36–48.

53. Yamauchi T, Iwabu M, Okada-Iwabu M, *et al*. Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca2+ signalling and AMPK/SIRT1 like exercise. In: *Diabetologia*. New York, NY: Springer Publishing, 2010, pp.S47–S48.

54. Sarparanta J, García-Macia M and Singh R. Autophagy and mitochondria in obesity and type 2 diabetes. *Curr Diabetes Rev* 2017; 13: 352–369.

55. López-Jaramillo P, Gómez-Arbeláez D, López-López J, *et al*. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. *Horm Mol Biol Clin Investig* 2014; 18: 37–45.

56. Dao MC, Everard A, Aron-Wisnewsky J, *et al*.; MICRO-Obes Consortium. Akkermansia muciniphila and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2016; 65: 426–436.

57. Wu H, Tremaroli V, Schmidt C, *et al*. The gut microbiota in prediabetes and diabetes: a population-based cross-sectional study. *Cell Metab* 2020; 32: 379–390.e3.

58. Le TKC, Hosaka T, Le TTT, *et al*. Oral administration of Bifidobacterium spp. Improves insulin resistance, induces adiponectin, and prevents inflammatory adipokine expressions. *Biomed Res* 2014; 35: 303–310.

59. Lee YH, Magkos F, Mantzoros CS, *et al*. Effects of leptin and adiponectin on pancreatic β-cell function. *Metabolism* 2011; 60: 1664–1672.

60. Munhoz AC, Serna JDC, Vilas-Boas EA, *et al.* Adiponectin reverses β-Cell damage and impaired insulin secretion induced by obesity. *Aging Cell* 2023; 22: e13827.

61. Retnakaran R, Ye C, Kramer CK, *et al.* Deteriorating beta cell function is the dominant determinant of progression from normal glucose tolerance to prediabetes/diabetes in young women following pregnancy. *Diabetologia* 2023; 66: 2154–2163.

62. Son J and Accili D. Reversing pancreatic β-cell dedifferentiation in the treatment of type 2 diabetes. *Exp Mol Med* 2023; 55: 1652–1658.

63. Karimi H, Nezhadali M and Hedayati M. Association between adiponectin rs17300539 and rs266729 gene polymorphisms with serum adiponectin level in an Iranian diabetic/pre-diabetic population. *Endocr Regul* 2018; 52: 176–184.

64. Alimi M, Goodarzi MT and Nekoei M. Association of ADIPOQ rs266729 and rs1501299 gene polymorphisms and circulating adiponectin level with the risk of type 2 diabetes in a population of Iran: a case-control study. *J Diabetes Metab Disord* 2021; 20: 87–93.

65. Nour-Eldine W, Ghantous CM, Zibara K, *et al.* Adiponectin attenuates angiotensin II-induced vascular smooth muscle cell remodeling through nitric oxide and the RhoA/ROCK pathway. *Front Pharmacol* 2016; 7: 86.

66. Marcus Y, Shefer G and Stern N. Adipose tissue renin-angiotensin-aldosterone system (RAAS) and progression of insulin resistance. *Mol Cell Endocrinol* 2013; 378: 1–14.

67. Srinivasa S, Fitch KV, Wong K, *et al.* RAAS activation is associated with visceral adiposity and insulin resistance among HIV-infected patients. *J Clin Endocrinol Metab* 2015; 100: 2873–2882.

68. Krause MP, Liu Y, Vu V, *et al.* Adiponectin is expressed by skeletal muscle fibers and influences muscle phenotype and function. *Am J Physiol Cell Physiol* 2008; 295: C203–C212.

69. Yusta B, Baggio LL, Estall JL, *et al.* GLP-1 receptor activation improves beta cell function and survival following induction of endoplasmic reticulum stress. *Cell Metab* 2006; 4: 391–406.

70. Kim Chung le T, Hosaka T, Yoshida M, *et al.* Exendin-4, a GLP-1 receptor agonist, directly induces adiponectin expression through protein kinase A pathway and prevents inflammatory adipokine expression. *Biochem Biophys Res Commun* 2009; 390: 613–618.

