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REVIEW

Weight Management / Intervention

Nutrition and exercise: Cornerstones of health with emphasis on obesity and type 2 diabetes management—A narrative review

Hye Jin Kim[1,2,3] | Oran Kwon[3,4]

[1]Laboratory of Developmental Biology and Genomics, College of Veterinary Medicine, Seoul National University, Seoul, Republic of Korea

[2]Korea Mouse Phenotyping Center (KMPC), Seoul, Republic of Korea

[3]Logme Inc., Seoul, Republic of Korea

[4]Department of Nutritional Science and Food Management, Graduate Program in System Health Science and Engineering, Ewha Womans University, Seoul, Republic of Korea

Correspondence
Oran Kwon, Department of Nutritional Science and Food Management, Graduate Program in System Health Science and Engineering, Ewha Womans University, Seoul 03760, Republic of Korea.
Email: orank@ewha.ac.kr

Summary

While a broad consensus exists that integrated nutrition and regular exercise are foundational for health maintenance and serve as a robust non-pharmacological strategy against cardiometabolic diseases, the nuanced interplay between these elements remains incompletely understood. Through multifaceted interactions, these factors profoundly influence primary metabolic organs, notably the skeletal muscle and adipose tissue. Despite the critical nature of this interactivity, a holistic understanding of the combined effects of physical activity and dietary practices is still emerging. This narrative review aims to elucidate the intertwined roles of nutrition and exercise. It provides a comprehensive overview of their synergistic dynamics and emphasizes the importance of a dual-focus approach in mitigating and managing cardiometabolic disorders, predominantly obesity and type 2 diabetes.

KEYWORDS
exercise, nutrition, obesity, type 2 diabetes

1 | INTRODUCTION

Over the years, extensive research endeavors have been devoted to elucidating the impact of nutrition and exercise on metabolic homeostasis and disease modulation across both human and animal paradigms. These comprehensive investigations, encompassing molecular, physiological, and phenotypic realms, have significantly expanded our understanding of optimizing health. Within this paradigm, parameters such as periodicity, intensity, duration, and modality, conjoined with strategic dietary interventions, play crucial roles. The scientific literature has recurrently highlighted the critical importance of diet and exercise as non-pharmacological pillars for enhancing cardiometabolic well-being.[1–4] Exercise regimens and dietary management constitute core components of lifestyle modification strategies aiming at cardiometabolic disorders, a stance strongly supported by an extensive compendium of clinical trial data.

However, despite these scientific advancements, the global incidence of obesity and cardiometabolic disorders is still rising.[5,6] This gap between academic progress and tangible health metrics may be attributed to motivation, prevailing needs, and implementation

Abbreviations: AET, aerobic exercise training; AKT, serine–threonine protein kinase; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BAT, brown adipose tissue; BMI, body mass index; CVD, cardiovascular disease; FA, fatty acid; FBG, fasting blood glucose; FMR, fat-to-muscle ratio; HbA1c, glycated hemoglobin; HIIT, high-intensity interval training; IMTG, intramuscular/intramyocellular triglyceride; IR, insulin resistance; LD, lipid droplet; LDL, low-density lipoprotein; mTOR, mammalian target of rapamycin; p70S6K, ribosomal S6 kinase; PI3K, phosphoinositide 3-kinase; RET, resistance exercise training; T2D, type 2 diabetes; TG, triglyceride; WAT, white adipose tissue.

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strategies. Moreover, the insufficient investigation into the combined effects of nutrition and physical exercise might contribute to this paradox. A comprehensive understanding of the physiological and molecular mechanisms is indispensable for a compelling appraisal of the benefits of a prudent diet and regular exercise. This understanding could then steer the development of future strategies based on the latest clinical and translational research insights. Moreover, it is imperative to examine the controversial molecular mechanisms identified in animal models for their potential relevance to human physiology. Such exploration could elucidate the complex interplay among target organs, which remains a significant challenge in human studies.

This narrative review is divided into two sections: the first examines the integrative impact of nutrition and physical exercise on managing obesity and type 2 diabetes (T2D), and the second addresses the fundamental biological targets implicated in nutritional and exercise-based interventions for obesity and T2D intervention. The initial section elucidates the objectives and benchmarks for obesity and T2D management, delving into evidence-based strategies about physical activity and dietary regulation that have shown potential in reducing the prevalence of these conditions while also highlighting the cumulative benefits of combining nutritional and exercise interventions. The subsequent section delves into the intersecting molecular and physiological pathways influenced by exercise and dietary patterns, focusing on the modulation of circadian rhythms as a therapeutic lever for obesity and T2D management. This review aims to inform and inspire the development of future personalized healthcare strategies, emphasizing the health advantages of a balanced diet combined with consistent physical exercise.

2 | METHODS

A comprehensive literature review was conducted in the PubMed database to ascertain the impact of dietary and exercise interventions on controlling obesity and T2D. The data extraction strategy is shown in Figure 1. The search strategy was expansive, encompassing a temporal span without restrictions and utilized a combination of keywords: "obesity" OR "T2D" AND "diet" OR "nutrition" OR "nutrients" OR "combined nutrition and exercise" AND "adipose tissue" OR "browning" OR "skeletal muscle" OR "muscle." We included all modalities of physical activity in our criteria. Publications not in Korean and English and those of pediatric or adolescent populations were excluded from consideration. Furthermore, research involving subjects with comorbid conditions beyond obesity and T2D, those narrowly concentrating on postmenopausal women, and studies examining pharmacological treatments like appetite suppressants, lipid absorption modulators, and GLP-1 receptor agonists were also excluded from the review.

3 | RESULTS

3.1 | The combined effects of nutrition and exercise in combating obesity and T2D

Obesity is a multifaceted and complex condition recognized as a primary risk factor for the onset of cardiometabolic diseases. The World Health Organization (WHO) defines overweight and obesity as "abnormal or excessive fat accumulation that presents a health risk."[5] The onset of obesity is fundamentally linked to an individual's

