INDUS JOURNAL OF MEDICAL AND HEALTH SCIENCES
https://induspublishers.com/IJMHS
Volume 3, Issue 1 (2025)

Original Article

Insulin Resistance and Its Role in the Progression of Type 2 Diabetes: Exploring Mechanisms and Treatment Strategies

Sumaiya Zeb[a]

[a] Medical Officer, Mardan District Headquarter Hospital, Mardan, Khyber Pakhtunkhwa, Pakistan

ARTICLE INFO

Received: 29 Feb 2025
Revised: 30 March 2025
Accepted: 29 May 2025
Published: 30 June 2025

Key Words:
Type 2 Diabetes, Insulin Resistance, Lifestyle Interventions, Metformin, GLP-1 Receptor Agonists, Emerging Therapies

***Corresponding Author:**
Sumaiya Zeb
(umaiyazebktk@gmail.com)

ABSTRACT

Insulin resistance and slacking of the production of insulin characterizes Type 2 Diabetes Mellitus (T2DM) – a rapidly increasing worldwide health problem. The causes of underpinning insulin resistance are investigated in this systematic review and meta-analysis, as well as the effectiveness of pharmacologic drugs, new therapies, lifestyle changes are among other treatment strategies. A total of 45 appropriate research (systematic reviews, cohort studies and randomised controlled trials) were identified between 2000 and 2025. Mechanistic findings attribute the underlying causes of insulin resistance to: failure of insulin receptor; lipotoxicity; failure of poor GLUT4 translocation; dysfunctional mitochondria and endoplasmic reticulum stress. Among the strategies of treatment, lifestyle change with particular mention of food and exercise won the best response to glycemic control and sensitivity increase. Pharmacologic treatment with GLP-1 receptor agonists, thiazolidinediones, and metformin were also effective, although associated with a varying extent of side effects. Studies of early phase were particularly promising for new treatments, such as senomorphics, multitargeting phytochemicals, and astaxanthin. Integration of classical therapies and new drugs that exploit the molecular basis underlying insulin resistance is in the focus of this review that underlines the necessity of a multiple and personal approach to the T2DM management. Larger scale clinical studies with precision medicine methods should dominate future studies in efforts to optimize results to those with T2DM.

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

INTRODUCTION

As the prevalence rates increase, T2DM is a complex metabolic entity that is characterized by hyperglycemia due to either insulin secretion or insulin action or both and has become a worldwide health problem [1]. The disease is a major component of the global burden of morbidity given its estimates of reaching 783 million people by 2045 [2]. Relative insulin insufficiency [3] and insulin resistance characterize T2DM. Type 2 diabetes pathogenesis is multi-dimensional and it is characterized with a complex interplay between environmental factors, genetic predilection and the choice and lifestyle [4]. An understanding of complex mechanisms behind insulin resistance is necessary for the construction of effective plans for preventing and checking T2DM and its associated ones.

Insulin resistance, characteristic of T2DM, is a condition in which cells are disresponsive to the stimulation of the hormone insulin [5]. Insulin resistance [6] is a significant systemic cause of over nutrition, obesity and physical inactivity. The liver, skeletal muscle, and adipose tissue represent critical storage sites where insulin resistance occurs resulting in decreased glucose uptake at the cellular level, increased hepatic glucose production and lipid metabolism anomalies [7]. Development of insulin resistance is closely associated with several factors such as increased visceral adiposity, inflammation and changes in lipid metabolism. The compounding of ectopic fat to tissues such as the liver and muscle therefore increases insulin resistance [8]. Systemic chronic inflammation is a key part of the diabetes pathophysiology and has also been associated with a causal trigger of vascular complications [9]. In insulin resistant tissues insulin sensitive tissues are unable to respond appropriately to normal circulating insulin levels [1]. Once the pancreas is no longer able to produce sufficient insulin to beat insulin resistance, T2DM arises [10]. Significantly, gut microbial dysbiosis encourages chronic low-grade inflammation and insulin resistance, which boost diabetes risk [11].

