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Physical exercise induces increased translocation of type 4 glucose transporters (GLUT4): a systematic review

El ejercicio físico induce una mayor translocación de los transportadores de glucosa tipo 4 (GLUT4): una revisión sistemática

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Abstract. The purpose of this study is to highlight the impact of exercise on increasing GLUT4 translocation in cell membranes. This study searches many journal databases, including Embase, Pubmed, Web of Science, and Scopus, as part of a systematic review methodology. Publications released during the last five years and publications mentioning were the inclusion criteria for this study physical exercise, GLUT4 and glucose uptake. The study's exclusion criteria were publications that were published in not reputable journals. 508 papers in all were found using the databases Scopus, Web of Science Pubmed, and Embase. For this systematic review, a total of 10 papers that satisfied the inclusion criteria were chosen and examined. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) evaluation guidelines for standard operations. The outcome of this comprehensive analysis study report that there is an increase and acceleration of GLUT4 translocation during physical exercise. This has the effect of increasing glucose uptake in the blood so that there is an increase in the need for glucose in the blood. We recommend that physical exercise be a preventive measure for each individual in terms of increasing blood glucose uptake which is useful for maintaining balanced glucose levels in the blood and maintain general body health.
Keywords: Physical training; GLUT4; Glucose; Insulin

Resumen. El propósito de este estudio es resaltar el impacto del ejercicio en el aumento de la translocación de GLUT4 en las membranas celulares. Este estudio busca en muchas bases de datos de revistas, incluidas Embase, Pubmed, Web of Science y Scopus, como parte de una metodología de revisión sistemática. Como criterios de inclusión para este estudio fueron las publicaciones publicadas durante los últimos cinco años y las publicaciones que mencionan el ejercicio físico, el GLUT4 y la captación de glucosa. Los criterios de exclusión del estudio fueron publicaciones publicadas en revistas no acreditadas. Se encontraron 508 artículos en total utilizando las bases de datos Scopus, Web of Science Pubmed y Embase. Para esta revisión sistemática, se eligieron y examinaron un total de 10 artículos que cumplieron con los criterios de inclusión. Este estudio cumplió con las pautas de evaluación de elementos de informes preferidos para revisiones sistemáticas y metanálisis (PRISMA) para operaciones estándar. El resultado de este estudio de análisis integral informa que existe un aumento y una aceleración de la translocación de GLUT4 durante el ejercicio físico. Esto tiene el efecto de aumentar la absorción de glucosa en la sangre, de modo que aumenta la necesidad de glucosa en la sangre. Recomendamos que el ejercicio físico sea una medida preventiva para cada individuo en términos de aumentar la captación de glucosa en sangre, lo que es útil para mantener equilibrados los niveles de glucosa en sangre y mantener la salud general del cuerpo.
Palabras clave: Entrenamiento físico; GLUT4; Glucosa; Insulina

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Introduction

According to data from the World Health Organization (WHO), 422 million people worldwide had diabetes mellitus in 2014, an increase of almost 400 percent from 109 million people in 1980. The number of diabetes patients worldwide increased 27.2% from 2014 to 2021. The actual number that occurred reached 537 million people in 2021. 115 million new cases of diabetes were diagnosed in the seven years between 2014 - 2021. Imagine how many people may not realize that they have diabetes melitus.

Based on information provided by the World Health Organization (WHO) in 2016 more than a quarter of adults worldwide were physically inactive (Qiu et al., 2023). The impact of inactivity in the body can increase insulin resistance, which is a pathologic situation wherein peripheral tissues do not respond appropriately to the physiological levels of insulin (Klimczak & Śliwińska, 2024). Many neurological disorders, nephropathy, cardiovascular disorders, or retinopathy can be caused by insulin resistance and hyperglycemia, which are very serious disease conditions (Klimczak & Śliwińska, 2024).

Exercise is the best preventive measure to prevent insulin resistance (Lin et al., 2022). Insulin resistance affects the uptake of insulin and GLUT4 to surface membranes and the distribution of GLUT4 between intracellular compartments (Knudsen et al., 2023). The primary action of insulin is the insulin-dependent transport of glucose to peripheral tissues, such as muscle and adipose (Saltiel, 2021). Thus, during exercise, the percentage glucose gradient from the interstitial space to the muscle cytoplasm is probably not much different from that at rest, because the concentration of cytoplasmic glucose levels is close to zero both at rest and during exercise except in the early minutes of exercise or during very intense exercise where cytoplasmic glucose concentration may actually increase (Richter, 2021). When the body does physical exercise, there will be an increase in glucose absorption in the muscles, thereby helping to lower blood glucose levels (Asfaw & Dagne, 2022). The mechanism of glucose distribution in muscles triggered by exercise occurs in several ways, namely through facilitated diffusion, membrane permeability to glucose, and