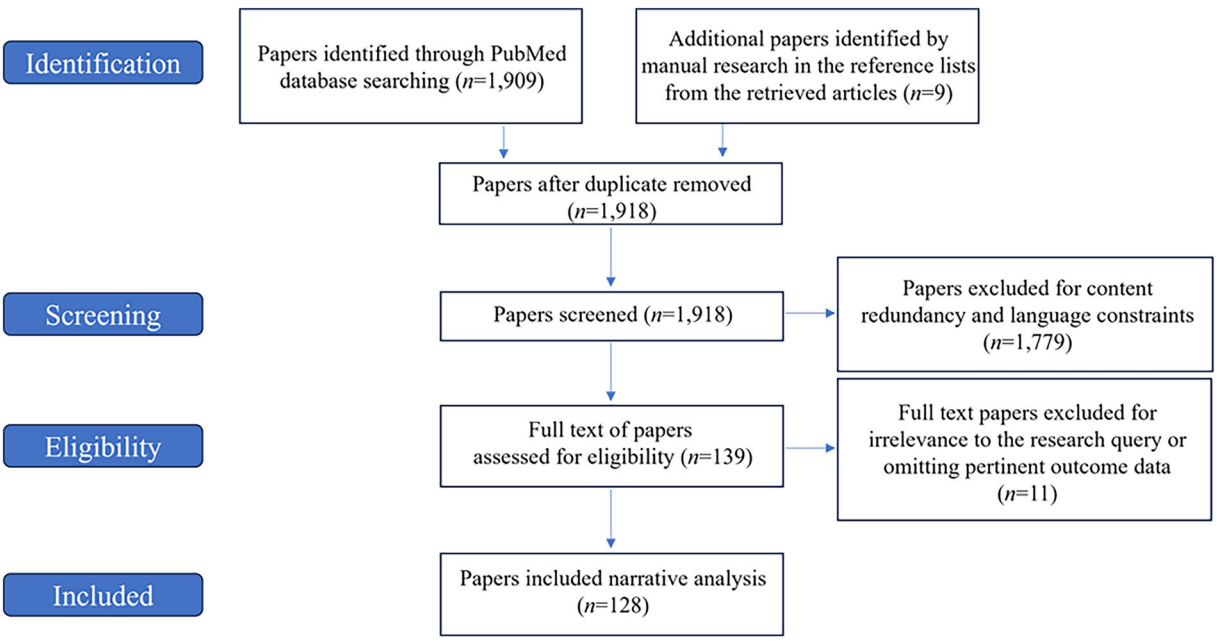


FIGURE 1 The data extraction strategy.

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ability to manage body fat and muscle mass, escalating the risk of various health complications. The emergence of obesity is frequently attributed to a combination of factors, which include excessive energy intake, insufficient physical activity, and genetic susceptibility. On the other hand, lifestyle modifications can effectively alleviate obesity and its associated disorders. In this review, our primary focus will be on the roles that fat and muscle play within the context of obesity. We will also explore how the combined impact of dietary practices and physical exercise can mitigate obesity by promoting metabolic changes within adipose tissue and skeletal muscle.

T2D is a metabolic disorder characterized by insulin resistance (IR) and reduced glucose storage capacity in hepatic and muscular tissues, leading to persistent hyperglycemia and associated complications. While T2D can manifest in any individual, it is predominantly linked to obesity, sedentary lifestyles, poor diet, and genetic predisposition. Notably, the increased risk of T2D is frequently linked to excess visceral fat, which potentiates inflammation and IR.[7,8] Early detection and effective management of T2D are imperative to avert or postpone associated complications, thereby optimizing health outcomes. Comprehensive therapeutic approaches combining balanced nutrition and regular exercise are advocated to enhance insulin sensitivity, regulate glycemic levels, and ameliorate overall metabolic wellness.

3.1.1 | Adipose tissue and skeletal muscles: Central targets in managing obesity and T2D

Extensive research on obesity and T2D underscores that body weight, body mass index (BMI), or body fat mass cannot singularly define these conditions. Contemporary understanding advocates a comprehensive approach that concurrently considers adipose tissue and skeletal muscle.

Adipose tissue

Adipose tissue, broadly categorized into white adipose tissue (WAT) and brown adipose tissue (BAT), is pivotal in maintaining energy equilibrium through its metabolic, cellular, and endocrine activities.[9] While WAT has traditionally been recognized for its roles in caloric storage and insulation, it is now understood as a dynamic endocrine organ. It secretes hormones such as leptin and adiponectin and produces a range of adipokines.[7] Furthermore, WAT orchestrates systemic energy homeostasis by modulating nutrient storage and utilization in skeletal muscle and liver through the release of adipocyte-derived exosomes.[10,11]

A comprehensive review of human trials revealed pronounced effects of both aerobic exercise training (AET) and resistance exercise training (RET)—either individually or synergistically—on biomarkers like adiponectin, omentin, leptin, interleukin-6, and resistin.[12] Parallelly, dietary strategies such as caloric restriction, probiotics, omega-3 polyunsaturated fatty acids (FAs), polyphenolic supplementations, and other nutritional interventions have been shown to enhance body composition and modulate inflammatory responses by attenuating leptin levels and amplifying adiponectin levels.[13] As such, strategically targeting WAT within exercise and dietary regimens may emerge as a cornerstone in developing therapeutic approaches for obesity and T2D.

The activation of BAT has been evidenced to counteract obesity in rodents and humans.[14–16] Historically, BAT was traditionally thought to be prevalent in rodents and diminished in humans post-neonatal development; however, recent evidence has identified its presence in adults, positioning it as a focal point in obesity research.[9,16–18] Studies indicate that cold exposure enhances glucose and FA uptake in the anatomical regions containing human BAT, a phenomenon associated with increased energy expenditure.[19] In rodent models, BAT functionality tends to decline as it undergoes adipogenic transdifferentiation into WAT, a process influenced by factors such as elevated ambient temperatures, aging, or a high-fat diet consumption.[20,21] Inferring from these findings, it is conceivable that individuals in thermoneutral environments may experience decreased BAT activity, which could be further compounded by the effects of aging or high-fat consumption. Current research indicates that individuals with active BAT display a lower prevalence of cardiometabolic disorders, elevated diet-induced thermogenesis, and a more favorable respiratory exchange ratio than those with inactive BAT.[22,23] Such data suggest that individuals with active BAT may experience increased energy expenditure and enhanced FA metabolism, offering insights into BAT's potential in mitigating obesity and T2D. However, a study assessing sedentary young adults reported no significant alterations in BAT volume or function following a 24-week exercise regimen.[24] These observations underscore the need for more rigorous research to elucidate the relationship among exercise, BAT-driven thermogenesis, and beige adipogenesis in humans.

Skeletal muscle

Skeletal muscle constitutes roughly 40% of the body mass in individuals uneffected by obesity, making it the largest organ in the humans body. Obesity increases IR, leading to subsequent disruptions in glucose uptake and storage within muscle tissues.[25–27] Clinical investigations have revealed that individuals with obesity are characterized by increased intramuscular or intramyocellular triglyceride (IMTG) levels, coupled with a reduced capacity for lipid beta-oxidation.[28–30] Elevated IMTG concentrations are inversely related to insulin-mediated glucose uptake.[31] Interestingly, a unique observation, termed the "athlete's paradox," has been noted, wherein elite endurance athletes exhibit remarkable insulin sensitivity despite possessing significant IMTG reservoirs.[31,32] The implications and mechanistic basses of this paradox warrant further investigation.

