Original Article
DOI: https://doi.org/10.70749/ijbr.v3i2.337

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Investigating the Role of Physical Activity and Exercise in Preventing Obesity and Type 2 Diabetes: A Mixed-Methods Approach

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ARTICLE INFO

Keywords

Physical Activity, Exercise, Obesity, Type 2 Diabetes Mellitus, Mixed-Methods Approach.

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Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History

Received: 15-12-2024
Revised: 01-02-2025
Accepted: 24-02-2025

ABSTRACT

Objective: This review aims to synthesize recent research on the impact of exercise and physical activity in preventing T2DM and obesity, using a mixed-methods approach. **Methods:** A thorough literature review was conducted, incorporating findings from 59 recent studies. The review combined quantitative data on physiological mechanisms, exercise modalities, and intensities, with qualitative insights into behavioral and psychological factors influencing exercise adherence. **Results:** The review elucidates how exercise enhances metabolic health through improved insulin sensitivity, glucose metabolism, and fat reduction. Different forms and intensities of physical activity were shown to have varied effects on metabolic health, with both aerobic and resistance exercises contributing to overall benefits. Qualitative research highlighted individuals' attitudes, motivations, and barriers to maintaining regular physical activity. Factors such as personal goals, social support, and psychological barriers were identified as critical determinants of exercise adherence. **Discussion:** The findings emphasize the need for targeted interventions and policies to promote regular physical activity. Strategies should address both physiological benefits and behavioral challenges, incorporating personalized approaches to enhance adherence and efficacy. **Conclusion:** Regular exercise plays a crucial role in reducing Type 2 Diabetes Mellitus (T2DM) and obesity while improving metabolic health. A mixed-methods approach combining physiological and qualitative research enhances understanding of these interactions. Exercise promotes glucose absorption by translocating GLUT4 to the cell surface and increases insulin sensitivity in skeletal muscles. It reduces hepatic glucose production, enhances mitochondrial biogenesis, and improves oxidative capacity. Additionally, exercise stimulates lipolysis, lowers triglycerides and LDL cholesterol, and increases HDL cholesterol. It also reduces chronic inflammation by modulating cytokines and adipokines, ultimately improving insulin sensitivity and overall metabolic function, making it essential for diabetes management.

INTRODUCTION

Obesity and Type 2 Diabetes Mellitus (T2DM) are complex and chronic diseases with multifactorial etiologies, influenced by genetic, environmental, and behavioral factors (1). Physical inactivity and sedentary lifestyles significantly contribute to the development and progression of both obesity and T2DM (2). Obesity is considered a global epidemic right now. Every year, the prevalence of obesity rises, posing more challenges to the healthcare and financial systems. In an effort to encourage doctors to approach obesity-related issues in novel ways, the American Medical Association agreed in 2013 to recognize obesity as a chronic and complicated condition (3). Although there are still many debates regarding the diagnosis of obesity as a disease, that is linked to serious consequences. Almost every body system, including hypertension, dyslipidemia, the cardiovascular system, arthritis, breast, colon, and endometrial cancers, is more susceptible to disease when an individual is obese. In this way, obesity impacts the rates of mortality and morbidity (4, 5).

Type 2 diabetes mellitus (T2DM) and obesity are closely associated conditions. Type 2 diabetes mellitus (T2DM) is more prevalent in obese people. Since obesity is one of the main risk factors for type 2 diabetes and is

highly prevalent in obese people, the term "diabesity" was used. A condition of hyperglycemia, hyperinsulinemia, and insulin resistance is known as type 2 diabetes (T2DM) (6). Type 2 diabetes mellitus increases the risk of cardiac disease in adults which is one of the main causes of death for people with diabetes, and obesity increases the risk of this condition (7). Additionally, pre-diabetic patient who have, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) have a higher risk of cardiovascular disease, which raises their risk of death from a heart attack or stroke (8). Glucose absorption into active skeletal muscles rises during any kind of physical activity (PA) through mechanisms that are independent of insulin. Glucoregulatory hormone-induced increases in hepatic glucose synthesis and free fatty acid mobilization (9, 10), which can be compromised by diabetes or insulin resistance, are responsible for maintaining blood glucose levels (10). The length and intensity of physical activity are closely correlated with reductions in blood glucose levels, and improvements in systemic and potentially hepatic insulin sensitivity can persist for up to 72 hours after engaging in any type of physical activity (11, 12). Regular exercise also enhances cardiovascular function (13, 14, 15), insulin sensitivity (12), β-cell activity (11), and intestinal microbiota (15), all of which may enhance diabetes and health management as well as lower the risk of disease.