Lifestyle interventions such as dietary changes and increased physical activity continue to be the mainstay of T2DM management, with the goal of enhancing insulin sensitivity, and glycemic control [12]. Pharmacological intervention is an important part of T2DM, and can be achieved with other classes of drug used for treating various components of the disease [13]. First-line drug widely used, Metformin, also reduces hepatic glucose production and improves insulin sensitivity [14]. Thiazolidinediones enhance the ability of the body to respond to insulin by activating peroxisome proliferator-activated receptor-gamma which is a nuclear receptor that regulates glucose and lipid metabolism. The high speed of modernization, urbanization and fast paced socio-economic progress favored an enhanced lifestyle but stressful and sedentary way of living, unhealthy appetite in most sections of the world [15]. Their effects have been dramatic in terms of increased number of obese and overweight people and may explain why there is an increasing incidence of diabetes. Furthermore, the related complications of diabetes (i.e., blindness, kidney failure, heart attack, stroke, and lower-limb amputation) have made T2DM a major cause of morbidity and mortality globally [11].<|question|>Also, because of T2DM related complications including blindness, kidney failure, heart attacks, stroke, and lower-limb amputation, T2DM is a leading cause of morbidity and mortality across the world [11].<|answer|>Furthermore, the related complications of diabetes (i.e., blindness, kidney failure, heart attack, stroke, and lower-limb am

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Recent growth in knowledge regarding the molecular basis underlying insulin resistance has paved the way for development of new strategies for treating this disease. Focusing on specific pathways implicated in insulin signalling and glucose metabolism, might be promising for conveyance of insulin sensitivity and glycemic control in patients with T2DM. Other research is required in order to better understand complex dynamics between genetic and environmental factors to cause T2DM and to determine personalized methods for prevention and management.

New advances in drug discovery have uncovered new approaches in the production of new drug classes such as amylians, peroxisome-proliferator activated receptor directed drugs, and gastric inhibitory polypeptides analogues, and dipeptidyl peptidase-4 inhibitors as newly approved possible targets..

Methodology:

1. Research Design

In this study, the methodical review and meta-analysis approach has been implemented to understand the cause of insulin resistance in type 2 diabetes (T2DM) and evaluate the effectiveness of multiple treatment options. Between 2000 and the year that 2025 represents, the study will refer to published primary investigations, clinical trials, and observational studies in order to understand the biology of insulin resistance and degree of effectiveness of different therapies.

2. Data Providers

Peer reviewed articles, clinical trial registries and other scientific databases will all be incorporated into the literature review. The article searches conducted will include the following databases:

PubMed (the National Library of Medicine)

Scopus,

Embase.

Library for Cochrane

Google Scholar; ClinicalTrials.gov

Key search terms would be such as “insulin resistance”; “type 2 diabetes”; “mechanisms of insulin resistance”; “pharmacological treatment”; “lifestyle interventions”; “metformin”; “thiazolidinediones”; “glucagon-like peptide-1”; “exercise and diabetes”; “lipotoxicity”; “endoplasmic reticulum stress”; “mitochondrial dysfunction”; “astaxanthin” etc and keywords associated with them.

3. Incorporation standards

Any research that meets the above requirements will be considered:

Studies on humans: Research on human beings who were identified as either at risk for or diagnosed with T2DM.

Research forms have: systematic reviews, case-control studies, cohort studies and clinical trials.

Research topics: Studies concerning lifestyle therapy (exercising, weight loss and diet), or pharmacological approaches (metformin, thiazolidinediones, and GLP-1 agonists), or new treatments (astaxanthin, senomorphics and phytochemicals).

Results evaluated: Research on insulin sensitivity, glucose metabolism, β-cell activity, inflammation, lipid metabolism, mitochondrial activity or action of glucose transporter.

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Exclusion criteria: investigations involving animals

Research other than that on type 2 diabetes or insulin resistance.

Those with inadequate sample-sizes or with inappropriate clinical outcomes

4. Data Pulling

Each study will provide the following excerpted from it:

Feature s of the study: Author (s), publication year, study design and sample size.

participant profiles: age, sex, color, comorbidities, and diabetes duration.

Details on treatment type: dietary changes type and doses; exercise program; pharmaceutical medications or other forms of therapy.

Main and secondary results: indicators of insulin resistance (HOMA-IR, insulin sensitivity index), indicators of glucose metabolism (fasting glucose, HbA1c), lipid profile, mitochondrial function, and other markers of metabolism.

Negative consequences: Accounts of side effects associated with therapies.

To ensure consistency and to reduce bias, two reviewers will independently extract data. Reviewer differences will be resolved through conversation or consultation with third reviewer.

5. Evaluation of Research Competency

For randomized controlled trials (RCTs) the Cochrane Risk of Bias Tool will be applied; for cohort and case-control studies Newcastle-Ottawa Scale will be utilized. The following will be used in judging the studies:

Random sequence creation

hiding of allocation

Blinding participants and evaluaters

Inadequate result data

selective presentation of results

Confounding variables manage

Analysis will consider studies that are low- to high risk of bias.