Lipid droplets (LDs) within skeletal muscle predominantly reside in two main domains: the subsarcolemmal and intermyofibrillar regions.[31,32] Evidence suggests that intermyofibrillar LD volume markedly decreases following high-intensity exercise, whereas subsarcolemmal LDs remain consistent.[32] This result indicates that intermyofibrillar LDs serve as a critical energy reservoir during exercise. Investigations involving elite endurance athletes have similarly documented decreased intermyofibrillar LDs after high-intensity

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workouts. Conversely, individuals with T2D tend to accumulate more subsarcolemmal LDs.[31] The higher total IMTG content observed in endurance athletes might be attributed to a greater concentration of intermyofibrillar LDs rather than subsarcolemmal LDs. This differential distribution and their response to exercise might offer valuable perspectives on muscle metabolic processes and the divergent IMTG storage patterns between athletes and those afflicted with metabolic disorders like T2D.

In an attempt to lose weight, patients with obesity often engage in extreme dieting or increased physical activity. However, the nutritional imbalance from extreme dieting can trigger protein breakdown in skeletal muscle, leading to decreased muscle mass and a subsequent decline in the overall metabolic rate.[33] Thus, a careful balanced approach to diet and exercise is crucial to protect skeletal muscle protein from the negative impacts of calorie and nutrient deficits. By providing adequate nutrient and caloric intake, individuals can maintain muscle health and mitigate the adverse effects of calorie restriction on muscle integrity. The inclusion of exercise, especially resistance training, enhaces muscle protein synthesis and helps maintain muscle mass.[34] Hence, an integrated strategy that aligns proper nutrition with exercise stands pivotal in addressing and improving the complexities of obesity and T2D.

Emerging biomarkers in obesity and T2D

In recent years, a growing body of research has focused on the fat-to-muscle ratio (FMR), a biomarker that indicates the proportion of fat to muscle mass, as a potent predictor for cardiometabolic risk factors.[35–37] Higher FMR values have shown positive correlations with IR,[37] elevated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values,[37–39] higher levels of low-density lipoprotein (LDL) cholesterol,[40] and a greater prevalence of metabolic syndrome in adults. Conversely, studies utilizing the muscle-to-fat ratio (MFR), which is the inverse of FMR, have found that a lower MFR is associated with increased triglyceride (TG), fasting blood glucose (FBG), glycated hemoglobin (HbA_{1c}), and high-sensitivity C-reactive protein levels in older adults, while negatively correlated with physical function.[35] These findings suggest that individuals with a high body fat percentage relative to muscle mass are more susceptible to T2D. Although the volume of studies utilizing FMR to assess cardiometabolic health is still less compared with traditional metrics like body weight or BMI, the emerging evidence suggests that FMR could become an important marker for assessing obesity-related cardiometabolic health in future studies.

The weight-adjusted waist index (WWI), a novel anthropometric measure of obesity, has recently gained scientific attention. WWI is calculated by dividing waist circumference (cm) by the square root of body weight (kg).[41] Recent research has revealed that WWI is a unique adiposity indicator that exhibits a linear positive correlation with both cardiometabolic morbidity and mortality. Its predictive capabilities are notable, particularly in forecasting the risk of cardiovascular disease (CVD) onset and all-cause mortality, and this predictive accuracy is further enhanced when used in combination with BMI.[41–43]

3.1.2 | Nutrition and exercise in combating obesity and T2D

Nutrition

The nutritional guidelines for obesity and T2D management have undergone marked advancements over the past several decades, reflecting a paradigm shift in understanding the complex relationship between diet and disease management. Although traditional dietary strategies focusing on calorie counting have achieved meaningful health improvements, a critical argument in contemporary nutritional science is that focusing exclusively on individual nutrients neglects the essential interactions between nutrients and bioactive molecules. These complex interactions are crucial for regulating gene transcription, modulating the structure and function of cellular membranes, influencing ion channel activities and electrophysiological processes, and affecting a myriad of biological pathways, as elucidated by Wu et al.[44]

The growing body of scientific literature emphasizes the critical role of diet quality as a fundamental determinant shaping the long-term impacts of dietary practices on the incidence and management of obesity and T2D.[45–47] Within the scope of obesity, a robust scientific consensus exists on the benefits of consuming a diet abundant in minimally processed, bioactive foods. This dietary pattern encompasses diverse fruits, non-starchy vegetables, whole grains, nuts, seeds, legumes, oils extracted from plants, yogurt, and fish—all noted for their nutrient density and health-promoting properties. Experts advise a moderate consumption of unprocessed red meats, poultry, eggs, and dairy products to balance the intake of essential nutrients with potential health risks. Moreover, dietary guidelines strongly caution against consuming foods high in refined starches, added sugars, processed meats, and other ultra-processed food items typically high in sodium, added sugars, or trans fats.

The adoption of regular, balanced meals and reduction of snaking or dining out frequency are recommended strategies to reduce the risk of overconsumption and to enhance caloric balance.[48,49] Experimental evidence from animal models has indicated that modifications in meal timing, independent of caloric intake, can influence obesity and its associated metabolic outcomes.[50,51] In a human study, data suggest that a higher caloric intake earlier in the day may leads to more pronounced benefits in terms of body weight reduction, waist circumference, FBG, insulin levels, and HOMA-IR in women with obesity compared with equivalent caloric reduction in the evening, even if their daily calorie intake is identical.[52] Conversely, a recent study indicated that the distribution of calories throughout the day does not significantly alter daily energy expenditure, metabolic rate, or weight loss outcomes. Yet, it has been observed that individuals consuming a greater calorie proportion in the morning report reduced appetite, which could potentially facilitate weight loss.[53] These insights are integral to formulating guidelines to optimize caloric distribution and nutritional quality to support effective weight management and enhance metabolic health.

For effective T2D management, nutritional strategies commonly prioritize consuming nutrient-dense foods evenly distributed across meals throughout the day to reduce fluctuations in blood glucose

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concentrations. Diets rich in dietary fiber are particularly recommended due to their role in modulating glycemic response and enhancing satiety, which can decrease the propensity for overconsumption.[54] Additionally, the concepts of dietary glycemic index (GI) and glycemic load (GL) have been examined within epidemiological studies for their associations with T2D risk, revealing significant correlations. A comprehensive meta-analysis of prospective cohort studies by Livesey et al.[45] provided robust evidence supporting the causal linkage between higher GI and GL with increased T2D incidence. This analysis suggests that while general food-based guidelines remain a cornerstone of dietary advice, incorporating knowledge about the GI or GL values of foods could refine and enhance the quality of food selection within the categories established by such guidelines.