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intracellular glucose metabolism (Flores-Opazo et al., 2020). GLUT is a component of the transporter of glucose and is the main facility accountable for the massive translocation of tiny molecules through cell membranes, including metabolites, poisons, and nutrients (T. Wang et al., 2020). Different glucose transporters, which generate 14 different glucose isoforms in different tissues and animals, mediate diffusion (Parker Evans et al., 2019). Over the past thirty years, several researchers have identified a glucose transporter that is triggered by muscle contractions during exercise and GLUT4. This research has increased our understanding of how glucose can be transported and absorbed in muscle and fat in response to insulin and physical exercise (Klip et al., 2019). An interesting question is how does the mechanism for glucose uptake become that high during physical exercise? Of course, increased blood flow and the preservation of plasma glucose levels through hepatic glucose synthesis is essential to ensure that glucose is continuously delivered to the muscles. However, glucose will not reach the muscles unless the muscular membrane's increased permeability to glucose (Richter, 2021).

The results of research on people who do athletic training have proven that they can increase GLUT4 in skeletal muscles (Barrett & Davis, 2023). In large quantities, skeletal muscle serves as the location of greatest glucose absorption. This occurs due to the presence of insulin and is facilitated by the GLUT4 or glucose transporter 4 translocation mechanism to the muscle fiber membrane's surface (Klip et al., 2019). It's commonly acknowledged that exercise can help prevent and cure metabolic illnesses (Espelage et al., 2020). It is unclear exactly which processes underlie exercise's positive impacts on metabolic health. Nonetheless, it is evident that consistent exercise has a significant impact on the individual overall energy metabolism and, in particular, on skeletal muscle's consumption of substrates (Lao et al., 2019). In fact, if glucose uptake in the legs could rise 100 times, the amount of glucose transported across the muscular membrane would likewise multiply 100 times. This is because otherwise the interstitial glucose concentration would increase, and this did not occur in the study (Richter, 2021).

It is known that physical exercise can increase glucose transporter type 4, but it is still unclear what the mechanism of the GLUT4 translocation process is during physical exercise. Therefore, this study aims to discuss in depth the mechanisms underlying the GLUT4 translocation process during physical exercise through a systematic review.

Materials and Methods

Study Design

This research is a type of systematic review research using searches from various journal databases such as Scopus, Web of Science Pubmed, and Embase.It is considered a key platform throughout the world as it brings together publications of scientific impact and relevance.

Eligibility Criteria

The inclusion criteria for this study include studies discussing glucose transporters, GLUT4, skeletal muscle, physical activity, and exercise published during the last five years (2019-2024). The study's exclusion criteria included publications published in journals with a non-reputable.

Procedure

Article titles, abstracts, and complete texts were vetted, confirmed, and entered into Mendeley software. During the first phase, 508 papers in all were found using the databases Scopus, Web of Science Pubmed, and Embase. Subsequently, 270 articles were filtered in the second step according to how well the title and abstract fit the criteria. Forty-three pieces were confirmed for additional processing in the third step. We now filter depending on whether the entire content is appropriate. Ten publications that satisfied the inclusion criteria were then chosen and examined for this systematic review in the last phase. A total of 10 papers that met the inclusion criteria were selected and scrutinized for this systematic review. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) assessment protocol is followed by this study for standard operating procedures.

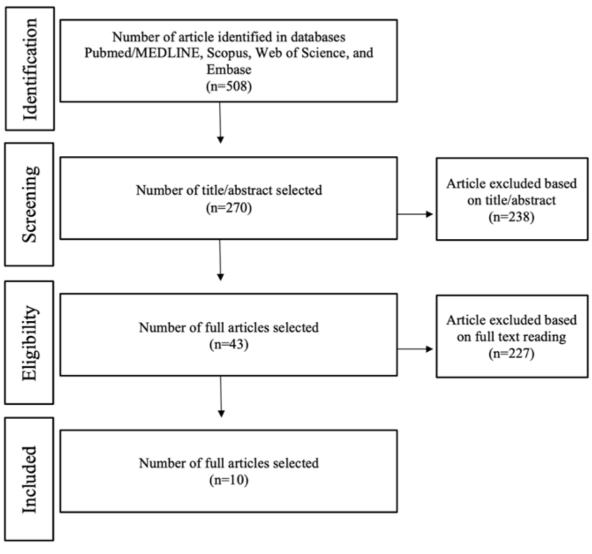

Figure 1. Process flowchart for selecting articles using PRISMA

Results

Table 1.
Results of a Review of The Effects of Physical Exercise Increase GLUT4 Translocation