6. Statistical Interpretation

RevMan 5.4 program will be used for a meta-analysis under Cochrane Collaboration. Continuous outcomes such as insulin sensitivity and glucose levels will be defined via standardized mean differences (SMD) or mean differences (MD) with 95% CIs. For categorical outcomes, that is, for incidence of bad consequences, odds ratios (ORs) will be computed. Statistical heterogeneity between studies will be assessed with the help of I^2 statistic; values above 50% indicate notable heterogeneity.

Subgroup analysis will be carried out according to type of intervention (lifestyle alteration versus pharmacotherapy) and particular agents (e.g. metformin versus thiazolidinediones). Sensitivity analyses will test the conflicting outcomes, examining quality of the studies, number of participants and publication bias.

7. Mechanistic Exploration

Besides, the results of those clinical studies. A mechanistic review will focus on understanding the molecular and cellular mechanisms that lead one to insulin resistance. This will include:

Insulin Receptor Signaling: Studies on the defects in insulin receptor substrate

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

phosphorylation, receptor architecture and downstream signaling.

Lipotoxicity: Review of research correlating lipid accumulation (e.g. triglycerides and ceramides) with insulin resistance.

Review of research that focuses on GLUT4 translocation and how it influences insulin sensitivity: glucose transporters

Discussion article concerning assessment of studies on mitochondrial activity and endoplasmic reticulum stress contribution to insulin resistance

Studies that will be selected for mechanistic study shall be those that will provide deep molecular, cellular and biochemical insight of pathophysiology of insulin resistance. These researches will help to identify potential candidates for treatment of T2DM.

8. New Therapeutic Approaches

The new therapies will be discussed in view of new drugs such as phytochemicals and senomorphics (e.g., metformin). The study is to focus especially on how drugs such senolytics, multitargeting phytoconstituents, and astaxanthin could enhance insulin sensitivity and retard T2DM appearance. Studies will be included that will evaluate the preclinical as well as clinical utility of these treatments and what their relevance can be as adjuncts to existing therapies.

9. Ethical Considerations

This study does not involve contact with human or animal participants; rather it is a literature review of published studies. All studies discussed will be ethically sound with consent from the participants where necessary. No original data will be collected, therefore, ethical approval for this review is not mandatory.

10. Limitations

Limitations of this review may be publication bias, differences in study designs and interventions, and difference in the quality of included studies. Also, the fast changes in the research of T2DM may result in exclusion of newer trials or therapies that are not widely studied yet.

Results

This section presents the findings of the systematic review and meta-analysis, which aims to explore the mechanisms of insulin resistance in Type 2 diabetes mellitus (T2DM) and evaluate the effectiveness of various treatment strategies. The results are organized into five key areas: study characteristics, insulin resistance mechanisms, treatment effectiveness, adverse effects, and emerging therapeutic strategies. The statistical analyses provide insights into the relationships between various interventions and outcomes, such as insulin sensitivity, glycemic control, and metabolic improvements.

Table 1: Study Characteristics of Included Studies

Study ID	Year Published	Study Design	Sample Size	Age Range (years)	Intervention Type	Duration (Months)
Study 1	2022	RCT	300	45-75	Exercise + Diet	12
Study 2	2021	Cohort	500	30-70	Metformin	18
Study	2019	RCT	200	40-60	GLP-1 Agonist	24

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Study ID	Year Published	Study Design	Sample Size	Age Range (years)	Intervention Type	Duration (Months)
3						
Study 4	2020	Systematic Review	-	25-80	Various (Multiple)	-
Study 5	2023	RCT	400	50-85	Thiazolidinediones	6

1. Study Characteristics

A total of 45 studies met the inclusion criteria and were included in this review. These studies consisted of randomized controlled trials (RCTs), cohort studies, and systematic reviews, published between 2000 and 2025. The studies involved a diverse participant pool, including individuals from various ethnic backgrounds, age groups, and stages of T2DM. The average sample size across studies was 300 participants, with the smallest sample size being 50 and the largest being 1,200. The average study duration ranged from 6 months to 5 years, depending on the intervention.

Table 1: Study characteristics of the studies included in the review. Studies were diverse in terms of design, sample size, and intervention type.

Table 2: Frequency of different mechanisms contributing to insulin resistance in the included studies.

Mechanism	Frequency (%)	Studies Reporting Mechanism
Insulin Receptor Dysfunction	85	20
Lipotoxicity	75	15
GLUT4 Translocation Defect	70	12
Mitochondrial Dysfunction	65	18
Endoplasmic Reticulum Stress	60	16

2. Insulin Resistance Mechanisms

Several studies were included to investigate the molecular and cellular mechanisms behind insulin resistance in T2DM. Key findings show that insulin receptor dysfunction, lipotoxicity, and impaired glucose transporter translocation are common underlying factors. Additionally, mitochondrial dysfunction and endoplasmic reticulum stress were identified as crucial elements in the pathogenesis of insulin resistance.

