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25 Molecules Expressed in the AMPK Pathway After Exercise in Type 2 Diabetes: Evidence Map

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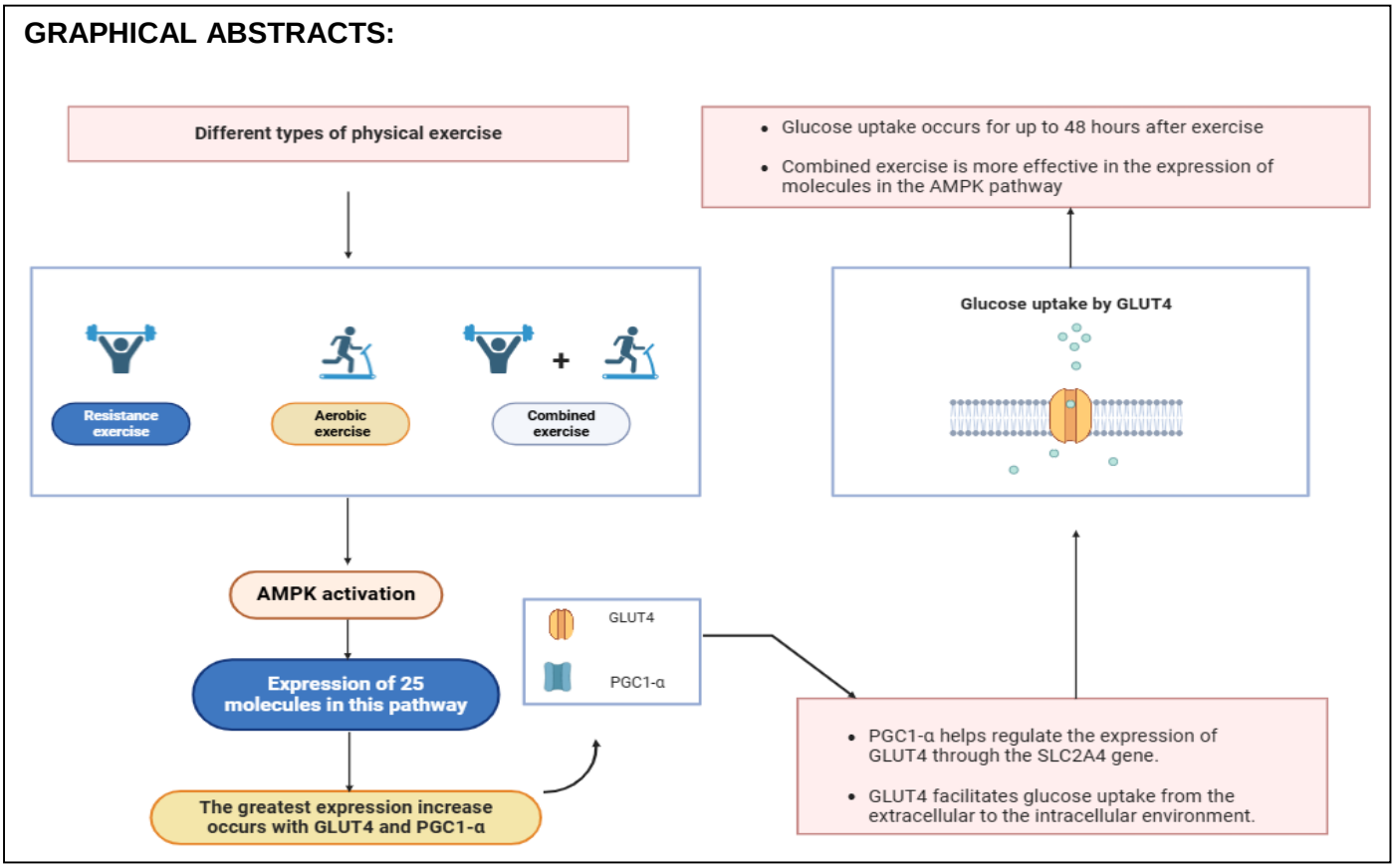
HIGHLIGHTS

- Combined exercise activates AMPK signaling more effectively than isolated exercises.
- AMPK pathway shows a marked rise in key molecules, especially GLUT4 and PGC1-α.
- Training volume, intensity, and frequency affect AMPK molecule expression levels.

ABSTRACT: This study investigates the expression of molecules in the AMPK pathway following physical exercise in people with type 2 diabetes, considering aerobic, resistance, and combined exercises. Although the literature indicates intracellular signaling in the AMP-activated protein kinase (AMPK) pathway occurs after exercise, it is essential to compile this information to support clinical decision-making. To summarize evidence on the expression of molecules in the AMPK pathway in people with type 2 diabetes following aerobic, resistance, and combined exercise. This integrative review included searches in MEDLINE/PubMed, SciELO, and Lilacs databases (2004-2024). After applying filters, duplicate evaluations, and screening titles and abstracts, nine studies met the eligibility criteria. An increase in the expression of 25 molecules, particularly GLUT4 and PGC1-α, was observed, with combined exercise proving more effective than aerobic and resistance exercises alone. Aerobic, resistance, and combined exercises can increase the expression of molecules in the AMPK pathway in people with type 2 diabetes, with combined exercise being the most effective. There are differences not only between exercise types but also in volume, intensity, and frequency.

Keywords: Aerobic exercise; resistance exercise; signaling route; GLUT4; glycemic control.

GRAPHICAL ABSTRACTS:



INTRODUCTION

The Type 2 diabetes (T2D) is a metabolic syndrome characterized by hyperglycemia, hyperinsulinemia, and tissue insulin resistance [1]. This metabolic disorder affects 90-95% of the 425 million people with diabetes worldwide [2]. Data from the International Diabetes Federation revealed that in Brazil alone, the number of people with T2D reached nearly 17 million in 2019 [3].