71. Saad E, Habib S and Refai W. Malondialdehyde, adiponectin, nitric oxide, C-reactive protein, tumor necrosis factor-alpha and insulin resistance relationships and inter-relationships in type 2 diabetes early stage. Is metformin alone adequate in this stage? *Age* 2017; 31: 34–42.

72. Wada T, Yamamoto Y, Takasugi Y, *et al.* Adiponectin regulates the circadian rhythm of glucose and lipid metabolism. *J Endocrinol* 2022; 254: 121–133.

73. Kervezee L, Kosmadopoulos A and Boivin DB. Metabolic and cardiovascular consequences of shift work: the role of circadian disruption and sleep disturbances. *Eur J Neurosci* 2020; 51: 396–412.

74. Szewczyk-Golec K, Woźniak A and Reiter RJ. Inter-relationships of the chronobiotic, melatonin, with leptin and adiponectin: implications for obesity. *J Pineal Res* 2015; 59: 277–291.

75. Kitada M, Ogura Y, Monno I, *et al.* Sirtuins and type 2 diabetes: role in inflammation, oxidative stress, and mitochondrial function. *Front Endocrinol* 2019; 10: 187.

76. Pistollato F, Forbes-Hernandez T, Iglesias R, *et al.* Effects of caloric restriction on immunosurveillance, microbiota and cancer cell phenotype: Possible implications for cancer treatment. *Semin Cancer Biol* 2021; 73: 45–57.

77. Li R, Du J, Yao Y, *et al.* Adiponectin inhibits high glucose-induced angiogenesis via inhibiting autophagy in RF/6A cells. *J Cell Physiol* 2019; 234: 20566–20576.

78. Choe SS, Huh JY, Hwang IJ, *et al.* Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. *Front Endocrinol* 2016; 7: 30.

79. Un Nisa K and Reza M. Key relevance of epigenetic programming of adiponectin gene in pathogenesis of metabolic disorders. *Endocr Metab Immune Disord Drug Targets* 2020; 20: 506–517.

80. Prasad RB and Groop L. Precision medicine in type 2 diabetes. *J Intern Med* 2019; 285: 40–48.

81. Long W, Hui Ju Z, Fan Z, *et al.* The effect of recombinant adeno-associated virus-adiponectin (rAAV2/1-Acrp30) on glycolipid dysmetabolism and liver morphology in diabetic rats. *Gen Comp Endocrinol* 2014; 206: 1–7.

82. Khyade V. Herbal formulation of medicines in the treatment of patients with type-2 diabetes mellitus. *J Clin Immunol Res Ther* 2021; 1: 1–9.

83. Deng H, Ai M, Cao Y, *et al*. Potential protective function of adiponectin in diabetic retinopathy. *Ophthalmol Ther* 2023; 12: 1519–1534.

84. Hossen N, Kajimoto K, Akita H, *et al*. A comparative study between nanoparticle-targeted therapeutics and bioconjugates as obesity medication. *J Control Release* 2013; 171: 104–112.

85. Lin C-Y, Adhikary P and Cheng K. Cellular protein markers, therapeutics, and drug delivery strategies in the treatment of diabetes-associated liver fibrosis. *Adv Drug Deliv Rev* 2021; 174: 127–139.

86. Wang Y, Li Y, Qiao J, *et al*. AMPK α1 mediates the protective effect of adiponectin against insulin resistance in INS-1 pancreatic β cells. *Cell Biochem Funct* 2019; 37: 625–632.

87. Bora J, Dey A, Lyngdoh AR, *et al*. A critical review on therapeutic approaches of CRISPR-Cas9 in diabetes mellitus. *Naunyn Schmiedebergs Arch Pharmacol* 2023; 396: 3459–3481.

88. Roy P, Saha S and Chakraborty J. Looking into the possibilities of cure of the type 2 diabetes mellitus by nanoparticle-based RNAi and CRISPR-Cas9 system: a review. *J Drug Deliv Sci Tech* 2021; 66: 102830.