Author	Sample Characteristics	Study Design	Intervention	Results
(Kido et al., 2023)	20 mice underwent research preparation and were divided into 2 groups, namely knockout mice and wild mice	Experimental	Rats ran for 30 minutes with an intensity of 75% of VO2 Max	The GLUT4 content increased significantly in the group of wild mice.
(Kartinah et al., 2024)	24 Male rats were divided into four groups, namely control group, diabetes mellitus intervention group, diabetes mellitus group undergoing continuous training, diabetes mellitus group undergoing HIIT	Experimental	Training in the training group was carried out six days a week for six weeks	There was a significant increase in GLUT4 levels in the HIIT group
(Knudsen et al., 2020)	Healthy young male undergoing exercise	Experimental	Training to kick 1 leg for 1 hour	Following exercise, there was an increase in GLUT4 following the biopsy technique examination.
(Carrillo et al., 2023)	Wistar rats aged 7 weeks participated in this research	Experimental	Five days of swimming training. Every day swim for 17 minutes.	There was an increase in GLUT4 levels in the training group
(Vidal Moreno de Vega et al., 2023)	16 untrained standardbred horses participated in this study	Experimental	Aerobic training 30 minutes per training session, 3 days a week for 8 weeks	Levels of GLUT4 increased in the training group.
(H. Wang et al., 2023)	28 Wistar rats aged 8 – 10 weeks contributed to this research	Experimental	Physical training for swimming for 4 x 30 minutes with 5 minute rest intervals for 3 - 4 weeks	There was an increase in GLUT4 levels in the training group
(Saki Kondo, et al, 2021)	Male Sprague–dawley rats participated in this study	Experimental	Swimming training for 6 hours divided into 2 sessions, namely 3 hours and rest then continued for 3 hours for 4 weeks	Levels of GLUT4 increased in the training group.
(Zhang et al., 2021)	A total of 61 male mice participated in this research	Experimental	Treadmill training for 60 minutes 5 x a week for 8 weeks	There was an increase in GLUT4 levels in the training group
(Rahmati-Ahmadabad et al., 2021)	In this study, a total of 72 male Wistar rats were split up into 6 groups: healthy control, healthy high intensity interval training (HIIT), healthy moderate intensity continuous training (MICT), and diabetic control, diabetes MICT, and diabetic HIIT.	Experimental	Treadmill training 60 minutes per session 5x a week for 6 weeks	There was a significant increase in GLUT4 in the healthy moderate intensity continuous training group
(Gorgey et al., 2020)	22 The research had 11 men with spinal cord injuries who were split into two groups: the first group received testosterone replacement treatment (TRT) together with resistance training (RT), while the second group (n=11) received TRT without any exercise. resistance exercise	Experimental	Resistance training, weight training on the ankles twice a week for 16 weeks	There was a significant increase in GLUT4 protein in the (TRT + RT) group compared to (TRT) alone

Discussions

Physical exercise has a beneficial effect on the body (Mariano et al., 2023). Research results from Caminiti et al., 2021 proves that a combination of aerobic exercise and resistance training can reduce blood pressure in the body. According to Pires et al., 2020 presented results that acute aerobic exercise sessions, resistance training, and combined training were able to lower blood pressure dramatically, both diastolic and systolic. During exercise, the permeability of muscle membranes to blood glucose increases 17 times compared to rest (Richter, 2021). Meanwhile, in skeletal muscle that showed increased insulin sensitivity, there was a 35-fold increase in membrane permeability to glucose (Richter, 2021).

For those with type 2 diabetes, a combination of strength training and aerobic exercise is strongly advised (Ambelu & Teferi, 2023). Both those with and without type 2 diabetes can benefit from exercise in terms of blood lipid profiles and glycemic management (Ambelu & Teferi, 2023). The results of research on people who did high intensity interval training (HIIT) showed that their blood glucose levels decreased (Al-Rawaf et al., 2023). A drop in blood glucose levels signifies a rise in muscle absorption of blood glucose caused by physical exercise (Kartinah et al., 2024). Glucose transporters (GLUT) are a group of membrane proteins that help glucose move across cell membranes (Cho & Shaw, 2024). The specific and main glucose transporter that promotes absorption of glucose in skeletal muscle is GLUT4 (Kartinah et al., 2024). GLUT4 is especially found in sensitive tissues such as insulin, adipose, skeletal muscle, and heart (Holman, 2020). GLUT4 has a significant impact in reducing blood glucose levels and insulin resistance (Yuan et al., 2022). In terms of human insulin-stimulated muscle glucose uptake, the majority of research show that submaximal exercise causes a 10-to 20-fold increase in glucose uptake in young people (Richter, 2021).