Contemporary management of obesity and T2D now incorporates dietary pattern-based interventions. Systematic reviews have provided evidence supporting the efficacy of dietary patterns such as the Mediterranean diet,[47,55] the Dietary Approaches to Stop Hypertension (DASH) diet,[56] low-carbohydrate diets,[57] the ketogenic diet,[58] and plant-based diets[59] in reducing the prevalence of obesity and T2D. These diets emphasize the consumption of fruits, vegetables, whole grains, lean proteins, and healthy fats, while minimizing processed foods and added sugars.

The ketogenic diet involves a substantial reduction in carbohydrate intake, prompting the body to enter a state of ketosis where it efficiently metabolizes fat for energy and produces ketones in the liver, which serve as an alternative energy source for the brain. The typical macronutrient distribution of a ketogenic diet includes approximately 65–80% of calories from fat, 20–25% from protein, and a mere 5–10% from carbohydrates. Several studies have shown that a ketogenic diet can suppress appetite and enhance feelings of fullness, which may reduce abdominal fat and overall weight loss. For individuals with T2D, a ketogenic diet can contribute to a reduction in carbohydrate consumption, thereby moderating glycemic excursions and potentially decreasing insulin requirements.[60] However, the long-term implications of such regimens are not yet fully understood, and there may be short-term benefits.[61] Additionally, the ketogenic diet may trigger side effects, including nutritional deficiencies stemming from the restriction of certain nutrient-rich food groups, an increase in harmful cholesterol levels due to its high-fat composition, and the onset of symptoms commonly referred to as the "keto flu," which includes headache, fatigue, and gastrointestinal discomfort.[62] Adherence to the ketogenic diet poses a challenge for many individuals due to these factors and the significant alterations it requires in habitual dietary patterns.

Exercise

The health benefits of regular exercise are no longer a subject of debate; the focus now lies in tailoring it to individual needs. This section discusses AET, RET, and high-intensity interval training (HIIT), which are recommended for preventing and managing obesity and T2D.

AET constitutes a mode of physical activity designed to bolster cardiorespiratory fitness by employing extensive muscle groups, rendering it indispensable to any comprehensive fitness regimen. AET modalities span brisk walking, running, swimming, hiking, or cycling.[63–65] Consistent participation in AET amplifies oxygen utilization within skeletal muscles and augments the cardiorespiratory system's capacity to transport oxygen.[63] This enhancement culminates in elevated aerobic capacity, facilitating heightened energy yield via glucose and lipid catabolism, consequently preventing fat accumulation and enhancing glucose uptake.[66] Specifically, AET contributes to the moderation of resting heart rate, regulation of blood pressure, increasing high-density lipoprotein (HDL) cholesterol levels, and diminution of LDL cholesterol and TG levels.[63,64] Hence, AET is globally acclaimed as a paramount intervention methodology for the prophylaxis and therapy of myriad metabolic maladies, encompassing obesity, T2D, CVD, hypertension, and hepatic steatosis. Reflecting the considerable benefits of AET, the WHO recommends that adults (aged 18–64) undertake at least 150–300 min of moderate-intensity or 75–150 min of vigorous-intensity AET per week.[64] Depending on factors like heart rate, VO_2 max, or musculoskeletal conditions, one can commence their fitness journey with low to moderate-intensity exercises and gradually progress to higher-intensity exercises as their fitness level improves.

RET is a type of physical activity that enhances skeletal muscle mass, strength, endurance, posture, autonomy, and body balance.[67] RET can be implemented using body weight, free weights, weight machines, resistance bands, or other equipment. RET is recognized as a crucial intervention for preserving and enhancing cardiometabolic health, given the emerging role of skeletal muscle as a metabolic regulator.[26] Additionally, enhancements in VO_2 max and improvements in LDL cholesterol, TG, and FBG have been observed in older adults at high cardiometabolic risk following RET.[68] Extended RET for 12 weeks or longer amplified muscle mass and the strength-to-mass ratio, particularly in older individuals.[69] Given studies highlighting a strong correlation between low muscle strength and increased mortality rates in older individuals or those with chronic diseases, RET is a highly appropriate intervention.[70–72] Ashton et al.[68] examined the effects of short-, medium-, and long-term RET on cardiometabolic health in adults, showing that medium-term interventions offered the most compelling results. However, these conclusions are based on the relative number of published studies, and it should not be inferred that medium-term RET is definitively the most effective.

HIIT consists of short (<45 s) to long (2–4 min) bursts of high-intensity exercise interspersed with recovery periods.[73] Despite necessitating less time commitment than continuous exercise, HIIT provides comparable efficacy due to its potent physiological effects,[74–76] rendering it a viable option for individuals with time constraints. In 2018, the Physical Activity Guidelines Advisory Committee evaluated scientific data contrasting HIIT with moderate-intensity continuous AET, specifically concerning cardiometabolic health benefits. As summarized by Campbell et al.,[77] the findings indicated that HIIT improves cardiometabolic risk factors like IR, blood pressure, and body composition in adults, mirroring the magnitude of effects induced by moderate-intensity AET. Significantly, HIIT proved more effective in overweight adults and those at higher risk for CVD and

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T2D, regardless of age or sex. However, HIIT may not be suitable for everyone, particularly individuals unaccustomed to high-intensity physical activity or those with underlying medical conditions.[76] Consequently, seeking consultation with a healthcare professional before initiating a HIIT regimen is highly advisable. A recent study suggested that after 12 weeks of moderate-intensity continuous exercise and HIIT, participants exhibited comparable metabolic enhancements irrespective of exercise intensity and volume differences. Moreover, both forms of exercise prompted structural alterations in the abdominal subcutaneous adipose tissue and impacted factors that regulate metabolism and inflammatory signaling pathways in adults with obesity.[78] These insights propose that the efficacy of exercise in boosting metabolism and altering adipose tissue is attributed to the act of exercising itself, not necessarily the specific exercise modality.

Combination of exercise and nutrition

Dietary interventions possess the potential to modulate adipose tissue metabolism,[79] while exercise interventions aim to amplify energy expenditure and enhance metabolic flexibility within adipose tissue.[80] Therefore, integrating exercise with a balanced diet can yield a synergistic metabolic response.[81]

As an illustration, integrating RET with an energy-restricted high-protein diet may facilitate weight reduction, engender favorable alterations in body composition, and amplify functional physical performance in adults with obesity.[82] Such a combination also enhances glycemic control and CVD risk markers in overweight and individuals with obesity diagnosed with T2D.[83] Recent investigations underscore that combining HIIT with carbohydrate and energy restriction dampens appetite.[84,85] Furthermore, HIIT can serve as a potent therapeutic avenue for obesity by elevating the serum levels of "Lac-phe," a conjugate of lactate and phenylalanine known to suppress appetite.[86]

Legaard et al.[87] conducted a 16-week intervention study focusing on the effects of dietary changes coupled with exercise in patients diagnosed with T2D within the preceding 7 years. While significant weight reduction was evident in the diet-only group, more substantial improvements were found in parameters associated with T2D in the combined group. Notably, the confluence of diet and exercise exhibited greater efficacy when exercise was performed six times weekly instead of thrice. The researchers posited that weight loss achieved through dietary strategies predominantly enhanced hepatic insulin sensitivity and augmented beta-cell insulin secretion. In contrast, exercise predominantly boosted peripheral insulin sensitivity.