The prevalence of T2D has been linked to genetic risk factors and social/environmental determinants, particularly lifestyle among the Brazilian population [4]. Given the complexity of T2D, various studies highlight the need for a multidisciplinary approach for its treatment and management [5]. Among interventions, physical exercise has been one of the most widely used non-pharmacological therapies due to its potential hypoglycemic effect on T2D [6], which can be explained by complex molecular mechanisms [7].

In this context, researchers have worked to understand which molecules and how they are involved in glucose uptake in T2D, in response to aerobic (AE), resistance (RT), and combined (CE) exercise. One of the most studied molecules today is AMP-activated protein kinase (AMPK) [8], which is activated by skeletal muscle contraction [6-9]. This activation induces a series of intracellular responses that aim to restore energy balance, including an increase in glucose uptake [10], improved insulin sensitivity in adipose and muscle tissue, and stimulation of fatty acid oxidation [11].

Although physical exercise is widely recognized for aiding in T2D management [10-12], an accurate understanding and comparison among different exercise modalities, such as aerobic, resistance, and combined exercise, on the AMPK pathway in people with T2D remains limited [13]. Better knowledge of its influence on the AMPK pathway will allow for optimized physical exercise prescriptions for T2D patients.

By identifying how these exercises affect AMPK pathway activation and its metabolic consequences, we aim to provide insights for developing more effective therapeutic strategies, particularly in the formulation and prescription of physical exercise. Thus, this study aimed to summarize evidence on the expression of molecules involved in the AMPK pathway in response to different exercise modalities in individuals with T2D.

MATERIAL AND METHODS

Characterization of Study Type and Guiding Question

This is an integrative literature review with a qualitative approach and descriptive nature [14]. Initially, the PICO strategy was used to answer the following research question: “Which molecules are expressed in

the AMPK signaling pathway in people with type 2 diabetes after performing aerobic, resistance, and combined exercise?"

The PICO acronym stands for: 1) "P" for population (people with type 2 diabetes); 2) "I" for intervention (aerobic, resistance, and combined exercise); 3) "C" for comparison (control groups or other types of exercise); and 4) "O" for outcome (expression of molecules involved in the AMPK signaling pathway) [15].

Search Strategies

Articles were searched in the MEDLINE/PubMed (Medical Literature Analysis and Retrieval System Online/National Library of Medicine), SciELO (Scientific Electronic Library Online), and Lilacs (Latin American and Caribbean Health Sciences Literature) databases, with a timeframe of 2004 to 2024. The article analysis period concluded in January 2024. Additional searches were also conducted through reference lists.

The descriptors used were found in Medical Subject Headings (MESH) and Health Sciences Descriptors (DECS) from BIREME, including "type 2 diabetes," "genes," "expression," "physical exercise," and "signaling pathway," in Portuguese, Spanish, and English. To narrow the search to the topic, Boolean operators "AND" and "OR" were used, along with filters for "the last 20 years," "languages: English, Portuguese, and Spanish," and "humans," as shown in Table 1.

Table 1. Search strategies in the databases, with a timeframe of 2004-2024

Databases	Search Strategies	Filters Applied
MEDLINE/ PubMed	(((((("training exercise"[Title/Abstract] OR "resistance training"[Title/Abstract] OR "high intensity interval training"[Title/Abstract] OR "endurance training"[Title/Abstract] OR "combined training"[Title/Abstract]) AND "Genes"[Title/Abstract]) OR "Molecules"[Title/Abstract] OR "AMPK"[Title/Abstract] OR "signaling pathway"[Title/Abstract]) AND "type 2 diabetes mellitus"[Title/Abstract] AND "Adult"[Title/Abstract]) OR (("protein s"[All Fields] OR "proteinous"[All Fields] OR "proteins"[MeSH Terms] OR "proteins"[All Fields] OR "protein"[All Fields]) AND "glucose transport"[Title/Abstract])) AND (("Enzymes"[Title/Abstract] AND "PCR"[Title/Abstract]) OR "Microarray"[Title/Abstract] OR "RT-PCR"[Title/Abstract])	Publication Year: 2004-2024 Language: English, Spanish, and Portuguese Sample: Humans
SciELO	(ab:("type 2 diabetes mellitus")) AND ("exercise") AND ("molecules") OR ("enzyme") OR ("proteins")	Publication Year: 2004-2024 Language: Portuguese, English, and Spanish Sample: Humans
Lilacs	(Exercise OR resistance training OR endurance training OR combined training) AND (Genes OR Signal way OR molecules OR AMPK) AND (PCR OR microarray OR rt-PCR)	Publication Year: 2004-2024 Language: Portuguese, English, and Spanish Sample: Humans

Eligibility Criteria

The inclusion criteria for this research were: primary and secondary studies that assessed the expression of molecules in type 2 diabetes through molecular techniques such as quantitative PCR (RT-PCR), microarray, or total RNA sequencing (RNA-Seq) and skeletal muscle biopsy; individuals of both sexes over 18 years of age, untrained, and diagnosed with type 2 diabetes; interventions that included combined, aerobic, and resistance exercises with acute or chronic analysis. Additionally, only studies with the following outcomes were included: 1) primary - expression of molecules in the AMPK pathway and 2) secondary - increased insulin sensitivity and blood glucose uptake.

In contrast, the exclusion criteria included studies that treated individuals with other types of interventions, unpublished study sources, or gray literature such as abstracts, theses, and dissertations, as well as basic research and studies that evaluated other outcomes.

Types of Studies Considered

This integrative review of the scientific literature considered observational analytical study designs, experimental and quasi-experimental research. Descriptive observational study designs were also included, such as case series, individual case reports, and cross-sectional descriptive studies, as well as systematic reviews that met the inclusion criteria.