The biggest location in the body for quantitative absorption of glucose is found in skeletal muscle (Dlamini & Khathi, 2023). Glucose transporter 4 translocation is a process facilitated by GLUT4 or glucose transporter 4 which moves entering the muscle fibers' surface membrane to facilitate more glucose to enter the cell (Knudsen et al., 2023). One essential process that promotes muscle glucose absorption during exercise is the translocation of GLUT4 from the intracellular to the sarcolemma and tubules (Richter, 2021). Exercise has a well-established ability to enhance skeletal muscle GLUT4 material (Kartinah et al., 2024). Increased glucose transporter expression provides an important step in supporting glucose utilization by skeletal muscle as the substrate of choice for exercise (Barrett & Davis, 2023). Regarding GLUT4, it is proven that various forms of sports training have a good influence on these elements. Increasing GLUT4 levels furthermore helps those with diabetic mellitus (Rahmati-Ahmadabad et al., 2021). 40% of total body mass is made up of skeletal muscle, thus controlling skeletal muscle glucose metabolism has a major impact on the body's blood glucose balance (T. Wang et al., 2020). Physical exercise can very effectively increase glucose uptake in skeletal muscles (H. Wang et al., 2023). GLUT4 provides cellular signaling mechanisms triggered by insulin to lower blood glucose levels by increasing blood glucose uptake (Cho & Shaw, 2024).

The mechanism by which physical exercise can increase GLUT4 is as follows. That when we exercise physically, the body will increase ROS (reactive oxygen species) as a form of physiological response (Shamsnia et al., 2023). After the muscle contracts and ROS increases, the sarcoplasmic reticulum Ca2+ release channels open in response to the activation of muscle contraction through the propagation of action potentials throughout the t tubule. Passively, Ca2+ ions permeate the cytoplasm, thereby increasing cytosolic Ca2+ between ten- and twenty-fold (Gejl et al., 2020). An increase in intracellular Ca2+ concentration triggers CaMKK activation (Tokumitsu & Sakagami, 2022). Activation of CaMKK will increase AMPK activity which is also very important and necessary for physical fitness, and research results show that exercise can increase these benefits by improving muscle function through AMPK regulation (Chen et al., 2023). Physical exercise also increases ATP requirements (Sorriento et al., 2021). Then, raising phosphorylated AMPK will raise the production of GLUT4, a protein involved in the transport of glucose (Kartinah et al., 2024). A number of lines of evidence point to AS160 phosphorylation alterations as a likely mediator of the insulin-stimulated increases in skeletal muscle glucose uptake after acute exercise (Pataky et al., 2020). The glucose transporter type 4 (GLUT4) facilitates glucose entry into skeletal muscle cells by providing a gradient in glucose concentration from the interstitial space (the area outside the muscle cell) to the cytoplasm (the inside of the muscle) (Richter, 2021). In order to enhance therapeutic approaches for metabolic conditions like type 2 diabetes, it is critical that we comprehend the molecular processes that control skeletal muscle metabolism (Dunn & Munger, 2020). In this systematic review, researchers have a limitation in discussing it, namely only looking at and analyzing the mechanism of GLUT4 translocation during physical exercise. For future research, we can discuss other glucose transporters that are associated with physical exercise.

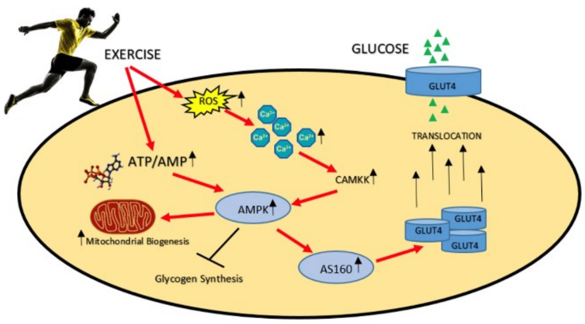

Figure 2. Mechanisms of physical exercise increase GLUT4 translocation

Conclusions

Physical exercise has a beneficial impact, especially on diabetes mellitus sufferers. When doing physical exercise, the muscles will contract more than when resting. This will have an impact on more glucose uptake through increasing GLUT4 translocation as a pathway for glucose to enter intracellularly. Physical exercise is highly recommended to maintain body health, especially for people with diabetes mellitus to keep blood glucose levels within normal limits.

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Conflicts of Interest

The authors declare no conflict of interest

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