Epidemiology

During 2019, diabetes affects over 463 million individuals globally (16). And prevalence of T2DM in the United States is 10.5% (17). T2D accounts for 90-95% of all cases (18). The International Diabetes Federation reports that in 2021, the diabetes affect 537 million individuals worldwide, accounting for around 10.5% of adult and elderly cases, or more than 1 in 10 cases. A projected rise is expected to cross 700 million in 2045 (19), driven by changes in habits and lifestyles as well as a shift in the demographics (20). According to data from the International Diabetes Federation (IDF), Pakistan has thirty-three (33) million people with diabetes, placing it third in the world for DM prevalence behind China and India. (21, 22). The prevalence of diabetes in Pakistan was 11.77%, 16.98%, and 17.1% in 2016, (23), 2018, (24), and 2019 (25). The International Diabetes Federation estimates that 26.7% of Pakistani adults have diabetes in 2022, or around 33,000,000 cases overall (26, 21, 22). 45 million South and Southeast Asian children over the age of 5 years may be affected by childhood obesity, which is sharply increasing in the region in conjunction with adult rates (27) but the highest obesity prevalence is observed among men and women in Polynesia and Micronesia (28). It was projected in 2015 that there would be 609 million obese adults and 1.9 billion overweight people in the world, respectively.

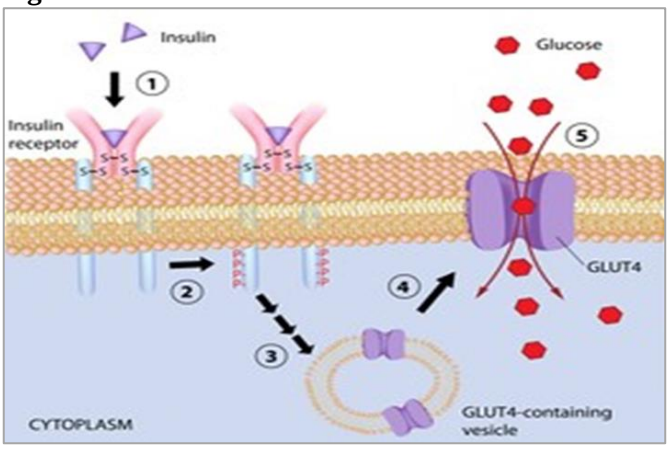
Physiological Mechanisms of Exercise in Obesity and T2DM Prevention:

Exercise and physical activity have a significant impact on a number of physiological processes linked to the onset of obesity and T2D. The risk of insulin resistance and T2D is decreased by physical activities and exercise, which improves insulin sensitivity, glucose absorption, and utilization in skeletal muscles (29). Research has shown that physical inactivity is a more reliable warning sign for long-term disease than conventional risk factors like obesity, diabetes, hypertension, and hyperlipidemia (30). Furthermore, regardless of fat, regular physical activity tends to protect against premature death. Exercise produces these effects through a variety of physiological pathways, including increased insulin sensitivity, muscle glucose uptake, lipid metabolism, inflammation, and more (31). Here's a detailed look at these mechanisms:

- **Improved Insulin Sensitivity**
- **Muscle Insulin Sensitivity**
- **Increased GLUT4 Expression**

Greater glucose absorption is made possible by exercise, which increases the transportation of glucose transporter type 4 (GLUT4) to the cell surface in skeletal muscle cells. In skeletal muscle, insulin promotes the absorption and use of glucose. A crucial part of the absorption process is played by GLUT4 (32). Glycogen is a fast-acting energy source that is produced from stored glucose and is utilized during physical activity (33). Exercise enhances the function of important proteins in the insulin signaling pathway, including protein kinase B, or Atk, phosphatidylinositol 3-kinase (PI3K), and insulin receptor substrate (IRS), which results in more efficient insulin action. These proteins are involved in the GLUT4 pathway. As seen in Figure 1, GLUT4 integrates into the membrane, enabling glucose to enter the cell (34).