Study Selection Process, Data Extraction, and Analysis

After conducting the search, all citations were grouped in the EndNote software, where duplicate studies were removed. Subsequently, titles and abstracts were screened by two independent reviewers who thoroughly evaluated the studies according to the inclusion criteria for the review. Potentially relevant sources were retrieved in full. The full text of the selected citations was evaluated in detail by two independent reviewers based on the inclusion criteria, with no discrepancies between them.

Reasons for excluding full-text sources that did not meet the inclusion criteria were recorded and reported in this review. The results of the search and study inclusion process were fully reported in the final integrative review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, shown in Figure 1.

Data were extracted from the articles included in the integrative review by two reviewers independently, using a data extraction tool developed by the reviewers themselves. The preliminary data extraction tool was revised as needed during the data extraction process for each included evidence source.

After data extraction, the publications were analyzed based on the following variables: article title; authors and year of publication; objectives; journal, database, and impact factor (IF); research method; study sample, and country (see Table 2). Table 3 includes the main molecules found. Subsequently, the interpretation of the obtained results was conducted through critical evaluation of the data (Table 4).

RESULTS

Initially, 133 articles were identified from the databases and reference lists. After applying filters, evaluating duplicates, and reading titles and abstracts, 123 articles were excluded. After a complete reading of the 57 eligible studies, only 9 articles met the eligibility criteria for this study and were included. The others that were excluded contained: therapeutic treatments based on other types of intervention (n=30) and articles that assessed other outcomes (n=18).

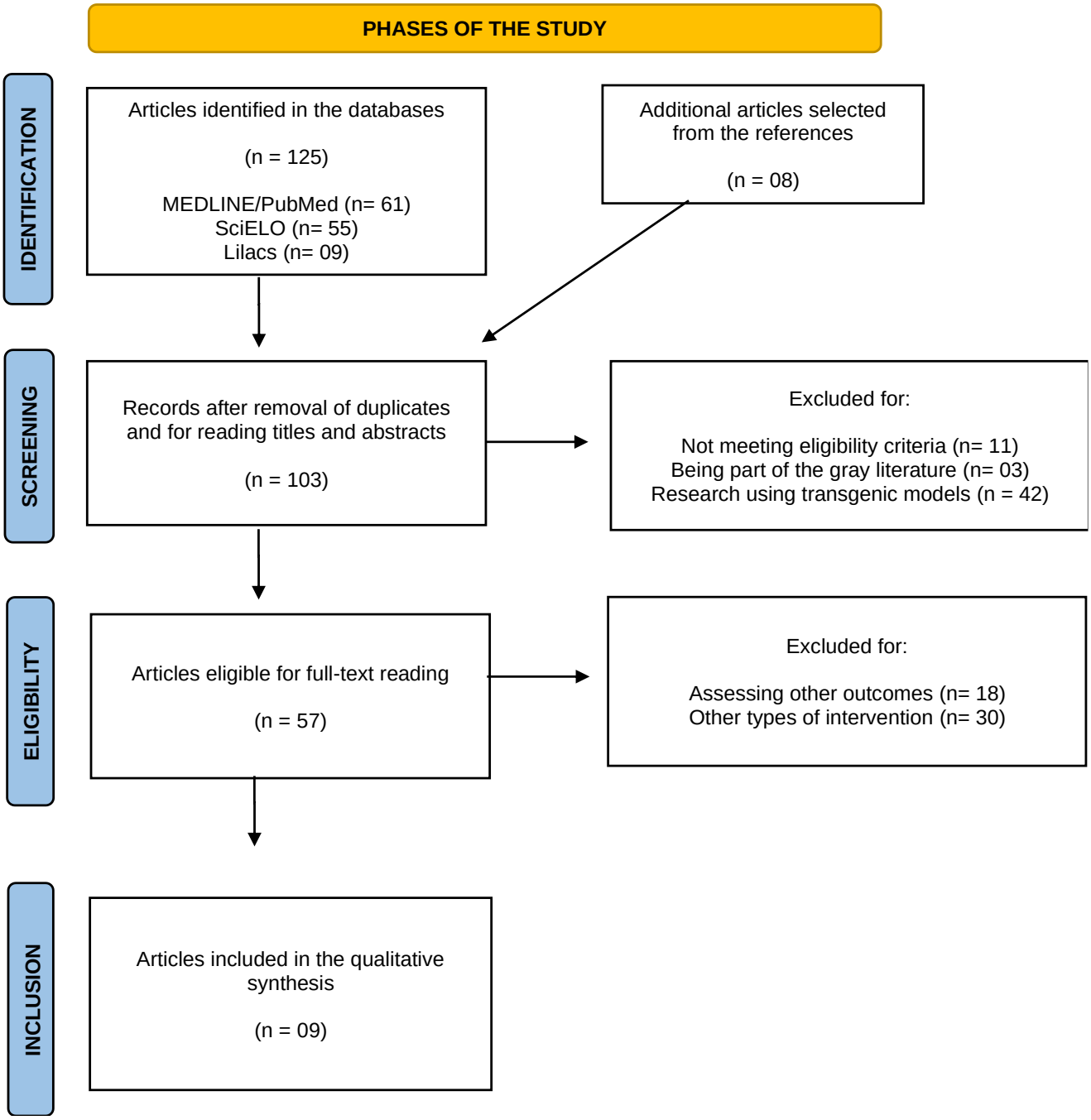


Figure 1. PRISMA Flowchart.

