Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU25518

Resistance Training in Type 2 Diabetes: Mechanisms and Clinical Translation

Zhifei Wu

School of Physical Education and Health, Guangxi Medical University, Nanning, China
20224273544@sr.gxmu.edu.cn

Abstract: Type 2 diabetes (T2D) is a global pandemic imposing substantial health and economic burdens, highlighting the critical need for effective non-pharmacological management strategies beyond medication. This paper comprehensively examines the biological mechanisms underpinning the therapeutic effects of resistance training (RT) in T2D and translates this evidence into clinical applications. The results of this paper demonstrate that RT enhances glycemic control by upregulating skeletal muscle GLUT4 expression through AMPK/HDAC5-MEF2 and Akt/AS160 pathways, and activates mTORC1 signaling to promote protein anabolism. Clinically, structured RT significantly reduces HbA1c, attenuates postprandial glucose fluctuations, and mitigates major complications. The rationale is to improve the prognosis of diabetic foot by enhancing plantar pressure distribution and endothelial function, which is expected to reduce renal inflammation and oxidative stress in a preclinical diabetic nephropathy model, and in combination with aerobic exercise, improve nerve conduction velocity and pain in diabetic peripheral neuropathy. Critically, RT demonstrates a unique "strength-metabolism coupling" effect, concurrently improving muscle strength and glycemic control, especially in elderly T2D patients with sarcopenia. This paper underscores RT as a potent, evidence-based cornerstone intervention for T2D management. It provides a crucial theoretical foundation for developing personalized RT prescriptions and integrating RT within multidisciplinary care models to optimize outcomes and reduce complication risks.

Keywords: Resistance training, Type 2 diabetes, Glycemic control, Diabetic complications.

1. Introduction

Diabetes mellitus represents a significant and escalating global health challenge, which is defined as a chronic metabolic disorder characterized by persistent hyperglycemia. This condition fundamentally arises from either an absolute deficiency in insulin secretion, which is a relative deficiency due to impaired insulin action (insulin resistance), or a combination of both factors. The sheer scale of the epidemic is starkly highlighted by the International Diabetes Federation (IDF), which reports that over 537 million adults worldwide were living with diabetes in 2021. Alarmingly, projections indicate a daunting 46% surge in prevalence by 2045, potentially affecting nearly 783 million individuals [1]. This trajectory underscores an urgent need for effective and sustainable management strategies. While pharmacotherapy has advanced, it also has significant limitations that

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.AU25518

persist. Challenges such as variable medication adherence among patients and the potential for adverse metabolic side effects-including weight gain, hypoglycemia, or gastrointestinal disturbances-remain substantial hurdles. These limitations strengthen the adage that "all medications carry inherent risks of toxicity". Thus, intensifying the demand for robust non-pharmacological interventions can reduce reliance on pharmaceutical agents.

Resistance training (RT) involves activities designed to improve muscular strength and endurance against an opposing force. Within the spectrum of exercise modalities is garnering increased attention. Emerging evidence suggests RT may confer unique metabolic advantages over traditional aerobic exercise regimens alone [2]. Its appeal is further amplified by attributes such as relatively low cost, minimal equipment requirements, and high feasibility for diverse populations, making it a practical option. Crucially, RT exerts potent effects on skeletal muscle glucose metabolism via mechanisms like glucose transporter type 4 (GLUT4) to the cell membrane and beneficial adaptations in mitochondrial function and density [3]. These adaptations directly counteract the core pathologies of T2D: insulin resistance and the age-related decline in muscle mass and function (sarcopenia). This combination often creates a debilitating dual burden for patients. Recent meta-analyses substantiate the efficacy of RT. They confirm reductions in glycated hemoglobin (HbA1c) and improvements in body composition (increased lean mass, decreased fat mass). Furthermore, hybrid training strategically combines RT with aerobic exercise. This approach demonstrates superior cardiometabolic benefits compared to either modality in isolation, offering a comprehensive approach.

Despite its compelling benefits and practical advantages, the widespread adoption of RT within diabetes care protocols remains limited. Significant barriers include insufficient training among clinicians regarding exercise prescription, particularly for RT, and persistent safety concerns when managing patients with prevalent comorbidities like cardiovascular disease, severe neuropathy, or retinopathy. Compounding this implementation gap is the nature of the existing evidence base. While preliminary data from case reports, small trials, and cohort studies suggest significant benefits, the absence of comprehensive systematic reviews and meta-analyses specifically focused on RT's role across diverse diabetic populations hinders the development of robust, evidence-based clinical practice guidelines. Consequently, this paper aims to critically synthesize the current evidence on RT in diabetes management. It will place particular emphasis on advancing the development of personalized exercise prescriptions tailored to individual patient characteristics, risk profiles, and preferences, and will explore the integration of RT within effective multidisciplinary intervention models involving physicians, diabetes educators, physiotherapists, and dietitians. The ultimate goal is to provide a stronger theoretical and practical foundation for optimizing diabetes management strategies and improving long-term patient outcomes.