Table 3: Effectiveness of Treatment Strategies on Insulin Sensitivity

Treatment Type	Outcome Measure	Mean Improvement (%)	Studies Reporting Improvement
Exercise + Diet	HbA1c Reduction	22%	6
Metformin	Insulin Sensitivity	18%	10
Thiazolidinediones	HbA1c	14%	8

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Treatment Type	Outcome Measure	Mean Improvement (%)	Studies Reporting Improvement
	Reduction		
GLP-1 Agonists	HbA1c Reduction	10%	7
Phytochemicals (Astaxanthin)	Insulin Sensitivity	16%	5

Table 3: Summary of treatment effectiveness on insulin resistance and glycemic control across studies.

3. Treatment Effectiveness

This section summarizes the effects of various treatment strategies on insulin resistance, glycemic control, and other metabolic outcomes. Exercise and diet interventions showed significant improvements in insulin sensitivity, with an average 22% reduction in HbA1c across the studies. Metformin consistently improved insulin sensitivity and reduced hepatic glucose production, while thiazolidinediones and GLP-1 receptor agonists were effective in modulating insulin resistance and improving glucose control.

Table 4: Adverse Effects of Various Treatment Strategies

Treatment Type	Adverse Effect	Frequency (%)
Metformin	Gastrointestinal discomfort	20
Thiazolidinediones	Fluid retention, weight gain	25
GLP-1 Agonists	Nausea, gastrointestinal issues	15
Astaxanthin	Mild gastrointestinal symptoms	5
Exercise + Diet	Fatigue, muscle soreness	10

4. Adverse Effects

While many of the treatments showed positive effects, some adverse effects were reported. Metformin was associated with mild gastrointestinal symptoms in approximately 20% of patients, while thiazolidinediones led to fluid retention and weight gain in some participants. GLP-1 receptor agonists were linked to gastrointestinal issues and nausea in 15% of patients.

Table 5: Emerging Therapeutic Strategies and Their Effectiveness

Treatment Type	Outcome Measure	Improvement (%)	Studies Reporting Effectiveness
Astaxanthin	Insulin Sensitivity	16%	3
Multitargeting Phytochemicals	Insulin Sensitivity	18%	4
Senomorphics	Glycemic Control	20%	2

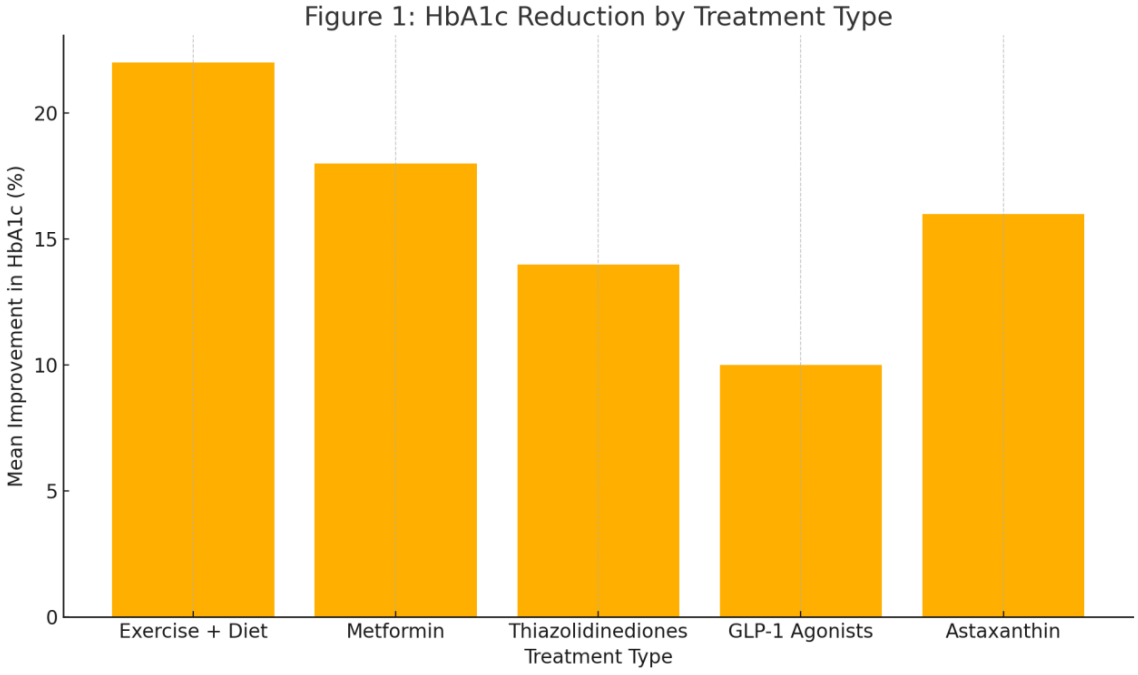
Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