Table 2. Basic characteristics of the studies included in this review

Authors, Year, and Country	Objectives	Journal, Database, and IF	Research Method	Sample	Intervention protocols	Sample collection for biochemical analysis
Holten et al. (2004) [16] Denmark	Analyze whether strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes.	Diabetes MEDLINE/PubMed IF = 7.7	Clinical Trial	n = 17 adults GC = 7 with normal glucose tolerance GI = 10 with type 2 diabetes	Supervised RT 3x/week, sessions of up to 30 min, over 6 weeks. Weeks 1-2: 3x10 repetitions (50% 1-RM). Weeks 3-6: 4x8-12 repetitions (70-80% 1-RM). Last 2 weeks: exhaustive sets (8-12 repetitions). Rest: >90 s between sets, >2 min between stations	The biopsies were performed 16 hours after the participants completed their last RT session.
Chris-Roberts et al. (2004) [17] USA	Valuate the relative contributions of improvements in insulin receptor signaling, GLUT4 protein expression, and GS activity to training-induced increases in insulin sensitivity.	Metabolism MEDLINE/PubMed IF = 9.8	Parallel Clinical Trial	n = 22 people GC = 16 nondiabetic GI = 6 with type 2 diabetes	Supervised AE 3x/week, starting at 60% VO2peak for 20 min per session, over 8 weeks of intervention. Progressive increase over 8 weeks to 70% VO2peak, 45 min, 4x/week. Heart rate used as an intensity indicator.	Muscle biopsies were performed before and after 8 weeks of AE.
Wojtaszewski et al. (2005) [18] Denmark	Investigate the effect of strength training and type 2 diabetes on the expression of isoforms and the heterotrimeric composition of AMPK in human skeletal muscle.	The Journal of Physiology MEDLINE/PubMed IF = 5.5	Parallel Clinical Trial	n = 17 adults GC = 7 with normal glucose tolerance (sex unspecified) GI = 10 with type 2 diabetes	Supervised RT, 3x/week, sessions up to 30 min, for 6 weeks. Weeks 1-2: 3x10 repetitions (50% 1 RM). Weeks 3-6: 4x8-12 repetitions (70-80% 1 RM). Last 2 weeks: exhaustive sets. Rest: ~90 s between sets, ~2 min between exercises. 3 RM test at the beginning and end of the training.	The biopsy time points were: 16 to 18 hours after the last training session, with 30 minutes of supine rest before performing biopsies of the vastus lateralis muscle of the trained (T) and untrained (UT) legs.
O'Gorman et al. (2006) [19] Ireland	Assess the impact of acute short-term exercise training on whole-body insulin-mediated glucose disposal and signaling transduction along the canonical insulin signaling cascade.	Diabetologia MEDLINE/PubMed IF = 8.2	Parallel Clinical Trial	n = 15 GC = 7 obese nondiabetic GI = 8 obese with type 2 diabetes (sex unspecified)	Supervised AE for 1 week at ~75% VO2peak for 1 hour on a stationary cycle ergometer. The intensity was determined based on heart rate (±5 beats per minute) corresponding to 75% VO2peak, measured by indirect calorimetry. Blood pressure and heart rate were monitored before, during, and after exercise.	The vastus lateralis muscle biopsies were performed at baseline and 16 hours after an acute exercise session and short-term physical training (7 days).
Wang, Simar e Whang (2009) [20] Australia	Review the morphological and metabolic adaptations of skeletal muscle to exercise training in adults with type 2 diabetes or impaired glucose tolerance.	Diabetes/Metabolism Research and Reviews MEDLINE/PubMed IF= 8.0	Systematic Review	n = 18 RCTs and non-randomized	RT a 50–80% 1RM, 2-3 sets of 8-10 repetitions. AE of Low intensity (1 study), moderate (6), high (6); 30-60 min/session (mean 48 ± 9 min). Combined exercise: AE (80–90% VO_2max) + RT (50%). Variation in the total duration of interventions: 4-52 weeks. Majority with supervision.	The sample timing was: interval between the last exercise session and biopsy: 16-96 h (median: 60 h; interquartile range: 80 h).

Cont.Table 2

Sriwijitkamol et al. (2007) [21] UK	Determine whether individuals with type 2 diabetes and moderate to severe obesity (BMI > 30 kg/m2) exhibit impaired AMPK signaling.	Diabetes PubMed IF = 7.7	Clinical Trial	n = 28 people GC = 8 obese nondiabetic and 8 lean nondiabetic GI = 12 obese with type 2 diabetes	Two acute protocols (50% and 70% VO_2max), 40 minutes of AE (cycling. A 4-6 week interval between sessions.	The vastus lateralis muscle biopsies were performed at four time points: before exercise (fasted and at basal rest), after 10 minutes, after 40 minutes of exercise, and 150 minutes post-exercise (during recovery).
Vind et al. (2011) [22] Denmark	Investigate whether type 2 diabetes is associated with abnormalities in insulin-induced site-specific phosphorylation of TBC1D4 in skeletal muscle; examine the effect of resistance exercise training on TBC1D4 and other key insulin signaling events in well-controlled obese individuals with and without type 2 diabetes.	Diabetologia MEDLINE/PubMed IF = 8.2	Clinical Trial	n = 26 obese men with type 2 diabetes GC = 13 obese men with normal glucose tolerance GI = 13 obese men with type 2 diabetes	AE on a stationary bike at ~65% VO_2max, with 4-5 sessions/week (20-35 min), for 10 weeks.	Skeletal muscle biopsies were obtained from the vastus lateralis muscle before and after insulin, 1–2 weeks prior to the training protocol, and 48 hours after the last exercise session.
Hussey et al. (2012) [23] Australia	Determine the effect of a single bout of exercise on GLUT4 gene expression in muscles of patients with type 2 diabetes and control subjects, accounting for age and body mass index.	Diabetes, Obesity and Metabolism MEDLINE/PubMed IF = 5.8	Clinical Trial	n = 18 adults GI = 9 people with type 2 diabetes GC = 9 people with normal glucose tolerance	A 60-minute session of AE (cycle ergometer) at ~55% peak power output (WMax).	Skeletal muscle biopsies were obtained at the beginning of the study, immediately after exercise, and 3 hours post-exercise.
García-Hermoso et al. (2023) [24] Spain	Investigate the effects of exercise training on exerkines in patients with type 2 diabetes to determine the ideal exercise prescription.	Journal of Sport and Health Science MEDLINE/PubMed IF = 11.7	Systematic Review of RCTs	n = 40 RCTs with 2,160 people in total 1,281 people with diabetes in GI 879 people with diabetes in GC	RT, CE, and AE protocols: Weekly frequency ranged from 2 to 5 sessions; session volume varied between 15 and 75 minutes across trials. Total intervention duration ranged from 8 to 96 weeks. Intensity for AE varied between 40–95% of HRmax, 40–85% of VO_2peak, and 50–80% of maximal oxygen consumption. RT intensity ranged from 40–80% of 1RM and 3.6 to 6 METs.	The timing of the sample collection was not specified.