Figure 1



(1) Insulin attaches itself to the cell membrane receptor. (2) This initiates the IRS and PI3K signaling cascade. (3) Akt is activated by PI3K. (4) GLUT4 vesicles are more easily transported to the cell membrane when Akt

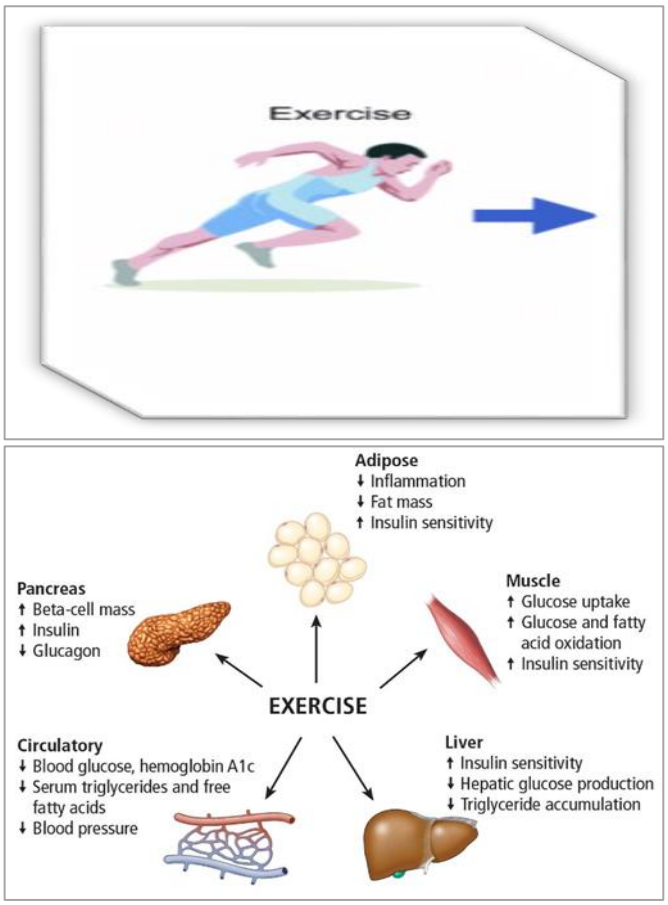
is activated. (5) Glucose can enter the cell when GLUT4 is incorporated into the membrane.

Hepatic Insulin Sensitivity

Blood glucose regulation is largely controlled by the liver. Exercise decreases the amount of glucose that the liver produces by decreasing gluconeogenesis and glycogenolysis and by raising insulin sensitivity in the liver (35). The term "insulin sensitivity" describes a cell's response to the effects of insulin. Increased sensitivity to insulin causes cells to react more effectively to decreased insulin levels, which lowers blood glucose levels by facilitating more efficient uptake of glucose by cells. Muscles require more glucose during exercise to meet their energy needs. As a result, muscle cells absorb more glucose from the blood. Muscles continue to absorb glucose more effectively after exercise because of their increased insulin sensitivity. Depending on how long and hard you exercise, this effect may last for hours or even days (36). Less insulin is needed by the liver to maintain normal glucose levels when insulin sensitivity is higher. Because insulin typically inhibits gluconeogenesis and glycogenolysis, this process decreases the glucose produced by the liver (37) as shown in Figure no 2.

Figure 2

Benefits of exercise on liver and other organs, including increased insulin sensitivity and decrease glycogenesis, gluconeogenesis and low TG accumulation in liver.