A randomized clinical trial study demonstrated that an intensive lifestyle regimen, encompassing both AET and RET over 12 months, coupled with dietary restrictions, was more effective in reducing HbA_{1c} levels in patients with T2D than a standard lifestyle intervention (comprising diet and exercise education). This intensified approach also reduced the usage of glucose-lowering medications.[88] However, a follow-up intervention utilizing the same protocol indicated that, while the intensive lifestyle strategy could induce diabetes remission in patients with T2D, there were no appreciable differences in metrics such as glycemic control, blood lipids, and body composition 12 months post-intervention when contrasted with the standard intervention.[89] Such outcomes underscore the premise that the efficacy of lifestyle interventions hinges upon rigorous oversight and enduring commitment.

Magkos et al.'s review[90] posits that sustaining weight loss through carbohydrate restriction can enhance metabolic benefits. Combined with increased oxygen consumption through regular exercise training, it can significantly improve outcomes for individuals with T2D. Notably, while weight gain is a known onset of T2D, the accumulation of excess adipose tissue further aggravates IR, compromising the metabolic function of crucial organs such as skeletal muscle, liver, and pancreas.[91] Thus, the primary emphasis should pivot towards adipose tissue reduction rather than merely targeting weight reduction in preventive and therapeutic strategies for T2D and obesity. Integrating dietary and exercise interventions is crucial to mitigate muscle loss depletion during weight loss efforts. However, as outlined in Table 1, research probing the combined effects of nutrition and exercise report heterogenous outcomes, highlighting the need for more rigorous and detailed researcch in this domain.

3.2 | Nutrition and exercise interventions: Mechanistic targets in the management of obesity and T2D

3.2.1 | Molecular mechanisms

Both physical activity and caloric restriction have been proven to boost insulin sensitivity. The discovery that exercise and caloric restriction stimulate the AMPK signaling pathway has positioned AMPK as a crucial target in T2D treatment.[102] AMPK activation has several beneficial effects on glucose metabolism, reinforcing its appeal for developing therapeutic strategies for T2D. Metformin, the most widely prescribed T2D drug, also activates AMPK to improve insulin sensitivity.[103]

During exercise, working muscles require a steady energy supply. As glycogen is metabolized to produce adenosine triphosphate (ATP), the adenosine monophosphate (AMP)/ATP ratio increases within the muscle cell, triggering AMPK activation.[102,104] Additionally, exercise-induced muscle contraction prompts calcium release from the sarcoplasmic reticulum within muscle cells. This surge in intracellular calcium levels stimulates AMPK activation.[104] Epinephrine and cortisol from adrenalin glands activate AMPK via particular signaling pathways, adding to the overall AMPK activation during exercise.[105]

Insulin orchestrates skeletal muscle metabolism by fostering glucose transport, glycogen synthesis, and protein synthesis through the phosphoinositide 3-kinase (PI3K)/serine–threonine protein kinase (AKT) signaling pathway.[106] Insulin-triggered phosphorylation of AKT induces the translocation of glucose transporter 4 to the cell membrane, thereby enhancing glucose uptake into skeletal muscle cells and activating glycogen synthase (GS). Activated GS converts

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TABLE 1 Synthesis of randomized controlled trial findings: Diet and exercise interplay in obesity and T2D management.

Study	Study design	Duration	Diet intervention	Exercise intervention	Result
Otten et al., 2017.[92]	Randomized control trial. Patients with T2D (53–66 years). Paleolithic diet (PD), $n = 15$ (male, $n = 10$; female, $n = 5$); PD + EX, $n = 14$ (male, $n = 9$; female, $n = 5$).	12 weeks	PD (ad libitum).	Supervised AET + RET: 3 times/week, total 60 min/day. AET: moderate-to-high intensity cycling, with a gradual increase in intensity from week to week. RET: upper and lower body, 2–4 sets, 10–15 reps.	1. Improve fat mass ($p < 0.001$) and metabolic balance including insulin sensitivity ($p < 0.001$), glycemic control ($p < 0.01$), and leptin ($p < 0.001$). 2. EX did not provide additional effects but preserved lean mass in men and increased cardiovascular fitness.
Often et al., 2019.[93]	Randomized control trial. Adults with overweight/obesity and T2D (52–66 years). PD, $n = 11$ (male, $n = 7$; female, $n = 4$); PD + EX, $n = 11$ (male, $n = 7$; female, $n = 4$).	12 weeks	PD (ad libitum).	Supervised AET + RET: 3 times/week, total 60 min/day. AET: moderate-to-high intensity cycling, with a gradual increase in intensity from week to week. RET: upper and lower body, 2–4 sets, 10–15 reps.	1. The combination of EX and PD was linked to favorable alterations in cardiovascular structure and function. 2. Decreased TG levels ($p = 0.038$).
Otten et al., 2018.[94]	Randomized control trial. Patients with T2D (30–70 years). PD, $n = 13$ (male, $n = 9$; female, $n = 4$); PD + EX, $n = 13$ (male, $n = 8$; female, $n = 5$).	12 weeks	PD (ad libitum).	Supervised AET + RET: 3 times/week, total 60 min/day. AET: moderate-to-high intensity cycling, with a gradual increase in intensity from week to week. RET: 30–40 min of RET upper and lower body.	1. PD reduced liver fat and IMCL content ($p < 0.05$). 2. There was a heterogeneous response to additional exercise training across organizations ($p < 0.05$).
Miller et al., 2021.[95]	Randomized control trial. Adults with overweight/obesity and T2D (50–75 years). PRT, $n = 100$ (male, $n = 64$; female, $n = 36$); PD + PRT, $n = 98$ (male, $n = 62$; female, $n = 36$).	24 weeks	Whey protein drink + vitamin D supplements	Supervised moderate-intensity PRT: 8–10 separate EXs, RPE: 12–15/20-point Borg scale, 2–3 days/week, 2–3 sets, 8–12 reps with weekly progressive overload (2–10% increments).	Whey protein + vitamin D did not augment the effects of PRT on glycaemic control, body composition, muscle strength, or cardiometabolic risk factors.
Wycherley et al., 2010.[83]	Randomized control trial. Patients with T2D (56.1 ± 7.5 years). CON, $n = 16$; CON + RET, $n = 17$; HP, $n = 12$; HP + RET, $n = 14$.	16 weeks	Isocaloric with moderate energy restriction (~6000 kJ/day for women, ~7000 kJ/day for men). CON: 53% CHO, 19% protein, 26% fat. HP: 43% CHO, 33% protein, 22% fat.	Supervised RET: 8 separate EXs, upper and lower body (except sit-up), 3 days/week, 70–85% 1-RM, 8–12 reps.	1. An energy-restricted HP diet combined with RT achieved more significant weight loss ($p \leq 0.04$) and more favorable changes in body composition ($p \leq 0.04$). 2. All treatments led to similar improvements in glycemic control and CVD risk markers. No difference between groups ($p \geq 0.17$).
Wycherley et al., 2008.[96]	Randomized control trial. Adults with overweight/obesity and T2D (52.4 ± 1.4 years). CON, $n = 16$ (male, $n = 10$; female, $n = 6$); CON + AET $n = 13$ (male, $n = 6$; female, $n = 7$).	12 weeks	HP, energy-restricted diet (~5000 kJ/day). 40% of total energy as protein, 20% as fat, and 40% as CHO.	Supervised + self-monitored AET: 4–5 times/week, 4 levels of progressive EXs intensity over 12 weeks (based on HR_{max}).	1. AET did not produce any additional improvement beyond what was achieved with calorie restriction alone. 2. Neither caloric restriction nor EX training had any discernible effect on flow-mediated dilation.