[2] **Legend:** IF = impact factor; CG = control group; IG = intervention group; n = sample; USA = United States of America; GS = glycogen synthase; GLUT4 = glucose transporter 4; BMI = body mass index; T2D = type 2 diabetes; AMPK = AMP-activated protein kinase; TBC1D4 = TBC1 domain family member 4; NE = not specified; RCT = clinical trial; RTC = randomized clinical trial; IGT = impaired glucose tolerance; W = weeks; VO_2max = maximum oxygen consumption; RM= Maximum repetition; METs = metabolic equivalents; HRmax = maximal heart rate; VO_2peak = peak oxygen consumption; AE = aerobic exercise; RT = resistance exercise; CE = combined exercise. Source: The authors (2024).

Characteristics of the Included Studies

A total of 3 studies were conducted in Denmark, 1 study in the United Kingdom, 1 study in the United States, 1 study in Ireland, 2 studies in Australia, and 1 study in Spain. All included studies were published between 2004 and 2024. Out of the 7 articles, only 1 was conducted about 5 years ago. Sample sizes were generally small, and there was not a substantially large variation among the studies. A total of 8 studies had samples ranging from 15 to 28 participants, and only 1 systematic review had a more significant sample, with approximately 2,160 individuals investigated.

Research Methods and Bibliometric Indicators

Regarding the research methods of the included studies, it was observed that approximately 77.8% were clinical trials (randomized and non-randomized) and 22.2% were systematic reviews. As for bibliometric indicators, 100% of the studies were published and indexed in international journals that addressed molecular, physiological, and human metabolism aspects, particularly related to diabetes. Furthermore, all articles were published in journals with an impact factor (IF) > 1.5, in English.

Temporal Scope and Content Analysis of the Journals

Regarding the temporal scope, it was noted that about 84.6% of the articles were published more than 7 years ago, and only 15.4% were published in the last 5 years. In terms of topic, all studies (100%) addressed physiological, molecular, and morphological aspects involving different physical training in individuals with type 2 diabetes. Concerning the intervention duration of the studies, there was a large variation, with 1 article reporting a single acute session of physical training; 1 article up to one week; 3 articles up to six weeks; 1 article that did not report the intervention duration; 1 article up to eight weeks; 1 article up to ten weeks; and 1 article with up to fifty-two weeks.

Table 3. List of acronyms, full names, and categories of molecules involved in the AMPK signaling pathway in type 2 diabetes (T2DM)

Acronym	Name	Category	Function	Coding gene
GLUT4	Glucose transporter 4	Protein	Transports glucose from the extracellular environment to the intracellular environment in adipose and muscle tissues	*SLC2A4*
IL-6	Interleukin 6	Interleukin	Regulates cell growth and differentiation and plays an important role in the immune response	*IL6*
IL-10	Interleukin 10	Cytokine	Deactivates macrophages	*IL10*
IL-15	Interleukin 15	Cytokine	Induces the proliferation of natural killer cells; cells of the immune and innate systems whose main function is to kill virus-infected cells	*IL15*
IL-18	Interleukin 18	Cytokine	This cytokine has been implicated in injury to various organs and in potentially fatal conditions characterized by a cytokine storm	*IL18*
PGC1-α	Peroxisome proliferator-activated receptor γ coactivator 1α	Transcription coactivator	Participates in energy metabolism, stimulates mitochondrial biogenesis, and promotes muscle tissue remodeling	*PPARGC1A*
Akt2 or PKB β	Protein kinase B (PKB) 2	Protein kinase	Plays a critical role in the regulation of glucose homeostasis	*AKT2*
Akt1 or PKB α	Protein kinase B (PKB) 1	Protein kinase	Plays a fundamental role in cell survival regulation, insulin signaling, angiogenesis, and tumor formation	*AKT1*
CaMK	Calcium/calmodulin-dependent kinase	Protein	Binds to calcium ions present in the cytoplasm and regulates various target proteins in cells	*CAMKK1*
TBC1D4 or AS160	Rac1 protein, TBC1 member of domain family 4, AKT substrate of 160 kDa	Protein	Regulates the translocation of GLUT4 in response to stimulation	*TBC1D4*
HKII	Hexokinase II	Enzyme	Enzyme of the glycolytic pathway that converts glucose to glucose-6-phosphate and regulates carbohydrate metabolism	*HK2*
p38 MAPK	38' mitogen-activated protein kinase	Protein	Involved in cell differentiation, apoptosis, and autophagy	*MAPK14*
GS	Glycogen synthase	Enzyme	Converts excess free glucose into a glycogen chain	*GYS2*
PI3K	Phosphoinositide 3-kinase	Enzyme	Phosphorylates AKT and is involved in various cellular functions such as growth, proliferation, differentiation, mobility, survival, and intracellular trafficking	*PI3K*
NR4A	Subfamily of the orphan nuclear receptor superfamily	Transcription factor	Involved in important biological processes, including carcinogenesis/apoptosis control, inflammation, vascular disease, development, and metabolism of dopaminergic neurons	*NR4A*
ADIPOQ	Adiponectin	Protein hormone	Exerts protective effects against inflammation and may positively modulate the endocrine system	*ADIPOQ*
TNF-α	Tumor necrosis factor-alpha	Cytokine	A group of cytokines that induce tumor cell death and have pro-inflammatory actions	*TNFA*
HDAC5	Histone deacetylase 5	Enzyme	Plays a critical role in transcriptional regulation, cell cycle progression, and developmental events	*HDAC5*
FETUA	Fetuin A	Glycoprotein	Modulates vascular calcification, the response to systemic inflammation, bone metabolism, and insulin activity	*AHSG*
LEP	Leptin	Hormone	Plays an important role in the regulation of energy homeostasis	*LEP*
ADSF	Resistin	Protein	Acts as an insulin antagonist and blocks the central action of leptin	*RET*
GHRL	Ghrelin	Hormone	Stimulates appetite and plays an important role in energy homeostasis	*GHRL*
APLN	Apelin	Protein	Regulates various biological functions, including fluid homeostasis, cardiovascular function, and insulin secretion	*APLN*
IRS1	Insulin receptor substrate 1	Protein	Involved in type 2 diabetes mechanisms, insulin resistance susceptibilities, and cancer progression	*IRS1*
IRS2	Insulin receptor substrate 2	Protein	Involved in the regulation of glucose homeostasis and lipid metabolism	*IRS2*