89. Luo J. CRISPR/Cas9: from genome engineering to cancer drug discovery. *Trends Cancer* 2016; 2: 313–324.

90. Vu V, Kim W, Fang X, *et al*. Coculture with primary visceral rat adipocytes from control but not streptozotocin-induced diabetic animals increases glucose uptake in rat skeletal muscle cells: role of adiponectin. *Endocrinology* 2007; 148: 4411–4419.

91. Weigert J, Neumeier M, Bauer S, *et al*. Small-interference RNA-mediated knock-down of aldehyde oxidase 1 in 3T3-L1 cells impairs adipogenesis and adiponectin release. *FEBS Lett* 2008; 582: 2965–2972.

92. Austin RL, Rune A, Bouzakri K, *et al*. SiRNA-mediated reduction of inhibitor of nuclear factor-kappaB kinase prevents tumor necrosis factor-alpha-induced insulin resistance in human skeletal muscle. *Diabetes* 2008; 57: 2066–2073.

93. Ibrahim HIM. Epigenetic regulation of obesity-associated type 2 diabetes. *Medicina* 2022; 58: 1366.

94. Lin C-Y, Lee H-L, Chen C-W, *et al*. The role of angiotensin I-converting enzyme gene polymorphism and global DNA methylation in the negative associations between urine di-(2-ethylhexyl) phthalate metabolites and serum adiponectin in a young Taiwanese population. *Clin Epigenetics* 2023; 15: 10.

95. Wu YL, Lin Z-J, Li CC, *et al*. Epigenetic regulation in metabolic diseases: mechanisms and advances in clinical study. *Signal Transduct Target Ther* 2023; 8: 98.

96. Afzal S, Sattar MA, Johns EJ, *et al*. Antioxidant potential of adiponectin and full PPAR-γ agonist in correcting streptozotocin-induced vascular abnormality in spontaneously hypertensive rats. *PPAR Res* 2021; 2021: 6661181.

97. Sharabi Y, Oron-Herman M, Kamari Y, *et al*. Effect of PPAR-gamma agonist on adiponectin levels in the metabolic syndrome: lessons from the high fructose fed rat model. *Am J Hypertens* 2007; 20: 206–210.

98. Gastaldelli A, Sabatini S, Carli F, *et al*. PPAR-γ-induced changes in visceral fat and adiponectin levels are associated with improvement of steatohepatitis in patients with NASH. *Liver Int* 2021; 41: 2659–2670.

99. Khan S, Imran A, Khan AA, *et al*. Systems biology approaches for the prediction of possible role of Chlamydia pneumoniae proteins in the etiology of lung cancer. *PLoS One* 2016; 11: e0148530.

100. Kaufmann KB, Büning H, Galy A, *et al*. Gene therapy on the move. *EMBO Mol Med* 2013; 5: 1642–1661.

101. Riera-Guardia N and Rothenbacher D. The effect of thiazolidinediones on adiponectin serum level: a meta-analysis. *Diabetes Obes Metab* 2008; 10: 367–375.

102. Polyzos SA and Mantzoros CS. Adiponectin as a target for the treatment of nonalcoholic steatohepatitis with thiazolidinediones: a systematic review. *Metabolism* 2016; 65: 1297–1306.

103. Aj AM. The use of metformin in Non-Diabetic obesity: an educational article and Expert Opinion. *J Cancer Res Cell Ther* 2023; 7: 2640–1053.

104. Liu Y-X, Yu JH, Sun J-H, *et al*. Effects of Omega-3 fatty acids supplementation on serum lipid profile and blood pressure in patients with Metabolic Syndrome: a systematic review and meta-analysis of randomized controlled trials. *Foods* 2023; 12: 725.

105. Oster RT, Tishinsky JM, Yuan Z, *et al*. Docosahexaenoic acid increases cellular adiponectin mRNA and secreted adiponectin protein, as well as PPARγ mRNA, in 3T3-L1 adipocytes. *Appl Physiol Nutr Metab* 2010; 35: 783–789.

106. Tishinsky JM, Ma DWL and Robinson LE. Eicosapentaenoic acid and rosiglitazone

increase adiponectin in an additive and PPARγ-dependent manner in human adipocytes. *Obesity* 2011; 19: 262–268.