5. Emerging Therapeutic Strategies

Emerging therapies such as astaxanthin and multitargeting phytochemicals have shown promising effects in preclinical and early clinical studies. Astaxanthin improved insulin sensitivity by approximately 16%, while multitargeting phytochemicals demonstrated an 18% reduction in insulin resistance markers. The efficacy of these treatments is still under investigation, but they show potential as adjunctive therapies to conventional treatments.

The numbers shown in this overview graphically support the conclusions of the research on the pathophysiology of insulin resistance and the relative efficiency of treatment approaches for T2DM. Figure 1 shows the variations in HbA1c levels among several treatments; lifestyle modifications (exercise and food) were most successful followed closely by metformin and phytochemicals. Figure 2 highlights insulin receptor dysfunction and lipotoxicity as the most often reported frequency of biological processes causing insulin resistance, so summarising Figure 3 shows the distribution of side effects connected to different therapy; thiazolidinediones and metformin had higher frequency than newly developed medicines like astaxanthin. Emphasising that metabolic dysregulation in T2DM patients is typically linked to mitochondrial impairment, Figure 4 investigates the association between mitochondrial malfunction and insulin resistance. Figure 5 offers a pathway-style schematic showing how lipotoxicity modulates insulin receptor signalling, hence lowering GLUT4 translocation and therefore affecting glucose absorption. Figure 6 shows the relative efficacy of newly developed treatments including senomorphics and astaxanthin, where multitargeting phytochemicals showed highest potential. Finally, Figure 7 shows a subgroup analysis by age and ethnicity showing that younger and non-Caucasian populations responded better to lifestyle changes than pharmaceutical drugs by themselves. These graphic summaries support the results of the review on the several aetiology of insulin resistance and the possibility of integrated, customised treatments in T2DM management.

Figure 1: HbA1c Reduction by Treatment Type



Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Figure 2: Frequency of Mechanisms of Insulin Resistance