(Continues)

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TABLE 1 (Continued)

Study	Study design	Duration	Diet intervention	Exercise intervention	Result
Campbell et al., 2012.[97]	Randomized control trial. Women with overweight (18–56 years). LP, $n = 21$; NP, $n = 16$; HP, $n = 17$.	12 weeks	All experimental diets were reduced by approximately 30% relative to the baseline data for each subject. >30% energy as fat. Three low-fat, hypo- and isoenergetic diets differing in protein: CHO ratio, LP (1 g protein: 4-g CHO), NP (1-g protein: 2-g CHO), or HP (1-g protein: 1-g CHO)	Supervised circuit training: 3 times/week, 60 min/day. AET: 65% of HR_{max} (gradually increased the intensity by 5% every 3 weeks to a maximum intensity of 80% by week 12) RET: 13 RET machines, upper and lower body, 3 days/week, 65% 1-RM (5% increments based on improvement), 8–15 reps.	1. All groups experienced similar improvements in metabolic health. Body weight ($p < 0.05$), BMI ($p < 0.05$), WC ($p < 0.05$), WHR ($p < 0.05$), SBP&DBP ($p < 0.05$), and RHR ($p < 0.0001$). 2. The NP diet was easier to follow and resulted in superior improvements in body fat, WC, WHR, and preservation of lean mass compared to the other two diets. 3. Both energy restriction and EX proved effective in promoting weight loss among individuals with overweight and obesity as well as reducing symptoms associated with metabolic syndromes.
Solomon et al., 2010.[98]	Randomized control trial. Patients with obesity and prediabetes (66 ± 1 years). Low GI diet + EX (LoGIX), $n = 10$; High GI diet + EX (HiGIX), $n = 12$.	12 weeks	The energy requirements were calculated based on the subject's resting metabolic rate multiplied by a sedentary activity factor of 1.2. Additionally, the macronutrient composition of the diets was matched across the different groups. LoGIX diet had a GI of 40 arbitrary units, and HiGIX diet had a GI of 80 arbitrary units.	Supervised AET: 5 times/week, 60 min/day. ≈85% of HR_{max}.	1. Lifestyle-induced weight loss has been shown to enhance insulin resistance in individuals with prediabetes 2. Postprandial hyperinsulinemia is reduced precisely following a low-GI diet ($p < 0.05$). 3. High-GI diet negatively affects the functioning of pancreatic β cells and intestinal K cells, despite achieving significant weight loss.
Johansen et al., 2017.[88]	Randomized control trial. Patients with T2D (30–70 years). LG, $n = 64$ (male, $n = 33$; female, n = 31); SG, $n = 34$ (male, $n = 18$; female, $n = 16$).	12 months	Restricted total energy intake for the first 4 months. Gradually reduced intake for 12 months. CHO: 45–60%, protein: 15–20%, fat: 20–35% (<7% saturated fat).	Supervised AET + RET (monitored with smartwatch) AET: 5–6 times/week, 30–60 min/day. RET: 2–3 times/week. Participants were encouraged to be physically active in their leisure time (≥10,000 steps/day).	1. HbA_{1c} decreased slightly in the intensive lifestyle group ($p = 0.15$). 2. The lifestyle intervention led to a substantial and parallel reduction in glucose-lowering medication.
Senkus et al., 2022.[99]	Randomized control trial. Older adults with obesity and prediabetes (65–74, 75 + years). EX, $n = 51$; EX + weight maintenance diet, $n = 47$; EX + weight loss diet,	12 months	Macronutrient intake of 25% calories from protein, 47% from carbohydrates, and 28% from fat. The weight maintenance and weight loss groups were given daily calorie goals	Supervised + self-monitored AET + RET (home-based and gym-based). AET: 90–150 min/week of moderate to vigorous intensity. RET: 2 times/week.	1. 12-month EX and dietary intervention, aimed at intentional weight loss, is an effective strategy for improving the AL ratio in older adults with obesity.

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TABLE 1 (Continued)