2. Biological mechanisms of resistance training in diabetes pathology

2.1. Upregulation of skeletal muscle GLUT4 transporter expression

RT improves glucose metabolism by adjusting the expression of GLUT4 in skeletal muscle through multi-pathway coordination. Acute exercise activates the AMPK/HDAC5-MEF2 axis, relieves epigenetic inhibition, and promotes GLUT4 transcription [3]. However, in chronic intervention, 12-week resistance training enhances GLUT4 vesicle transposition through Akt/AS160 phosphorylation, and the GLUT4 protein of skeletal muscle in T2D patients is increased [4]. Clinical research shows that 16 weeks of resistance training reduced HbA1c and increased muscle glucose uptake in diabetic patients [2].

DOI: 10.54254/2753-8818/2025.AU25518

2.2. mTOR signaling pathway activation and protein anabolism

Resistance training robustly activates the mTORC1 signaling pathway, a master regulator of muscle protein anabolism. Mechanical loading triggers integrin-FAK-PI3K/Akt signaling, phosphorylating TSC2 to relieve mTORC1 inhibition, thereby enhancing ribosomal biogenesis and translation initiation. This pathway synergizes with exercise-induced IGF-1 to amplify 4E-BP1 phosphorylation by 3.2-fold via IRS-1/PI3K, as validated in human muscle biopsies [4]. Critical translational evidence comes from a 2022 RCT (n=45): leucine supplementation (2.5g/meal) combined with resistance training increased myofibrillar protein synthesis rates by 40% in older diabetics through Sestrin2-mTORC1 binding [5].

3. Systematic analysis of clinical evidence

3.1. Glycemic control efficacy

3.1.1. HbA1c reduction

RT can significantly increase GLUT4 protein expression by 40% in the trained muscle of diabetic subjects, facilitating greater insulin-mediated glucose transport into muscle cells [4]. The enhancement of Glucose Homeostasis leads to HbA1c reduction finally. Combined exercise training demonstrates significant efficacy in improving glycemic control among patients with T2D, as evidenced by hemoglobin HbA1c reduction in multiple meta-analyses. The glycated hemoglobin metric reflects chronic hyperglycemia exposure, with each 1% reduction in HbA1c correlating with a 21% decrease in diabetes-related mortality risk. Notably, combined aerobic and resistance training (CART) emerges as a particularly effective intervention through complementary physiological mechanisms. A 2024 meta-analysis revealed that CART achieved superior HbA1c reduction compared to single-mode exercise or non-exercise controls, with a standardized mean difference (SMD) of -0.37 (95% CI: -0.60 to -0.13) [5]. This substantial decrease stems from dual metabolic adaptations: aerobic exercise enhances hepatic insulin sensitivity and mitochondrial oxidative capacity, while resistance training increases skeletal muscle mass and GLUT4 transporter density, collectively improving postprandial glucose disposal.

The dose-dependent relationship between exercise intensity and HbA1c reduction is particularly noteworthy. Another research demonstrated that high-intensity resistance exercise (≥75% 1-RM) yielded nearly triple the HbA1c reduction (-0.61%) compared to low-to-moderate intensity regimens (-0.23%). This intensity effect may relate to greater activation of AMP-activated protein kinase pathways. This activation promotes glucose uptake independent of insulin signaling—a critical advantage for patients with established insulin resistance [6]. Moreover, longitudinal studies suggest that sustained CART interventions (≥12 weeks) can maintain HbA1c reductions for over 6 months post-intervention. This finding highlights its durability as a therapeutic strategy [2].

Clinically, these findings advocate for personalized exercise prescriptions incorporating both modalities. Optimal protocols involve 150 minutes/week of moderate aerobic exercise (e.g., cycling at 50-70% HRmax) paired with 2-3 resistance sessions targeting major muscle groups (e.g., leg presses at 70-80% 1-RM). For elderly patients, modified programs using bodyweight resistance or aquatic exercises show comparable HbA1c improvements. These modified programs also carry a lower injury risk. When combined with pharmacotherapy, CART may enhance efficacy. Studies report up to 23% greater HbA1c reduction when metformin is paired with structured exercise versus monotherapy. These synergistic effects position CART as a cornerstone intervention for mitigating

DOI: 10.54254/2753-8818/2025.AU25518

diabetes complications. Importantly, HbA1c reductions directly translate to decreased risks of retinopathy, nephropathy, and cardiovascular events [2, 6].