[3]Source: the authors (2024), adapted from Gene/PubMed (2024).

Table 4. Synthesis of Evidence

Authors and Year	Main Results Found
Holten et al. (2004) [16]	After unilateral resistance training (RT), patients with type 2 diabetes (T2D) showed a 40% increase in GLUT4 density ($p<0.05$). No difference in GLUT4 protein thickness was observed between the analyzed groups ($p>0.05$). Increases in insulin action were noted in the T2D group, along with elevated protein levels of GLUT4, PKB, and GS ($p<0.05$). Significant increases in insulin receptor protein content were found ($p<0.05$).
Chris-Roberts et al. (2004) [17]	Eight weeks of aerobic training (AT) increased GLUT4 expression by 38% and 22% in non-diabetic and diabetic individuals, respectively ($p<0.05$). AKT expression increased in both groups after 8 weeks of AT ($p<0.05$). Total GS activity increased by 46% and 45% in non-diabetic and diabetic individuals, respectively, in response to AT ($p<0.01$).
Wojtaszewski et al. (2005) [18]	Basal AMPK activity and the expression of protein/mRNA of catalytic isoforms (α1 and α2) and regulatory isoforms (β1, β2, γ1, γ2a, γ2b, and γ3) of AMPK were independent of T2D. Protein content of α1 (+16%), α2 (+14%), and β1 (+29%) was higher, while γ3 content was lower (-48%) in human muscles after RT compared to untrained muscles ($p<0.01$).
O'Gorman et al. (2006) [19]	Short-term physical training increased insulin-mediated glucose elimination in obese T2D patients ($p<0.05$), but not in obese non-diabetic individuals ($p>0.05$). Activation of IRS1, IRS2, PI3K associated with phosphotyrosine, and phosphorylated AKT substrate, AS160, an important functional Rab GTPase activator for GLUT4, remained unchanged after acute or chronic exercise.
Wang, Simar e Whang (2009) [20]	Beneficial adaptations to AT, RT, and endurance training (ET) were primarily observed in muscle fiber area, capillary density, glycogen, glycogen synthase, and expressions of GLUT4 protein.
Sriwijitkamol et al. (2007) [21]	Low and moderate intensity AT acutely stimulated the expression of the PGC1 gene, peaking after a 150-minute rest period ($p<0.05$).
Vind et al. (2011) [22]	Phosphorylation of TBC1D4 showed no differences among the studied groups ($p>0.05$), but the study revealed an increase of TBC1D4 of approximately 20% within groups ($p<0.05$). Proteins AKT1 and AKT2 showed significant differences between groups. AKT1 expression increased by 20% in the control group after exercise, while the group with T2D increased AKT1 expression by up to 50% ($p<0.05$). AKT2 increased in both groups (control and diabetic) by 30% to 40%, respectively.
Hussey et al. (2012) [23]	After one session of AT, GLUT4 expression was similar in both groups ($p<0.05$), remaining elevated and showing reduction only after 3 hours post-intervention. At rest, the T2D group had lower expression of PGC1-α compared to the control group. However, after intervention, PGC1-α increased in both groups ($p<0.05$). PGC1-α gene manifestations were identified in T2D patients after acute exercise. Increases in AMPK and p38 MAPK phosphorylation enhanced the effects on GLUT4 expression after AT.
García-Hermoso et al. (2023) [24]	Different exercise modalities induced changes in levels of adiponectin, fetuin-A, fibroblast growth factor-21, IL-6, IL-10, leptin, resistin, and TNF-α in T2D, but did not have significant effects on apelin, IL-18, and ghrelin compared to controls.

[4]**Legend:** TNF-α = tumor necrosis factor-alpha; GS = glycogen synthase; GLUT4 = glucose transporter 4; T2D = type 2 diabetes mellitus; AMPK = AMP-activated protein kinase; TBC1D4 = TBC1 domain family member 4; IL-6 = Interleukin 6; IL-10 = Interleukin 10; PA = physical exercise; CaMK = calcium/calmodulin-dependent kinase; HDAC5 = histone deacetylase 5; IL-18 = Interleukin 18; NR4A = subfamily of the orphan nuclear receptor superfamily; CG = control group; IG = intervention group; p38 MAPK = p38 mitogen-activated protein kinase; PGC1-α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K = phosphoinositide 3-kinase; IRS1 = insulin receptor substrate 1; IRS2 = insulin receptor substrate 2; AE = aerobic exercise; RT = resistance exercise; CE = combined exercise. Source: The authors (2024).

DISCUSSION

The results of this study provided valuable insights into the expression of different molecules in the AMP-activated protein kinase (AMPK) pathway in individuals with type 2 diabetes (T2D) in response to aerobic, resistance, and combined exercises. Most studies indicated that regardless of the exercise modality practiced, activation of the AMPK pathway in people with diabetes can only occur through muscle contraction. Among the 25 molecules found in this pathway were cytokines/interleukins, proteins, enzymes, transcription factors, co-transcriptional activators, and protein hormones. Another significant finding in this study was the expression of the GLUT4 protein and the transcriptional co-activator PGC1-α in the majority of the included research [25-26].