Mitochondrial Biogenesis

Regular exercise leads to mitochondrial biogenesis and increased oxidative capacity, enhancing the muscles' ability to oxidize glucose and fatty acids, thus improving overall glucose utilization (38). Adenosine triphosphate (ATP), the primary source of chemical energy in cells, is produced mostly by mitochondria, which is why they are referred to as the cell's powerhouses (39). The process that creates new mitochondria inside of a cell is called mitochondrial biogenesis (40). Periodic exercise initiates this process via various molecular pathways, including the activation of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) (41) The PGC-1α-NRF-1/2-TFAM pathway controls mitochondrial biogenesis. When it was first discovered that PGC-1α was elevated in thermogenic tissues in reaction to cold, this resulted in the expression of several respiratory chain genes, an increase in mtDNA content, and an increase in the number of mitochondria. Additionally, PGC-1α enhances mitochondrial function by inducing OxPhos subunit production, which in turn increases mitochondrial respiration. Even if it is indirect, PGC-1α is definitely essential for mitochondrial replication. NRF-1 and NRF-2 attach themselves to the promoter region of numerous mitochondrial genes, including TFAM, which is triggered by PGC-1α overexpression. It has been discovered that PGC-1α stimulates both NRF-1 and NRF-2, and that the effects of PGC-1α on mitochondrial biogenesis are blocked by a double negative allele of NRF-1. Consequently, NRF-1 and NRF-2 function after PGC-1α, controlling not only OxPhos-related genes but also TFAM, leading to a rise in mitochondrial respiration and mtDNA replication/transcription (42).

Lipid Metabolism and Oxidation

Exercise improves the muscles capacity to oxidize fats that stimulates lipolysis (breakdown of fat stores) by increasing the activity of enzymes like hormone-sensitive lipase, lowering the amount of intramuscular lipids and the lipotoxicity and this lipotoxicity is associated with insulin resistance (43). This process of lipolysis mobilizes fatty acids from adipose tissue to be used as an energy source during prolonged exercise. Exercise enhance the muscles' capacity to oxidize fatty acids, contributing to the reduction of fat mass over time (44). Frequent exercise reduces visceral fat, which is linked to decreased inflammation and better insulin sensitivity. Exercise positively affects lipid profile, leading to improved cholesterol levels. Exercise raises good cholesterol, or high-density lipoprotein (HDL), and lowers triglycerides and bad cholesterol, or low-density lipoprotein (LDL) (45).

Inflammatory Pathways

By lowering pro-inflammatory cytokines and raising anti-inflammatory cytokines, exercise reduces chronic inflammation (46). TNF-α (tumor necrosis factor-alpha)

and IL-6 (interleukin-6) are examples of pro-inflammatory cytokines that are produced by immune cells and adipose (fat) tissue in response to infection or stress. They have been connected to the development of insulin resistance and are known to induce inflammation (47). Chronic inflammation caused by high levels of these cytokines can impair the function of insulin. Regular physical activity has been shown to decrease the production and release of TNF-α and IL-6 from adipose tissue and immune cells, thereby reducing systemic inflammation and improving insulin sensitivity (48). However, anti-inflammatory cytokines contribute in tissue healing and repair by lowering inflammation. IL-10 (Interleukin-10) and adiponectin are examples of such cytokines.