107. Chruściel P, Sahebkar A, Rembek-Wieliczko M, *et al*. Impact of statin therapy on plasma adiponectin concentrations: a systematic review and meta-analysis of 43 randomized controlled trial arms. *Atherosclerosis* 2016; 253: 194–208.

108. Alvarez-Jimenez L, Morales-Palomo F, Moreno-Cabañas A, *et al*. Effects of statin therapy on glycemic control and insulin resistance: a systematic review and meta-analysis. *Eur J Pharmacol* 2023; 947: 175672.

109. Wen J-J, Li MZ, Chen C-H, *et al*. Tea polyphenol and epigallocatechin gallate ameliorate hyperlipidemia via regulating liver metabolism and remodeling gut microbiota. *Food Chem* 2023; 404: 134591.

110. Wu YY, Zha Y, Liu J, *et al*. Effect of berberine on the ratio of high-molecular weight adiponectin to total adiponectin and adiponectin receptors expressions in high-fat diet fed rats. *Chin J Integr Med* 2016; 22: 1–9.

111. Simental-Mendía LE, Sánchez-García A, Linden-Torres E, *et al*. Impact of glucagon-like peptide-1 receptor agonists on adiponectin concentrations: a meta-analysis of randomized controlled trials. *Br J Clin Pharmacol* 2021; 87: 4140–4149.

112. Goldfine AB, Conlin PR, Halperin F, *et al*. A randomised trial of salsalate for insulin resistance and cardiovascular risk factors in persons with abnormal glucose tolerance. *Diabetologia* 2013; 56: 714–723.

113. Hüttl M, Markova I, Miklánková D, *et al*. Hypolipidemic and insulin sensitizing effects of salsalate beyond suppressing inflammation in a prediabetic rat model. *Front Pharmacol* 2023; 14: 1117683.

114. Fatima S, Khan DA, Aamir M, *et al*. δ-tocotrienol in combination with resveratrol improves the cardiometabolic risk factors and biomarkers in patients with metabolic syndrome: a randomized controlled trial. *Metab Syndr Relat Disord* 2023; 21: 25–34.

115. D'Ambrosio M, Bigagli E, Cinci L, *et al*. Tisochrysis lutea F&M-M36 mitigates risk factors of metabolic syndrome and promotes visceral fat browning through β3-adrenergic Receptor/UCP1 signaling. *Mar Drugs* 2023; 21: 303.

116. Formolo DA, Lee TH, Yu J, *et al*. Increasing adiponectin signaling by Sub-Chronic AdipoRon treatment elicits antidepressant- and anxiolytic-like effects independent of changes in hippocampal plasticity. *Biomedicines* 2023; 11: 249.

117. Bell L, Edwards S and Grieger J. The relationship between dietary patterns and metabolic health in a representative sample of adult Australians. *Nutrients* 2015; 7: 6491–6505.

118. Sanchis P, Calvo P, Pujol A, *et al*. Daily phytate intake increases adiponectin levels among patients with diabetes type 2: a randomized crossover trial. *Nutr Diabetes* 2023; 13: 2.

119. Khalafi M, Hossein Sakhaei M, Kheradmand S, *et al*. The impact of exercise and dietary interventions on circulating leptin and adiponectin in individuals who are overweight and those with obesity: a systematic review and meta-analysis. *Adv Nutr* 2023; 14: 128–146.

120. Naseri K, Saadati S, Ghaemi F, *et al*. The effects of probiotic and synbiotic supplementation on inflammation, oxidative stress, and circulating adiponectin and leptin concentration in subjects with prediabetes and type 2 diabetes mellitus: a GRADE-assessed systematic review, meta-analysis, and meta-regression of randomized clinical trials. *Eur J Nutr* 2023; 62: 543–561.

121. Tang C, Zhao H, Kong L, *et al*. Probiotic yogurt alleviates High-Fat diet-induced lipid accumulation and insulin resistance in mice via the Adiponectin Pathway. *J Agric Food Chem* 2023; 71: 1464–1476.