3.1.2. Postprandial Glucose (PPG) fluctuation dynamics

RT improves PPG primarily through long-term enhancement of insulin sensitivity. This enhancement is mediated by several key adaptations. RT increases skeletal muscle mass, providing a larger reservoir for glucose disposal and glycogen storage, thereby lowering PPG. Furthermore, RT improves insulin signaling pathways. It does this by upregulating insulin receptor content, Akt/PKB activity and GLUT4 translocation. This upregulating enables more efficient glucose uptake into muscle cells for a given insulin concentration. RT also reduces intramyocellular lipid (IMCL) depots. Accumulation of IMCL impairs insulin signaling; this reduction potentially occurs via increased lipid oxidation and clearance, thus ameliorating insulin resistance. Collectively, these adaptations—increased muscle mass, enhanced intracellular signaling, and reduced IMCL—enhance muscle insulin sensitivity. This enhanced sensitivity facilitates greater post-meal glucose clearance and lowers PPG.

Postprandial glucose fluctuation dynamics are a critical focus in T2D management. Exercise is emerging as a key modulator. While one study revealed comparable glycemic benefits between morning and evening exercise sessions, emphasizing consistency over timing specificity. A more nuanced perspective arises from exercise-nutrient interaction research. Strategic nutrient timing further optimizes outcomes. Low-carbohydrate post-exercise meals prolong insulin sensitivity enhancements. Conversely, interrupting prolonged sitting with activity "snacks" mitigates hyperglycemic spikes [7]. These findings collectively highlight the multifactorial nature of glycemic control. They advocate for personalized exercise protocols that integrate temporal, nutritional, and modality considerations. This integration aims to address postprandial dysmetabolism effectively.

3.2. Complication prevention

3.2.1. Diabetic foot

Approximately 18 million people suffer from diabetic foot ulcers each year around the world, and these ulcers are about 80% of amputations among people with diabetes and are related to an increasing risk of death [8]. RT plays a critical role in preventing diabetic foot complications. This is achieved by addressing modifiable risk factors associated with ulcer development. Diabetic foot ulcers (DFUs) often arise from peripheral neuropathy, impaired circulation, and abnormal plantar pressure distribution, all of which resistance exercise may mitigate. The International Working Group on the Diabetic Foot (IWGDF) guidelines endorse foot-specific exercises, including resistance training, to improve plantar pressure redistribution and ankle mobility, thereby reducing mechanical stress on vulnerable areas [8]. RT enhances lower limb muscle strength, which stabilizes gait patterns and improves plantar pressure distribution—a key factor in preventing ulceration [9]. Mechanistically, resistance training improves endothelial function by increasing nitric oxide synthesis and peripheral blood flow, counteracting diabetes-induced microvascular dysfunction [8]. Enhanced circulation supports tissue oxygenation and nutrient delivery, critical for maintaining skin integrity in high-risk patients. Furthermore, resistance exercise improves proprioception and joint flexibility, reducing the risk of trauma from repetitive stress or gait abnormalities [8]. Current evidence, though limited to small-scale trials, suggests that resistance training reduces neuropathy progression by 30% in prediabetic cohorts, highlighting its prophylactic potential [8]. However,

DOI: 10.54254/2753-8818/2025.AU25518

protocols must avoid weight-bearing activities in patients with pre-ulcerative lesions. Future research should standardize resistance modalities (e.g., elastic bands, seated machines) and dosage to establish evidence-based guidelines for DFU prevention.

3.2.2. Diabetic Kidney Disease (DKD)

Diabetic kidney disease (DKD) develops in 30–40% of patients with diabetes and accounts for over 50% of chronic kidney disease (CKD) cases globally. RT may mitigate DKD by improving insulin sensitivity, reducing oxidative stress, and modulating inflammatory pathways. In type 2 diabetic rat models, structured exercise interventions reduced renal inflammation markers by 37% (TNF-α, $p<0.01$) and 42% (IL-6, $p<0.001$), decreased oxidative stress marker malondialdehyde (MDA) by 29% ($p<0.05$), and elevated antioxidant enzymes glutathione peroxidase (GPx) by 31% ($p<0.01$) and superoxide dismutase (SOD) by 24% ($p<0.05$) [10]. Critically, exercise lowered serum fetuin-A – a key mediator of insulin resistance and renal damage – by 19.5% ($p<0.01$), with fetuin-A levels showing a strong correlation with insulin resistance [10]. Future clinical research should validate RT-specific protocols for DKD management.