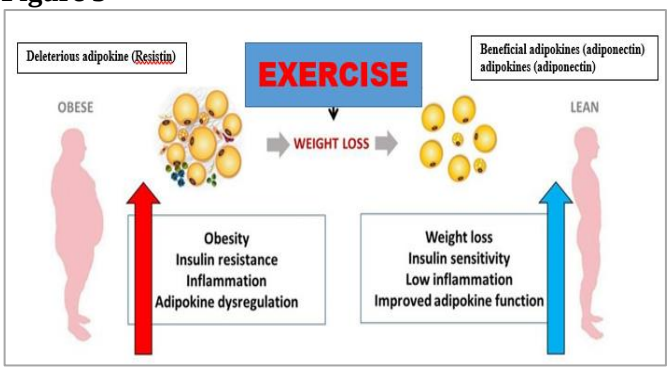
Hormonal Regulation

Adipokines

Exercise increases the secretion of beneficial adipokines, such as adiponectin, which enhances insulin sensitivity, and decreases the levels of deleterious adipokines, such as resistin (49). Adipokines are signaling proteins secreted by adipose tissue (fat cells) that play significant roles in regulating metabolic processes, inflammation, and insulin sensitivity (50). Adiponectin is one of the key beneficial adipokines. It has several positive effects on metabolic processes. Adiponectin enhances the body's sensitivity to insulin, which means that cells are more responsive to insulin, allowing for better glucose uptake from the bloodstream. This helps in maintaining normal blood glucose levels and decreases the risk of insulin resistance and T2D.

Resistin is an example of a deleterious adipokine. Exercise decreases the levels of these deleterious adipokines which have several negative impacts on metabolic health (51). Resistin impairs insulin signaling pathways, which can lead to decreased insulin sensitivity. This implies that cells are less sensitive to insulin, which raises blood glucose levels and may contribute to the development of insulin resistance and type 2 diabetes. (See Figure 3).

Figure 3



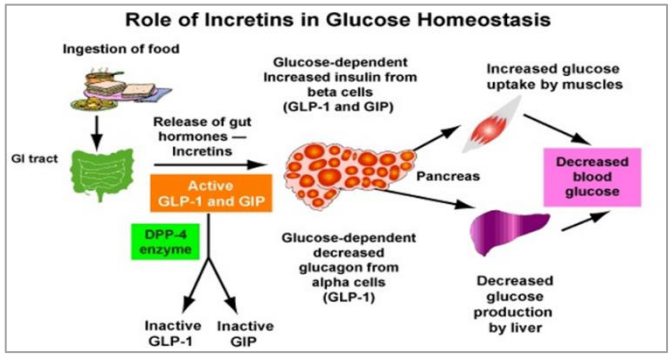
Exercise increases the secretion of beneficial adipokines (adiponectin) which enhances insulin sensitivity, weight loss, reduce inflammation and improve physical health and decreases the levels of deleterious adipokines (resistin). Increased level of resistin cause insulin resistance, induce inflammation and obesity.

Incretin

The two recognized incretin hormones are GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide). Gut peptides known as incretin hormones are released following the consumption of nutrients and cause hyperglycemia and insulin production to increase (52). An essential hormone in glucose metabolism, GLP-1, may be secreted more often when somebody gets physically active. The intestinal L-cells secrete it mostly in reaction to the consumption of nutrients (53). In the gut, the presence of nutrients including lipids and carbs stimulates the release of GLP-1. When blood glucose levels rise, GLP-1 increases the amount of insulin released by pancreatic beta-cells. After a meal, this lowers blood sugar levels (see Figure 4) (53). It promotes the health and survival of beta-cells, which are responsible for insulin production. It can stimulate beta-cell proliferation and inhibit apoptosis (programmed cell death). GLP-1 inhibits the release of glucagon, a hormone that raises blood sugar levels by encouraging the liver to produce more glucose and it enhances the feeling of fullness, reducing food intake. Physical activity has been shown to increase the secretion of GLP-1 (53).

Figure 4

role of incretins hormones (GLP-1 and GIP) in blood glucose regulation. Gut peptides known as incretin hormones are released following dietary consumption and act to increase the secretion of insulin. DPP4 inactivate GLP-1 and GIP (incretins hormones), act as antagonist to GLP-1 and GIP and regulate blood sugar level.



Glycogen Storage

Glycogen is referred to as stored carbohydrate in the liver and muscles, and it serves as a readily available source of energy during physical activity (54). Physical activity lowers postprandial blood glucose levels and improves the muscles ability to store glycogen, which supports glucose homeostasis. Regular physical activity can improves the efficiency and capacity of the body's various systems, including the muscular and

cardiovascular systems so that muscles adapt several ways to increase their capacity to store glycogen (55). Physical activity increases glycogen synthase activity, an enzyme that is responsible for converting glucose to glycogen. Exercise enhances its activity, leading to more efficient glycogen synthesis. Resistance training leads to muscle growth (hypertrophy), which provides more space to store glycogen.