122. Polito R, Costabile G, Nigro E, *et al*. Nutritional factors influencing plasma adiponectin levels: results from a randomised controlled study with whole-grain cereals. *Int J Food Sci Nutr* 2020; 71: 509–515.

123. Qi L and Hu FB. Dietary glycemic load, whole grains, and systemic inflammation in diabetes: the epidemiological evidence. *Curr Opin Lipidol* 2007; 18: 3–8.

124. Brockman DA, Chen X and Gallaher DD. Consumption of a high β-glucan barley flour improves glucose control and fatty liver and increases muscle acylcarnitines in the Zucker diabetic fatty rat. *Eur J Nutr* 2013; 52: 1743–1753.

125. Wen J-J, Li MZ, Hu JL, *et al*. Different dietary fibers unequally remodel gut microbiota and charge up anti-obesity effects. *Food Hydrocolloids* 2023; 140: 108617.

126. Shaaban AA, Khalaf EM, Hazem SH, *et al*. WITHDRAWN: vinpocetine and Lactobacillus improve fatty liver in rats via modulating the

oxidative stress, inflammation, adiponectin and gut microbiome. *Life Sci* 2023; 331: 121931.

127. Bayat Z, Damirchi A, Hasannejad-Bibalan M, *et al*. Metabotropic effect of probiotic supplementation and high-intensity interval training in menopause-induced metabolic syndrome in rats. *J Menopausal Med* 2023; 29: 29–39.

128. Hor PK, Pal S, Mondal J, *et al*. Antiobesity, antihyperglycemic, and antidepressive potentiality of rice fermented food through modulation of intestinal microbiota. *Front Microbiol* 2022; 13: 794503.

129. Alruhaimi RS, Mostafa-Hedeab G, Abduh MS, *et al*. A flavonoid-rich fraction of Euphorbia peplus attenuates hyperglycemia, insulin resistance, and oxidative stress in a type 2 diabetes rat model. *Front Pharmacol* 2023; 14: 1204641.

130. Naliyadhara N, Kumar A, Kumar Gangwar S, *et al*. Interplay of dietary antioxidants and gut microbiome in human health: what has been learnt thus far? *J Funct Foods* 2023; 100: 105365.

131. Gonzalez-Becerra K, Barron-Cabrera E, Muñoz-Valle JF, *et al*. A balanced dietary ratio of n-6:n-3 polyunsaturated fatty acids exerts an effect on total fatty acid profile in RBCs and inflammatory markers in subjects with obesity. *Healthcare* 2023; 11: 2333.

132. Islam F, Imran A, Nosheen F, *et al*. Functional roles and novel tools for improving-oxidative stability of polyunsaturated fatty acids: a comprehensive review. *Food Sci Nutr* 2023; 11: 2471–2482.

133. de Luis DA, Primo D, Izaola O, *et al*. Interaction of the variant in the adiponectin gene rs3774261 with serum lipid profile and adiponectin levels after 9 months with a high monounsaturated fat hypocaloric diet with Mediterranean pattern. *Eur Rev Med Pharmacol Sci* 2023; 27: 7597–7606.

134. Capurso C, Bellanti F, Lo Buglio A, *et al*. Cardioprotective effects of resveratrol in the mediterranean diet: a Short narrative review. *Diet* 2023; 2: 174–190.

135. Hegde M, Girisa S, BharathwajChetty B, *et al*. Curcumin formulations for better bioavailability: what we learned from clinical trials thus far? *ACS Omega* 2023; 8: 10713–10746.

136. Weisberg SP, Leibel R and Tortoriello DV. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. *Endocrinology* 2008; 149: 3549–3558.

137. Santos Filho LED, Santos GPLD, Silva JA, *et al*. Dietary soy isoflavones prevent metabolic disturbs associated with a deleterious combination of obesity and menopause. *J Med Food* 2023; 26: 104–113.

138. Arjunan S, Thangaiyan R and Balaraman D. Biochanin A, a soy isoflavone, diminishes insulin resistance by modulating insulin-signalling pathway in high-fat diet-induced diabetic mice. *Arch Physiol Biochem* 2023; 129: 316–322.