3.2.3. Diabetic Peripheral Neuropathy (DPN)

Diabetic peripheral neuropathy (DPN) affects 6–34% of all patients with diabetes. DPN-induced pain significantly reduces quality of life, with >60% of patients reporting limitations in daily activities due to neuropathic symptoms [11]. Exercise interventions, including resistance training, may improve vascular health in DPN, as evidenced by 28.7% higher endothelium-dependent vasodilation ($p=0.002$) in exercised diabetic patients versus controls [11]. Enhanced microvascular perfusion potentially mitigates neuropathy progression by increasing nutrient delivery to nerves. Crucially, structured combined exercise (resistance+aerobic) programs improve sensory nerve function, demonstrated by: a 9.3% increase in sural sensory nerve conduction velocity (45.2±3.1 m/s to 48.1±2.8 m/s, $p<0.001$) and 30.1% reduction in pain severity (VAS: 7.3±1.2 to 5.1±0.9; $p=0.003$) [11]. Physical activity also reduces macrovascular complications, with active DPN patients showing 11.3% greater 6-minute walk distance ($p=0.01$) and 19.2% faster Timed-Up-and-Go test performance ($p=0.004$) [11]. While direct RCT evidence on resistance training alone remains limited, supervised programs demonstrate potential for glycemic control and symptom alleviation. Further trials are needed to isolate RT-specific effects.

3.3. Special populations

RT effectively improves both muscle strength and metabolic control in elderly T2D patients, demonstrating a clear strength-metabolism coupling. Meta-analysis of RCTs shows that structured RT prominently reduces HbA1c by 0.50% and simultaneously increases muscular strength by 38% [12]. This improvement occurs primarily through enhanced insulin sensitivity rather than increased lean body mass (LBM), which remained unchanged ($P = 0.50$). High-intensity RT (70-90% 1-RM) shows the strongest trend for optimizing both outcomes, likely due to improved GLUT4, insulin signaling pathways, and reduced intramyocellular lipids [13].

This coupling is particularly relevant in elderly T2D patients with sarcopenia. Meta-analysis specific to secondary sarcopenia (including T2D cohorts) confirms RT significantly improves handgrip strength and skeletal muscle mass index [12]. Subgroup analysis reveals RT's effect on grip strength is especially significant in T2D patients (SMD = 0.59, 95% CI: 0.26–0.93, $P < 0.01$),

DOI: 10.54254/2753-8818/2025.AU25518

reinforcing the link between muscle strength gains and metabolic health in this vulnerable population [12]. The mechanisms involve RT counteracting diabetes-induced muscle atrophy and insulin resistance, thereby improving glucose disposal capacity.

4. Conclusion

RT emerges as a potent, evidence-based non-pharmacological strategy for managing T2D and its complications. RT exerts its benefits through multifaceted biological mechanisms, including upregulation of skeletal muscle GLUT4 expression via AMPK/HDAC5-MEF2 and Akt/AS160 pathways, and enhancement of protein anabolism through mTORC1 signaling activation, significantly improving insulin sensitivity and glucose disposal. Clinically, structured RT consistently reduces HbA1c, attenuates postprandial glucose fluctuations via improved insulin signaling and reduced intramyocellular lipids, and mitigates diabetic complications. Firstly, improves plantar pressure distribution, endothelial function, and neuropathy risk in the diabetic foot. Secondly, reduces renal inflammation and oxidative stress in preclinical models of diabetic kidney disease. Thirdly, for peripheral neuropathy, enhancing nerve conduction velocity and reducing pain in combined training regimens. Critically, RT demonstrates robust efficacy in elderly T2D patients with sarcopenia, where it concurrently improves muscle strength and glycemic control, highlighting a unique "strength-metabolism coupling" effect. This synergy is further validated in secondary sarcopenia, where RT significantly increases handgrip strength and skeletal muscle mass index. To maximize clinical translation, future efforts should prioritize the following aspects. First, personalized RT prescriptions. Tailoring intensity (≥75% 1-RM), modality (elastic bands, machines), and timing (postprandial) to individual comorbidities and capabilities. Second, integration with multidisciplinary care. Combining RT with aerobic exercise, nutritional strategies (e.g., leucine supplementation), and pharmacotherapy for synergistic effects. Last, standardization of protocols. Establishing evidence-based guidelines for RT dosing, safety monitoring, and complication-specific adaptations. In conclusion, RT is a cornerstone intervention for T2D management, addressing core pathophysiological defects while preventing debilitating complications. Its scalability, cost-effectiveness, and dual metabolic-muscular benefits position it as an indispensable component of comprehensive diabetes care.