Autonomic Nervous System

The autonomic nervous system, which is a component of the peripheral nervous system, regulates involuntary physiological processes like blood pressure, respiration, digestion, and heart rate. Exercise influences hormones like cortisol and adrenaline, which affect the ANS and glucose metabolism. More glucose is released from the liver by the liver whenever insulin levels drop, along with glucagon and epinephrine (adrenaline) levels rising. Muscle and fat cells in the body become less sensitive to insulin when growth hormone and cortisol levels rise concurrently. More glucose is therefore available in the bloodstream. The significance of consistent physical activity in preserving metabolic health and averting ailments like type 2 diabetes is shown by these physiological advantages (56).

DISCUSSIONThe effectiveness of physical activity in preventing obesity and T2DM depends on various factors, including the type, duration, frequency, and intensity of exercise. Aerobic activities such as brisk walking, cycling, and swimming are recommended for improving cardiovascular fitness and weight management. An effective and time-saving method for improving insulin sensitivity and metabolic health is high-intensity interval training (HIIT) (57). Resistance training (Push-up, Weightlifting) offers unique benefits in preserving lean body mass and enhancing muscular strength, particularly among older adults at risk of sarcopenia (progressive decrease of strength and muscle mass with aging) and metabolic dysfunction. Furthermore, incorporating flexibility, balance, and functional exercises can enhance general physical function and lower the chance of injuries and falls, thereby promoting long-term adherence to an active lifestyle (58).

Exercise regimen adherence is still a major difficulty for many people, even with the well-established health advantages of physical activity. Exercise practices are significantly shaped by behavioral and psychosocial elements, such as motivation, self-efficacy, social support, and environmental constraints. Strategies for encouraging sustained engagement in physical activity include goal-setting, behavior change techniques, and social support networks incorporated into tailored interventions. Furthermore, active living settings can be produced by taking care of environmental aspects including workplace wellness programs, transportation infrastructure, and access to safe recreational areas (59).

CONCLUSION

Exercise is important in reducing T2DM and obesity. They also provide a variety of benefits for enhancing metabolic health and general well-being. Comprehensive understanding of the complex relationships among physical activity, obesity, and T2DM is possible through the use of a mixed-methods approach that combines quantitative research, physiological evaluations, and qualitative research. Various physiological process involve in reduction of T2DM and obesity. Many of which are discussed in this review article. Some quick review of theses process are as, during physical activity and exercise more glucose is absorbed when skeletal muscle cells translocate GLUT4 to the cell surface, which is enhanced by exercise. The skeletal muscle uses and absorbs glucose more efficiently when insulin is present. Exercise decreases the amount of glucose that the liver produces by decreasing gluconeogenesis and glycogenolysis and by raising insulin sensitivity in the liver. Regular exercise leads to mitochondrial biogenesis and increased oxidative capacity. Regular physical activity activates various metabolic pathways, including PGC-1α which in turn drives mitochondrial biogenesis and improved oxidative capacity. "Oxidative capacity" describes a muscle's ability to consume oxygen in the mitochondria during oxidative phosphorylation, which produces ATP. Because they contain more mitochondria (due to mitochondrial biogenesis) and these mitochondria work well, muscles have a greater capacity to make ATP. The ability of the muscles to oxidize lipids is enhanced by exercise, which promotes lipolysis, the breakdown of fat stores. Frequent exercise lowers triglycerides and LDL cholesterol, which is bad cholesterol, and increases HDL cholesterol, which is good cholesterol. By lowering pro-inflammatory cytokines (such as TNF-α, IL-6) and raising anti-inflammatory cytokines (such as IL-10, adiponectin), exercise reduces chronic inflammation as well. Exercise also reduces the levels of harmful adipokines like resistin and increases the release of good adipokines like adiponectin, which improves insulin sensitivity.

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