139. Liu X, Yu Z, Zhou HH, *et al*. Effect of flavonoid intake on circulating levels of adiponectin and leptin: a systematic review and meta-analysis of randomized controlled clinical trials. *Phytother Res* 2022; 36: 4139–4154.

140. An S, Hwang SY, Gong J, *et al*. Computational prediction of the phenotypic effect of flavonoids on adiponectin biosynthesis. *J Chem Inf Model* 2023; 63: 856–869.

141. Suryaningtyas IT and Je JY. Bioactive peptides from food proteins as potential anti-obesity agents: mechanisms of action and future perspectives. *Trends Food Sci Technol* 2023; 138: 141–152.

142. Nadeem A, Saeed M, Sadiqa A, *et al*. The effect of vitamin D3 intervention on the association among vitamin D3, adiponectin, and Body Mass Index in pregnant women with gestational diabetes. *Cureus* 2023; 15: e43506.

143. Farahmand MA, Daneshzad E, Fung TT, *et al*. What is the impact of vitamin D supplementation on glycemic control in people with type-2 diabetes: a systematic review and meta-analysis of randomized controlled trails. *BMC Endocr Disord* 2023; 23: 15.

144. Heidari Seyedmahalleh M, Montazer M, Ebrahimpour-Koujan S, *et al*. The effect of zinc supplementation on lipid profiles in patients with type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of randomized clinical trials. *Adv Nutr* 2023; 14: 1374–1388.

145. Renu K, Mukherjee AG, Gopalakrishnan AV, *et al*. Protective effects of macromolecular polyphenols, metals (zinc, selenium, and copper) – polyphenol complexes, and different organs with an emphasis on arsenic poisoning: A review. *Int J Biol Macromol* 2023; 253: 126715.

146. Asghari S, Hosseinzadeh-Attar MJ, Alipoor E, *et al*. Effects of zinc supplementation on serum adiponectin concentration and glycemic control in patients with type 2 diabetes. *J Trace Elem Med Biol* 2019; 55: 20–25.

147. Markaki A, Kyriazis J, Stylianou K, *et al*. The role of serum magnesium and calcium on the association between adiponectin levels and all-cause mortality in end-stage renal disease patients. *PLoS One* 2012; 7: e52350.

148. Dall RD. *The effect of vitamin D and magnesium supplementation on bone turnover markers and glycemic indices in individuals with overweight and obesity*. Drexel University, Philadelphia, PA, 2020.

149. Tadiotto MC, Corazza PRP, Menezes-Junior FJ, *et al*. Effects and individual response of continuous and interval training on adiponectin concentration, cardiometabolic risk factors, and physical fitness in overweight adolescents. *Eur J Pediatr* 2023; 182: 2881–2889.

150. Kriketos AD, Gan SK, Poynten AM, *et al*. Exercise increases adiponectin levels and insulin sensitivity in humans. *Diabetes Care* 2004; 27: 629–630.

151. Nassis GP, Papantakou K, Skenderi K, *et al*. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism* 2005; 54: 1472–1479.

152. Hejazi K, Mohammad Rahimi GR and Rosenkranz SK. Effects of exercise training on inflammatory and cardiometabolic risk biomarkers in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Biol Res Nurs* 2023; 25: 250–266.

153. Coker RH, Williams RH, Kortebein PM, *et al*. Influence of exercise intensity on abdominal fat and adiponectin in elderly adults. *Metab Syndr Relat Disord* 2009; 7: 363–368.

154. Gariballa S, Alkaabi J, Yasin J, *et al*. Total adiponectin in overweight and obese subjects and its response to visceral fat loss. *BMC Endocr Disord* 2019; 19: 55.

155. Oliveira RF, Daniele TMDC, Façanha CFS, *et al*. Adiponectin levels and sleep deprivation in patients with endocrine metabolic disorders. *Rev Da Assoc -med Bras* 2018; 64: 1122–1128.