This supports the studies by Jeon [27] and Santos and coauthors [26], which have demonstrated that through physical exercise, skeletal muscles contract and alter cellular energy status, leading to increased metabolic demand in the body and changes in the AMP ratio. The phosphorylation of AMPK induced by different proteins activates PGC1-α and results in a peak in ATP production, facilitating the movement of vesicles containing GLUT4 to the plasma membrane [28-18]. Once GLUT4 is at the membrane, it can capture circulating glucose in the blood and transport it into the cells through facilitated diffusion [29]. Thus, blood glucose is reduced and transformed into ATP in the cytoplasm of the cell, and this entire process results in energy production for up to 48 hours, aiding in glycemic control of T2D [6-30].

Similarly, Wang, Simar, and Whang [20] highlighted that aerobic (AE), resistance (RE), and combined (CE) exercises are related to increases in muscle fiber area and capillary density, glycogen, glycogen synthase, and GLUT4 protein expressions in individuals with T2D. These same exercises can also induce changes in levels of adiponectin, fetuin-A, fibroblast growth factor-21, IL-6, IL-10, leptin, resistin, and TNF-α in T2D [31]. While AE appears to play a role more related to the expression of PGC1-α, mitochondrial adaptation, and oxidative capacity in skeletal muscles [21], RE is more associated with GLUT4 expression, muscle hypertrophy, and protein synthesis regulation [16].

Recent studies have supported the combination of these two exercise modalities, showing that combined exercise may be the best option for individuals with T2D aiming to maintain metabolic and cardiovascular control [32]. This was well elucidated in a meta-analysis by García-Hermoso and coauthors [24], where the authors compiled 40 randomized clinical trials and investigated 2,160 individuals with T2D in Spain. The authors highlighted that both exercise modalities led to significant positive changes in combined exercise, which were in turn related to changes in glycated hemoglobin (mean difference [MD] = 0.81%, 95% CI: 0.95% to 0.67%) and fasting blood glucose (MD = 23.43 mg/dL, 95% CI: 30.07 mg/dL to 16.80 mg/dL).

Beyond the training modality, this same study demonstrated that other variables that may be related to increased expression of molecules in the AMPK pathway and glycemic control in T2D include the volume and frequency of training per week, intensity, and total duration of intervention. Slightly stronger effects were observed with aerobic protocols, resistance, or high-intensity interval training (HIIT) at moderate to vigorous intensity, and with programs lasting over 24 weeks that included at least 3 sessions per week and more than 60 minutes per session.

The effects of molecular expression in the AMPK pathway can be readily observed after chronic exercise [33]. This was evidenced in a clinical trial conducted by Chris-Roberts and coauthors [17], where 8 weeks of AE increased GLUT4 expression by 38% and 22% in non-diabetic and diabetic individuals, respectively ($p<0.05$). The expression of serine protein kinase (AKT) increased in both groups after 8 weeks of AE ($p<0.05$). The total activity of glycogen synthase (GS) increased by 46% and 45% in non-diabetic and diabetic individuals, respectively, in response to AE ($p<0.01$). However, the high heterogeneity between the groups (control group with 16 individuals and intervention group with only 6 participants) may have influenced these results.

It appears that even a single session of physical exercise is capable of activating the AMPK pathway and increasing molecular expression [34]. In this regard, Hussey and coauthors [23] sought to analyze the expression of GLUT4 mRNA after a single session of aerobic exercise. Eighteen individuals were evaluated, nine of whom had T2D and nine with no previous history of comorbidities. The intervention consisted of AE lasting 60 minutes at 55% of VO^2max. The results demonstrated that GLUT4 mRNA levels increased post-exercise in the T2D group ($p<0.05$), remaining elevated and only showing a decrease after 3 hours of the exercise intervention. However, when comparing the control and intervention groups, both increased GLUT4 expression, with no significant differences between them ($p>0.05$).

Not only does aerobic exercise have molecular effects, but resistance exercise has also demonstrated significant molecular effects in the AMPK pathway (18). In Holten and coauthors [16], a 6-week unilateral resistance exercise intervention was able to increase insulin action in the T2D group, elevate PKB and glycogen synthase levels, and induce significant increases in insulin receptor protein content ($p<0.05$). This

same study showed that RE increased GLUT4 density by 40% in individuals with T2D ($p<0.05$). However, there was no difference in GLUT4 protein thickness between the control and intervention groups ($p>0.05$).

On the other hand, the authors showed that despite no differences in the expression of molecules like GLUT4 when comparing the intervention and control groups [16], discrepancies may be observed regarding increased insulin sensitivity in adipose and muscle tissues, as well as greater glucose disposal in individuals with T2D [19].

This exercise-induced increase in insulin sensitivity is regulated by a signaling mechanism known as AMPK-TBC1D4 [34]. This relationship was recently confirmed by several authors [31], who demonstrated that the phosphorylation of Rac1 protein and TBC1 domain family member 4 (TBC1D4) may provide a mechanism for exercise-induced improvements in muscle insulin sensitivity in individuals with T2D, particularly in those with higher insulin resistance, specifically the obese.

It is known that individuals with obesity tend to have greater insulin resistance [7]. Therefore, it is important to determine whether individuals with T2D and this clinical condition exhibit impaired AMPK signaling [21]. In view of this, a recent study [22] evaluated 26 male individuals with obesity divided into two groups: the intervention group (individuals with obesity and T2D) and the control group (obese individuals without diabetes).