Study	Study design	Duration	Diet intervention	Exercise intervention	Result
	$n = 49$. (Total male, $n = 62$, female, $n = 85$).		based on estimates of TEE obtained from the measured resting metabolic rate at baseline. Notably, daily calorie goals for participants in the weight loss group were 500 kcal/d less than the baseline TEE.		2. Metabolic improvement by changing the AL ratio. BMI ($p < 0.001$), WC ($p < 0.001$), SAAT ($p = 0.026$), total Ab volume ($p = 0.003$), insulin ($p < 0.001$), HDL-c ($p < 0.001$), hsCRP ($p = 0.001$), IL-6 ($p = 0.010$).
Bragg et al., 2022.[100]	Randomized control trial. Older adults with obesity (70.2 ± 4.7 years). EX, $n = 48$; EX + weight maintenance diet, $n = 44$; EX + weight loss diet, $n = 42$.	12 months	EX + weight maintenance group: TEE was determined by multiplying their measured resting energy expenditure by an activity factor of 1.7. EX + weight loss group: reducing their daily calorie intake by 500 kcal compared with their baseline TEE.	Supervised AET + RET (home-based and gym-based). AET: 90–150 min/week of moderate intensity. RET: 2 times/week for the first 12 weeks of the intervention and twice monthly.	1. Older adults with obesity can substantially reduce their cardiometabolic risk by participating in either EX combined with weight maintenance or EX accompanied by weight loss through moderate caloric restriction. 2. The exercise plus weight loss group showed significant risk reduction ($p = 0.012$) compared with the exercise group.
Stomby et al., 2020.[101]	Randomized control trial. Patients with T2D (30–70 years). PD, $n = 15$ (male, $n = 10$; female, $n = 5$); PD + EX, $n = 13$ (male, $n = 8$; female, $n = 5$).	12 weeks	PD (ad libitum).	Supervised AET + RET: 3 times/week, total 60 min/day. AET: moderate-to-high intensity. RET: upper and lower body, 2–4 sets, 10–15 reps.	1. 12-week lifestyle interventions, which involved implementing a PD with or without structured high-intensity EX, significant weight loss and improvements in insulin sensitivity were observed. 2. The two groups had no notable differences in these effects.
Legaard et al., 2023.[87]	Randomized control trial. Newly diagnosed patients with T2D (<7 years) (58.2 ± 9.8 years). CON, $n = 20$ (male, $n = 13$; female, $n = 7$); DCON, $n = 21$ (male, $n = 14$; female, $n = 7$); MED, $n = 20$ (male, $n = 13$; female, $n = 7$); HED, $n = 21$ (male, $n = 13$; female, $n = 8$).	16 weeks	~25–30% energy deficit per day with a macronutrient distribution within the range of 45–60 E% carbohydrate, 15–20 E% protein and 20–35E% fat (<7E% saturated fat).	Supervised AET + RET. MED: (AET: 2 times/week and AET + RET: 1 time/week, Total 150–165 min/week). HED: (AET: 4 times/week and AET + RET: 2 time/week, Total 300–330 min/week). AET: 60–100% of $HR_{max.}$ RET: main muscle group, 8–12 reps aimed at a resistance consistent with 0–3 reps in reserve.	1. Adults diagnosed with T2D within a span of 7 years can experience enhanced late-phase insulin secretion by incorporating exercise and weight loss through dietary modifications over a 16 week. 2. The most notable improvements were observed when exercising six times weekly (late phase insulin sensitivity index, DCON vs. HED, $p = 0.004$).

Abbreviations: AET, aerobic exercise training; AL, adiponectin to leptin ratio; CHO, carbohydrate; CON, control group; CVD, cardiovascular disease; DBP, diastolic blood pressure; DCON, diet control group; EX, exercise; E%, energy percent; FBG, fasting blood glucose; GI, glycemic index; HED, high exercise dose group; HP, high-protein; HR_{max}, maximal heart rate; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; LG, lifestyle group; LP, low-protein; MED, moderate exercise dose group; NP, normal-protein; PD, paleolithic diet; PRE, rate of perceived exertion; PRT, progressive resistance training; RHR, resting heart rate; RM, repetition maximum; SAAT, subcutaneous adipose tissue determined by MRI; SBP, systolic blood pressure; SG, standard care group; TEE, total energy expenditure; Total Ab volume, total abdominal fat volume determined by MRI; T2D, type 2 diabetes; VLCD, very-low-calorie diet; WC, waist circumference; WHR, waist to hip ratio.

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glucose-6-phosphate to glycogen, storing it as a glucose reserve for future energy usage. This process helps regulate blood glucose levels. Insulin also enhances protein synthesis in skeletal muscle by phosphorylating p70 ribosomal S6 kinase (p70S6K1) via AKT-mediated mammalian target of rapamycin (mTOR)C1 activation.[107–109] This knowledge is critical to developing strategies to enhance insulin sensitivity, thus bettering insulin response and overall glycemic control in individuals affected by this condition.

The mTOR/p70s6K signaling pathway is among the most extensively investigated pathways. It interprets a variety of environmental cues, such as nutrient availability, growth factors, and energy status, and regulates anabolic mechanisms for skeletal muscle growth and regeneration. Several factors, including RET, a protein-rich diet, and hormones such as insulin, growth hormone, insulin-like growth factor-1, and testosterone, influence this pathway. Dysregulation of this pathway is implicated in numerous muscle-wasting conditions.[107–109]

3.2.2 | Physiological mechanisms

Most studies investigating the benefits of exercise in T2D have employed low- or moderate-intensity regimens, such as walking or jogging for at least 30 min daily.[110–112] Nevertheless, time constraints pose a significant challenge in maintaining a regular exercise routine. Therefore, the potential of HIIT methods—which require shorter exercise durations—to improve T2D outcomes would constitute a valuable intervention. Little et al.[113] demonstrated that even six sessions of HIIT over 2 weeks can rapidly reduce hyperglycemia and augment the oxidative capacity of skeletal muscle in patients with T2D, with exercise totaling 75 min per week. Mitranun et al.[114] compared the effects of a 12-week HIIT regimen with continuous exercise in 43 patients with T2D aged 50–70 who were on glucose-lowering medications but did not use exogenous insulin. HIIT and continuous exercise improved FBG, with a more significant magnitude effect noted in the HIIT group. The study also reported that only HIIT improved HbA_{1c} levels. However, a 2019 systematic review concluded that evidence supporting HIIT efficacy for T2D improvement was limited.[115] This finding was mainly due to insufficient studies for definitive conclusions and the apparent limitation that HIIT methodologies are not generally applicable across all conditions.

Skeletal muscle accounts for approximately 80% of insulin-mediated glucose uptake in the postprandial state, which is significantly impaired in individuals with T2D. Although evidence directly linking increases in muscle mass and strength to enhanced glucose uptake is limited, a strong association between improvements in glucose uptake and muscle mass/strength is widely recognized. In a meta-analysis conducted by Jansson et al.,[116] the researchers investigated the effect of RET on HbA_{1c} improvement in adult patients with T2D. Their findings revealed a significant reduction in HbA_{1c} levels following RET, with greater strength gains corresponding to more critical benefits. Interestingly, they found no statistically significant difference between AET and RET methods in improving HbA_{1c} in patients with T2D, indicating that both forms of exercises are practical for this population.

Several animal studies have illuminated the role of circadian rhythms in metabolic dysregulation and the onset of various diseases. These studies have also demonstrated the circadian modulation of gene expression associated with mitochondrial function within skeletal muscle.[117,118] Furthermore, adipose tissue of mice subjected to treadmill exercise at different times displayed distinct responses when the activity occurred during their early active phase, corresponding to the post-awakening period in humans, RNA sequencing of this adipose tissue indicated a pronounced engagement of thermogenic and mitochondrial pathways, which play a critical role in lipid metabolism.[119] These findings underscore the profound influence of circadian rhythms in orchestrating genetic regulation and metabolic physiology,[120] suggesting that the timing of interventions may be crucial in maximizing therapeutic outcomes.