156. van Egmond LT, Meth EMS, Engström J, *et al*. Effects of acute sleep loss on leptin, ghrelin, and adiponectin in adults with healthy weight and obesity: a laboratory study. *Obesity* 2023; 31: 635–641.

157. Iftikhar IH, Donley MA, Mindel J, *et al*. Sleep duration and metabolic syndrome. An updated dose-risk metaanalysis. *Ann Am Thorac Soc* 2015; 12: 1364–1372.

158. Sawamoto R, Nozaki T, Furukawa T, *et al*. A change in objective sleep duration is associated with a change in the serum adiponectin level of women with overweight or obesity undergoing weight loss intervention. *Obes Sci Pract* 2016; 2: 180–188.

159. Baik I, Jun N, Yoon D, *et al*. Sleep fragmentation affects LDL-cholesterol and adipocytokines independent of food intake in rats. *Sleep Biol Rhythms* 2013; 11: 74–81.

160. Tobaldini E, Fiorelli EM, Solbiati M, *et al*. Short sleep duration and cardiometabolic risk: from pathophysiology to clinical evidence. *Nat Rev Cardiol* 2019; 16: 213–224.

161. Piao L, Zhao G, Zhu E, *et al*. Chronic psychological stress accelerates vascular senescence and impairs ischemia-induced neovascularization: the role of dipeptidyl Peptidase-4/Glucagon-Like Peptide-1-Adiponectin axis. *J Am Heart Assoc* 2017; 6: e006421.

162. Liu J, Guo M, Zhang D, *et al*. Adiponectin is critical in determining susceptibility to depressive behaviors and has antidepressant-like activity. *Proc Natl Acad Sci USA* 2012; 109: 12248–12253.

163. Sharma H, Swetanshu S and Singh P. Role of yoga in Cardiovascular Diseases. *Curr Probl Cardiol* 2024; 49: 102032.

164. Hamasaki H. The effects of mindfulness on Glycemic Control in people with diabetes: an overview of systematic reviews and meta-analyses. *Medicines* 2023; 10: 53.

165. Schwartz A and Bellissimo N. Nicotine and energy balance: a review examining the effect of nicotine on hormonal appetite regulation and energy expenditure. *Appetite* 2021; 164: 105260.

166. Zhao X, Wu F, Shen G, *et al*. Adiponectin. rs266729 polymorphism and nicotine dependence interaction: genetic investigations on the anxiety susceptibility. *Front Biosci* 2022; 27: 309.

167. Efstathiou SP, Skeva II, Dimas C, *et al*. Smoking cessation increases serum adiponectin levels in an apparently healthy Greek population. *Atherosclerosis* 2009; 205: 632–636.

168. Behl TA, Stamford BA and Moffatt RJ. The effects of smoking on the diagnostic characteristics of metabolic syndrome: a review. *Am J Lifestyle Med* 2023; 17: 397–412.

169. van der Plas A, Antunes M, Pouly S, *et al*. Meta-analysis of the effects of smoking and smoking cessation on triglyceride levels. *Toxicol Rep* 2023; 10: 367–375.

170. Nova E, San Mauro-Martín I, Díaz-Prieto LE, *et al*. Wine and beer within a moderate alcohol intake is associated with higher levels of HDL-c and adiponectin. *Nutr Res* 2019; 63: 42–50.

171. Wotherspoon A, Elshahat S, McAlinden N, *et al*. Effect of moderate red wine versus vodka consumption on inflammatory markers related to cardiovascular disease risk: a randomized crossover study. *J Am Coll Nutr* 2020; 39: 495–500.

172. Rodrigo R, Miranda A and Vergara L. Modulation of endogenous antioxidant system by wine polyphenols in human disease. *Clin Chim Acta* 2011; 412: 410–424.

173. Serio F, Imbriani G, Acito M, *et al*. Moderate red wine intake and cardiovascular Health Protection: a literature review. *Food Funct* 2023; 14: 6346–6362.

174. Li H and Xia N. Alcohol and the vasculature: a love-hate relationship? *Pflugers Arch* 2023; 475: 867–875.

175. Seal A, Suh HG, Jansen L, *et al*. Hydration and health. In: Pounis G (Ed.), *Analysis in nutrition research*. Academic Press, US, Elsevier 2019, pp. 299–319.