The intervention consisted of 10 weeks of AE, comprising 4 to 5 days per week with a duration of 20 to 35 minutes at 65% of VO2 max. The findings demonstrated that phosphorylation of TBC1D4 showed no differences between the studied groups ($p>0.05$), but the study revealed an increase in TBC1D4 of approximately 20% within groups ($p<0.05$). In this same study, AKT1 and AKT2 proteins exhibited significant differences between groups. While AKT1 expression increased by 20% in the control group after AE, the group with individuals with T2D increased the expression of this molecule by up to 50% ($p<0.05$). Meanwhile, AKT2 increased in both groups (control and intervention), with values ranging between 30% and 40%, respectively.

Similar to this study, a clinical trial conducted in the UK [21] investigated 28 individuals (control group = 8 obese non-diabetic individuals and 8 lean non-diabetic individuals; intervention group = 12 obese individuals with T2D). After 10 weeks of low to moderate intensity aerobic exercise, the expression of the PGC1-α gene was acutely stimulated, peaking after a 150-minute rest period ($p<0.05$). PGC1-α, after being activated by AMPK and calcium/calmodulin-dependent kinase (CaMK), is responsible for increasing GLUT4 expression in individuals with T2D [26]. Furthermore, it regulates other genes (such as SLC2A4 itself), activates mitochondrial biogenesis, maintains glycemic homeostasis, and promotes the increase/remodeling of type I fibers (red and slow fibers) [35].

Different intervention protocols and the biochemical responses observed

Intervention protocols, especially resistance (RT) and aerobic (AE) exercises, play a crucial role in the biochemical responses observed in the muscles of individuals with type 2 diabetes. In studies such as those by Holten and coauthors [16] and Wojtaszewski and coauthors [18] participants performed RT three times a week with varying intensities and volumes over 6 weeks. The results showed improvements in insulin-mediated glucose uptake and the expression of glucose transporter-related proteins, such as GLUT4. Another interesting aspect was the relationship between exercise intensity and biochemical responses, which was observed with higher intensity and training volume in the final weeks of the intervention protocol. These variables contribute to favorable adaptations in insulin signaling, as evidenced by improvements in protein phosphorylation and the isoenzymatic composition of the AMPK pathway.

Moreover, AE protocols also produced significant responses, as seen in the studies by O'Gorman and coauthors [19] and Vind and coauthors [22] which used different aerobic exercise intensities in their interventions. By combining intensity with duration of AE, associations were found with improvements in insulin-mediated glucose disposal and various aspects of cellular signaling related to glucose metabolism. Exercise intensity was a critical factor in determining favorable effects on insulin signaling pathways, with programs that included progressive increases in exercise intensity and duration showing more pronounced responses. An example of this was the response in groups performing exercises at 60% to 80% of VO2peak.

Finally, the difference in sample collection times [36] and methods has also been highlighted [37, 38] as a factor that may influence biochemical responses in humans. In the studies by Sriwijitkamol and coauthors. (2007) [21] and García-Hermoso and coauthors (2023) [24], more specifically, muscle tissue samples were collected at different time intervals post-exercise. The analysis of acute and recovery biochemical responses revealed that the time elapsed after the exercise session could be crucial for understanding the adaptations of glucose metabolism and proteins involved in the insulin signaling process. Sample collection between 16 and 96 hours after exercise demonstrated that the time window for biochemical response measurements

could be an important aspect to consider in the specific muscle adaptations in individuals with type 2 diabetes. Therefore, intervention protocols, exercise intensity, volume, and sample collection timing play critical roles in biochemical responses and training adaptations.

Overall, the results of this review suggest that the expression of molecules in the AMPK pathway induced by aerobic, resistance, and combined exercises may be important for metabolic control of T2D and provide multisystem benefits. However, much of the regulation of these molecules by exercise in individuals with T2D remains unknown and presents several challenges for its validation in clinical/therapeutic practice. Therefore, in treating patients with T2D, it is necessary to clarify these aspects and determine whether the expression of molecules in the AMPK pathway can directly impact glycemic control in this target population.

Strengths and Limitations of the Study

Most studies analyzing the expression of molecules present in the AMPK pathway do not examine these effects in individuals with type 2 diabetes and impaired glucose tolerance after different modalities of physical exercise. As strengths of our study, we highlight the fact that we conducted this analysis and avoided comparing research involving humans and transgenic models, aiming to increase the homogeneity of the sample in our research. Furthermore, we emphasize that most of the studies were clinical trials, and all articles included in the research were published in high-impact journals (>1.5). Thus, we believe that the results of this study are of great utility, as they provide initial data that have not yet been substantially studied.

However, we recognize that our study also has limitations. First, significant heterogeneity was found in the results for the molecules present in the AMPK pathway, which may be explained by the differences between studies in terms of variations in employed methods, exercise protocols, and studied samples. Despite the positive effects of physical exercise on molecular expression in the AMPK pathway being demonstrated in our study, our data cannot be generalized, since the sample from 8 of the 9 included studies was relatively small and not representative of the studied population, which diminishes its external validity.

Other limiting factors included the temporality of the studies and the lack of transparency in some of them. Only 1 study was published in the last five years. In general, the clinical trials did not specify whether randomization was performed or if participants or researchers were blinded during the interventions to reduce the risk of bias in the research. Only one systematic review included did this blinding. Nevertheless, most studies used a short intervention time, which may have prevented the observation of the long-term effects of physical exercise.

Therefore, additional research is suggested, especially randomized clinical trials, to assess the expression of molecules in the AMPK pathway in individuals with type 2 diabetes and their relationship with glycemic variables after different modalities of exercise, aiming to identify whether both are associated with better glycemic control in this target population.

CONCLUSION

It is concluded that physical exercise can increase the expression of molecules involved in the AMPK pathway in individuals with type 2 diabetes. However, when comparing exercise modalities, the studies indicated that combined exercise appears to be more effective than either resistance or aerobic exercise performed in isolation. Furthermore, there seems to be a difference not only between the types of exercises but also among the volume, intensity, and frequency of training

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