Circadian rhythms are also pivotal in the regulation of blood glucose levels. Savikj et al.[121] explored the differential effects of HIIT performed at varying times of the day on blood glucose fluctuations in middle-aged men with T2D over 2 weeks. The study's results indicated that HIIT in the morning increased blood glucose at various intervals post-exercise, whereas afternoon HIIT reduced blood glucose at multiple points during the day. These findings suggest that exercise timing can influence the glycemic response to HIIT in men with T2D. Concurrently, another study observed that while high-intensity aerobic exercise enhanced cardiorespiratory fitness independent of exercise timing, the glycemic benefits were more substantial when the exercise was performed in the evening.[122]

A recent study demonstrated that enhancements in cardiometabolic health resulting from precision nutrition interventions were dictated by a tissue-specific (skeletal muscle or liver) IR phenotype.[123] Individuals with the muscle IR phenotype showed more pronounced improvement in cardiometabolic health when they adopted a low-fat, high-protein, and high-fiber diet. In contrast, those with a liver IR phenotype gained the most from a diet rich in monounsaturated FAs. Given these findings, exercise recommendations intended to boost insulin sensitivity should also be personalized to reflect individual metabolic characteristics rather than being universally applied. This tailored approach could provide an adequate nutrition and exercise strategy for individuals with IR who are obese or overweight, even when skeletal muscle mass is above average, or for patients with lean T2D.

An integrated approach incorporating both AET and RET has been broadly endorsed as the most effective strategy for mitigating IR.[124,125] It is pertinent to mention that a recent review, which examined the correlation and evaluated the association of combined AET and RET interventions on glycemic control in individuals with T2D, deduced that augmenting the volume or frequency of exercise yielded more significant benefits than modifying the type or intensity of exercise.[126] The consensus in endocrinology historically asserted that IR was an initiator of hyperinsulinemia. Recent studies, however, challenge this notion, suggesting that hyperinsulinemia may, in fact,

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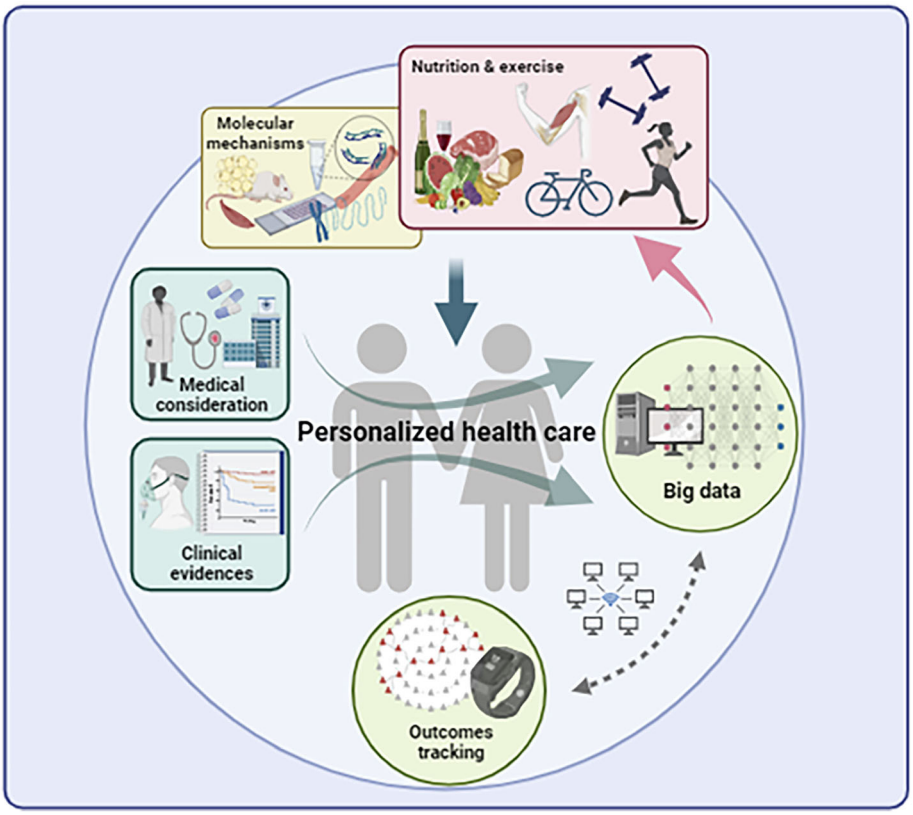


FIGURE 2 The need for a multidisciplinary approach to evidence-based personalized healthcare.

precipitate IR. A confluence of factors, including genetic background, adherence to a Western dietary pattern, and over-nutrition, may lead to elevated insulin secretion, irregular insulin pulsatility, or a decrease in hepatic insulin clearance, thus inducing hyperinsulinemia. This disruption can skew the homeostasis of the insulin-growth hormone-insulin-like growth factor axis towards energy conservation and FA synthesis while simultaneously suppressing fat mobilization, ultimately promoting the pathogenesis of obesity and T2D.[127] Therefore, targeted interventions aimed at normalizing or reducing circulating insulin levels may play an essential role in preventing and managing obesity and T2D.

4 | CONCLUSION AND FUTURE DIRECTIONS

This scoping narrative review synthesized the existing literature on nutrition, exercise, and their combined role in mitigating obesity and T2D. Our integrated approach, depicted in Figure 2, underscores the necessity of integrating insights from various scientific domains. We evaluated the impact of adipose tissue and skeletal muscle as central to these conditions. We reviewed comprehensive data from molecular studies and clinical trials focusing on nutritional elements, dietary strategies, and exercise regimens by factoring in individual physiological and medical characteristics. The fundamental and clinical research highlighted in this review should be pursued with increased detail. At the same time, advancements in artificial intelligence technologies should continue to facilitate the collecting and processing vast amounts of data. Indeed, while acknowledging the fundamental importance of a combined approach of nutrition and exercise in managing cardiometabolic disease, it is clear that this "knowledge" alone is insufficient to conquer these diseases. It is imperative to construct personalized healthcare strategies that integrate with various fields to optimize their efficacy and bridge the chasm between theoretical knowledge and practical implementation. It is essential to remember that nutritional needs can vary significantly from person to person based on age, sex, weight, physical activity level, and co-existing health conditions. Therefore, personalized dietary advice can be incredibly beneficial for individuals aiming to combat obesity or manage T2D through nutritional modifications.

AUTHOR CONTRIBUTIONS

Hye Jin Kim and **Oran Kwon**: Conceptualization; writing—original draft; writing—review and editing; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Hye Jin Kim https://orcid.org/0000-0002-0816-6369

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