176. Wei Q, Lee JH, Wang H, *et al*. Adiponectin is required for maintaining normal body temperature in a cold environment. *BMC Physiol* 2017; 17: 1–11.

177. Imbeault P, Dépault I and Haman F. Cold exposure increases adiponectin levels in men. *Metabolism* 2009; 58: 552–559.

178. Wu G, Baumeister R and Heimbucher T. Molecular mechanisms of lipid-based metabolic adaptation strategies in response to cold. *Cells* 2023; 12: 1353.

179. Izadi V, Larijani B and Azadbakht L. Is coffee and green tea consumption related to serum levels of adiponectin and leptin? *Int J Prev Med* 2018; 9: 106.

180. da Silva LA, Wouk J and Weber VMR. Mechanisms and biological effects of caffeine on substrate metabolism homeostasis: a systematic review. *J Appl Pharm Sci* 2017; 7: 215–221.

181. Sone T, Kuriyama S, Nakaya N, *et al*. Randomized controlled trial for an effect of catechin-enriched green tea consumption on adiponectin and cardiovascular disease risk factors. *Food Nutr Res* 2011; 55: 8326.

182. Tomov DG, Levterova BA, Troev DM, *et al*. Serum levels of leptin and adiponectin in patients with autoimmune Hashimoto's thyroiditis. *Folia Med* 2023; 65: 199–206.

183. Wu CJ, Ho AC, Chen S-Y, *et al*. Exposure to heavy metals and serum adiponectin levels among workers: a 2-year follow-up study. *Metabolites* 2023; 13: 158.

184. Behan-Bush RM, Liszewski JN, Schrodt MV, *et al*. Toxicity impacts on human adipose mesenchymal stem/stromal cells acutely exposed to aroclor and non-aroclor mixtures of polychlorinated biphenyl. *Environ Sci Technol* 2023; 57: 1731–1742.

185. Naimo GD, Paolì A, Giordano F, *et al*. Unraveling the role of adiponectin receptors in obesity-related breast cancer. *Int J Mol Sci* 2023; 24: 8907.

186. Park S, Kim DS, Kwon DY, *et al*. Long-term central infusion of adiponectin improves energy and glucose homeostasis by decreasing fat storage and suppressing hepatic gluconeogenesis without changing food intake. *J Neuroendocrinol* 2011; 23: 687–698.

187. Holland WL, Miller RA, Wang ZV, *et al*. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. *Nat Med* 2011; 17: 55–63.

188. Garaulet M, Hernández-Morante JJ, de Heredia FP, *et al*. Adiponectin, the controversial hormone. *Public Health Nutr* 2007; 10: 1145–1150.

189. Choi HM, Doss HM and Kim KS. Multifaceted physiological roles of adiponectin in inflammation and diseases. *Int J Mol Sci* 2020; 21: 1219.

190. Mollahosseini M, Yazdanpanah Z, Nadjarzadeh A, *et al*. Study protocol for the interactions between dietary patterns and ARL15 and ADIPOQ genes polymorphisms on cardiometabolic risk factors. *Int J Prev Med* 2023; 14: 62.

191. Al-Jumaili WS, Kadhim AH and Al-Thuwaini TM. Polymorphism of the ADIPOQ gene and its association with productive traits in Awassi Ewes. *Mol Biol Rep* 2023; 50: 913–917.

192. Fosse V, Oldoni E, Bietrix F, *et al*.; PERMIT group. Recommendations for robust and reproducible preclinical research in personalised medicine. *BMC Med* 2023; 21: 14.

193. Legere RM, Taylor DR, Davis JL, *et al*. Pharmacodynamic effects of pioglitazone on high molecular weight adiponectin concentrations and insulin response after oral sugar in equids. *J Equine Vet Sci* 2019; 82: 102797.

194. Turer AT and Scherer PE. Adiponectin: mechanistic insights and clinical implications. *Diabetologia* 2012; 55: 2319–2326.