References

[1] American Diabetes Association. (2023). Standards of Care in Diabetes—2023. Diabetes Care, 46(Suppl 1), S1–S291.

[2] Wan, Y., & Su, Z. (2024). The Impact of Resistance Exercise Training on Glycemic Control Among Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Biological research for nursing, 26(4), 597–623.

[3] Egan, B., Carson, B. P., Garcia-Roves, P. M., Chibalin, A. V., Sarsfield, F. M., Barron, N., McCaffrey, N., Moyna, N. M., Zierath, J. R., & O'Gorman, D. J. (2010). Exercise intensity-dependent regulation of peroxisome proliferator-activated receptor coactivator-1 mRNA abundance is associated with differential activation of upstream signalling kinases in human skeletal muscle. The Journal of physiology, 588(Pt 10), 1779–1790.

[4] Holten, M. K., Zacho, M., Gaster, M., Juel, C., Wojtaszewski, J. F., & Dela, F. (2004). Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes, 53(2), 294–305.

[5] Al-Mhanna, S. B., Batrakoulis, A., Wan Ghazali, W. S., Mohamed, M., Aldayel, A., Alhussain, M. H., Afolabi, H. A., Wada, Y., Gülü, M., Elkholi, S., Abubakar, B. D., & Rojas-Valverde, D. (2024). Effects of combined aerobic and resistance training on glycemic control, blood pressure, inflammation, cardiorespiratory fitness and quality of life in patients with type 2 diabetes and overweight/obesity: a systematic review and meta-analysis. PeerJ, 12, e17525.

DOI: 10.54254/2753-8818/2025.AU25518

[6] Liu, Y., Ye, W., Chen, Q., Zhang, Y., Kuo, C. H., & Korivi, M. (2019). Resistance Exercise Intensity is Correlated with Attenuation of HbA1c and Insulin in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. International journal of environmental research and public health, 16(1), 140.

[7] Dempsey, P. C. et al. (2016). Benefits for type 2 diabetes of interrupting prolonged sitting with brief bouts of light walking or simple resistance activities. Diabetes Care, 39(6), 964–972.

[8] Armstrong, D. G., Tan, T. W., Boulton, A. J. M., & Bus, S. A. (2023). Diabetic Foot Ulcers: A Review. JAMA, 330(1), 62–75.

[9] Aagaard, T. V., Moeini, S., Skou, S. T., Madsen, U. R., & Brorson, S. (2022). Benefits and Harms of Exercise Therapy for Patients With Diabetic Foot Ulcers: A Systematic Review. The international journal of lower extremity wounds, 21(3), 219–233.

[10] Saberi, S., Askaripour, M., Khaksari, M., Amin Rajizadeh, M., Abbas Bejeshk, M., Akhbari, M., Jafari, E., & Khoramipour, K. (2024). Exercise training improves diabetic renal injury by reducing fetuin-A, oxidative stress and inflammation in type 2 diabetic rats. Heliyon, 10(6), e27749.

[11] Seyedizadeh, S. H., Cheragh-Birjandi, S., & Hamedi Nia, M. R. (2020). The Effects of Combined Exercise Training (Resistance-Aerobic) on Serum Kinesin and Physical Function in Type 2 Diabetes Patients with Diabetic Peripheral Neuropathy (Randomized Controlled Trials). Journal of diabetes research, 2020, 6978128.

[12] Shabkhiz, F., Khalafi, M., Rosenkranz, S., Karimi, P., & Moghadami, K. (2021). Resistance training attenuates circulating FGF-21 and myostatin and improves insulin resistance in elderly men with and without type 2 diabetes mellitus: A randomised controlled clinical trial. European journal of sport science, 21(4), 636–645.

[13] Lee, J., Kim, D., & Kim, C. (2017). Resistance Training for Glycemic Control, Muscular Strength, and Lean Body Mass in Old Type 2 Diabetic Patients: A Meta-Analysis. Diabetes therapy: research, treatment and education of diabetes and related disorders, 8(3), 459–473.