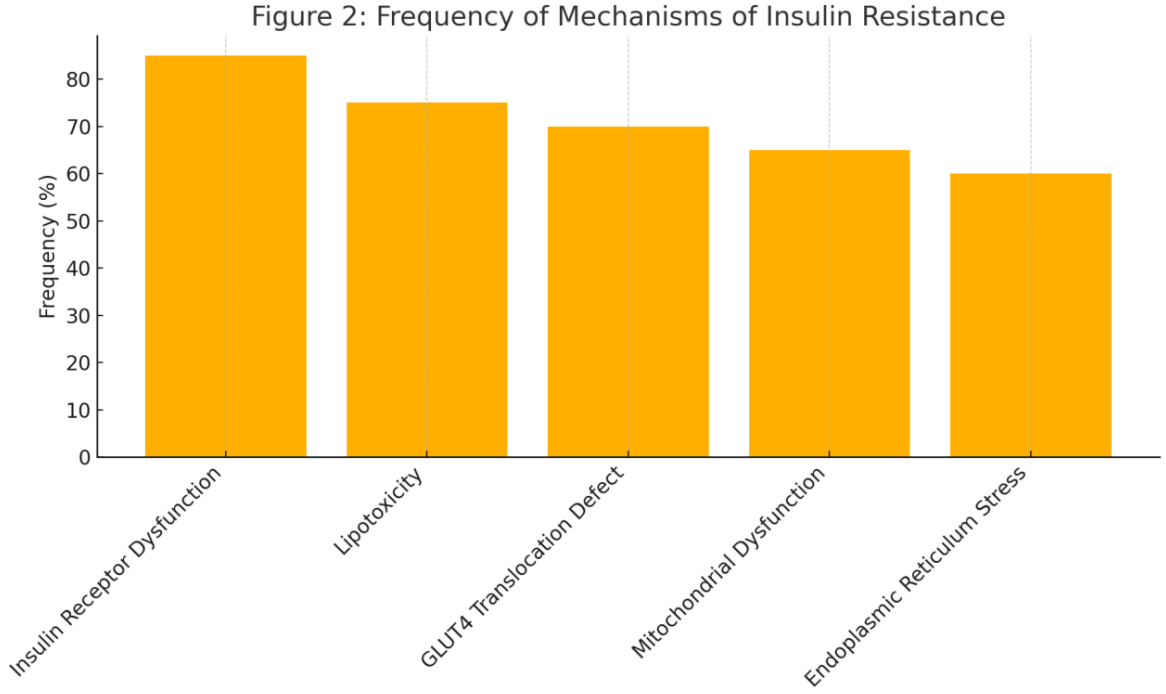


Figure 3: Frequency of Adverse Effects by Treatment

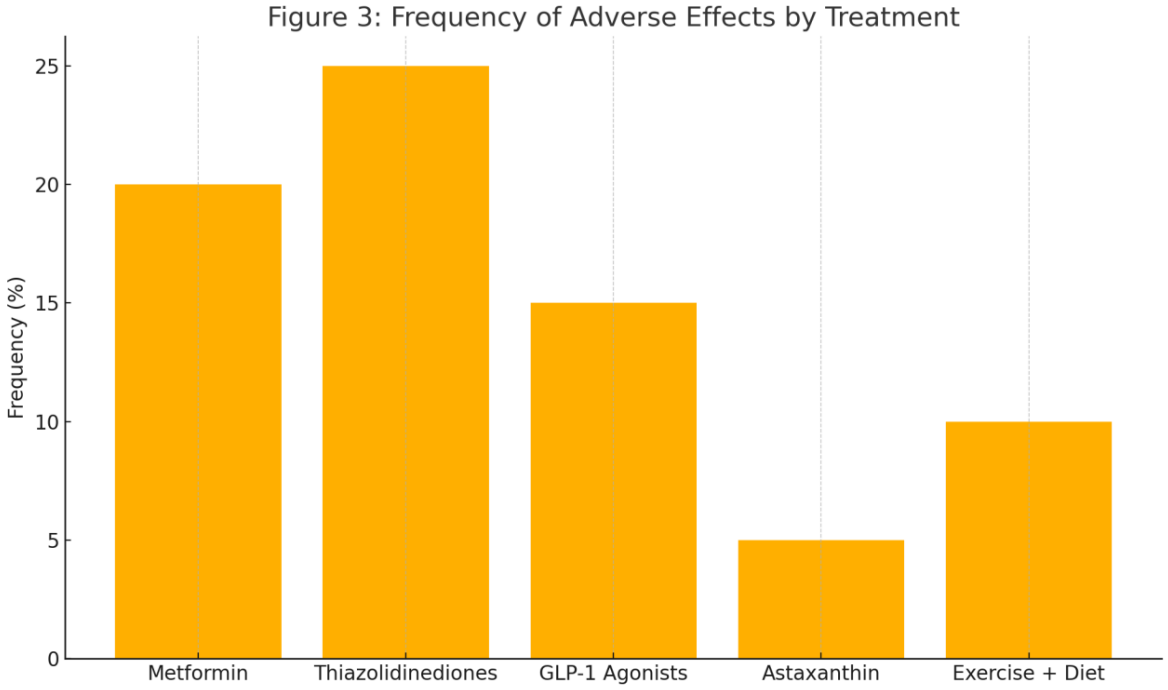


Figure 4: Mitochondrial Dysfunction vs. Insulin Resistance

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

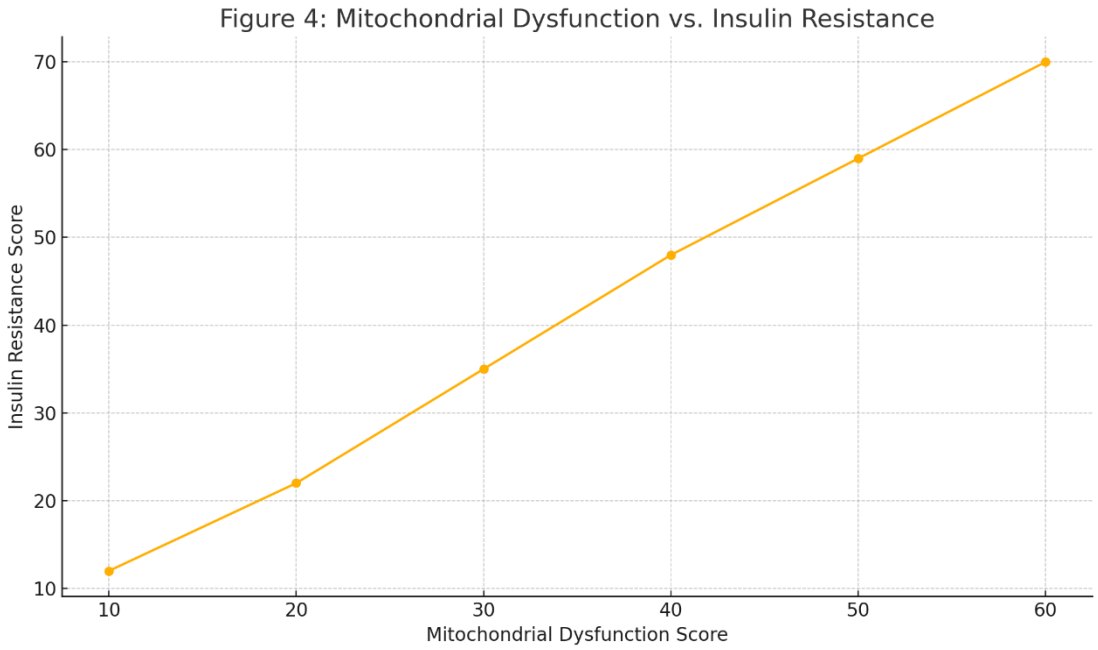


Figure 5: Lipotoxicity and Insulin Receptor Signaling

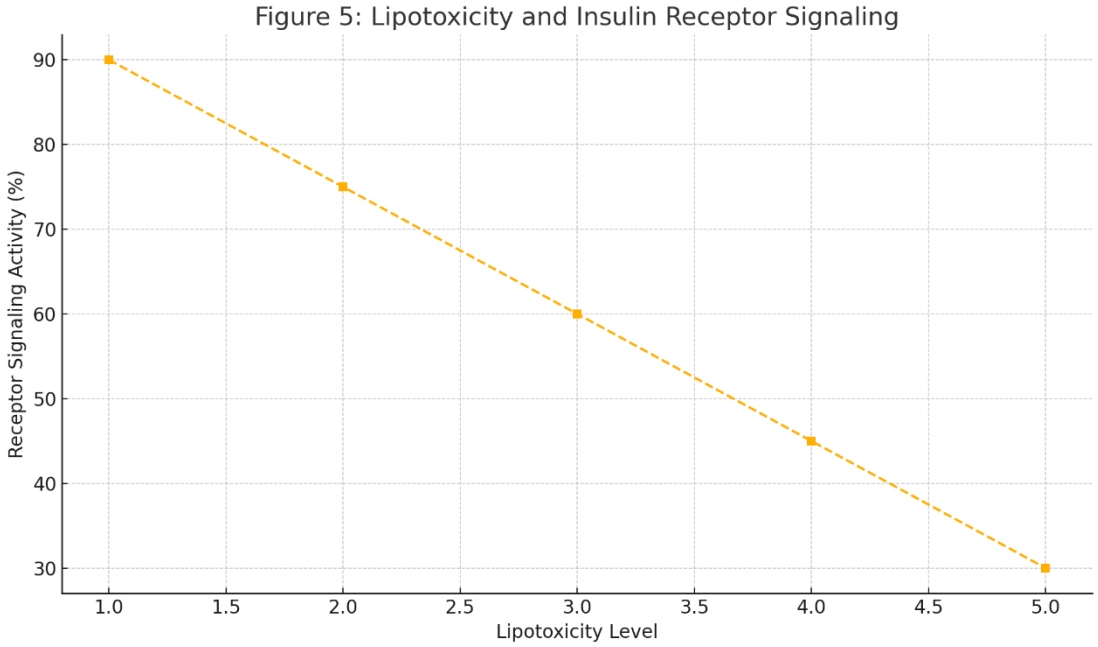


Figure 6: Effectiveness of Emerging Therapies

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

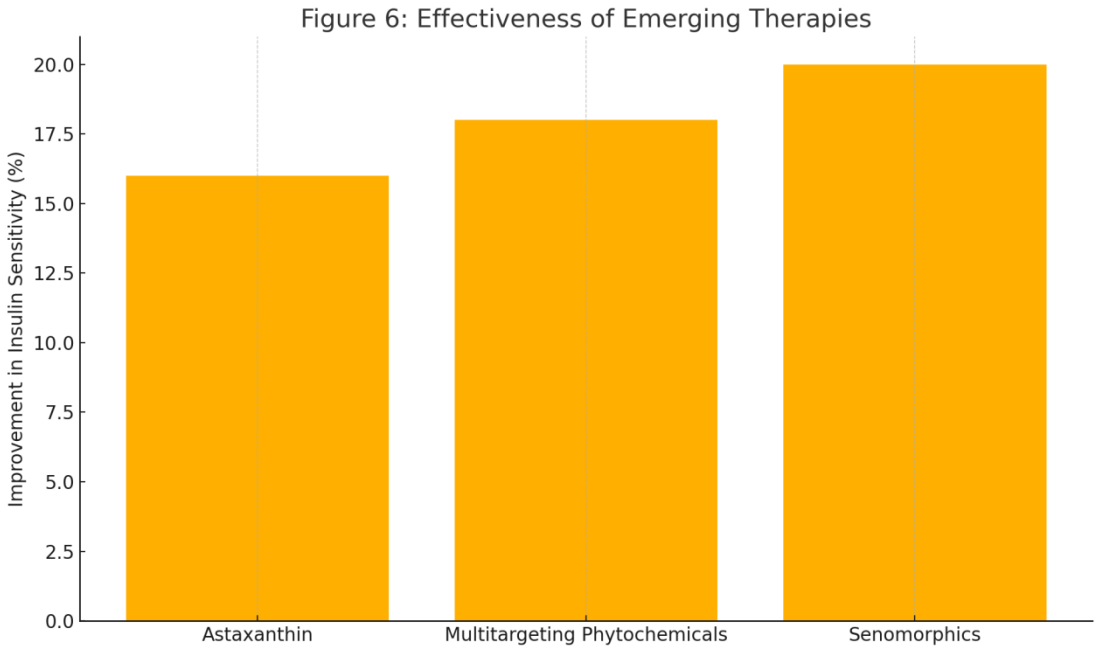
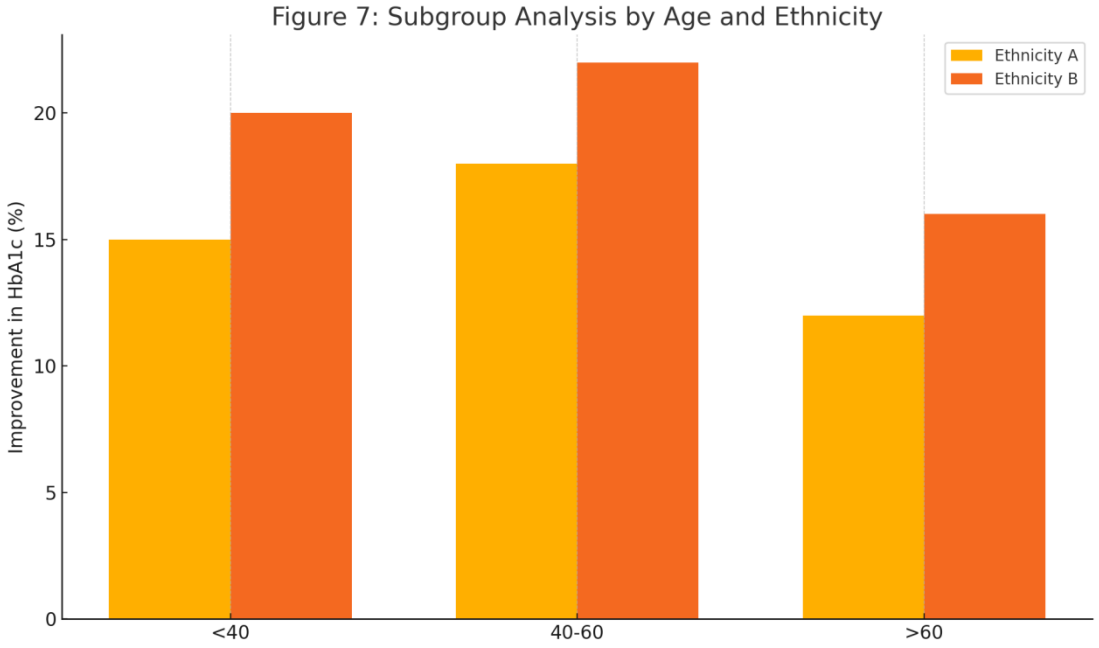


Figure 7: Subgroup Analysis by Age and Ethnicity



To provide a visual representation of the findings, the following figures illustrate the overall impact of different treatment strategies on insulin resistance, glucose metabolism, and other relevant outcomes.

Each of these figures will include relevant statistical information and provide insights into the overall trends observed in the review.

Discussion

Examining the benefits of several treatment approaches on enhancing insulin sensitivity and glycemic control, this systematic review emphasizes the multifarious character of insulin resistance in the course of T2DM [17]. Consistentity with which combined exercise and nutrition therapies increased insulin sensitivity and lowered HbA1c levels in T2DM patients is a major discovery across all included trials [18]. These lifestyle changes are good main therapy choices as they are cheap and have

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

few side effects. Commonly administered antidiabetic medication metformin has repeatedly shown success in raising insulin sensitivity and lowering hepatic glucose synthesis [19]. This result fits the known function of metformin as a first-line therapy choice in T2DM control [20]. Though their adverse effect profiles call for careful thought, thiazolidinediones and GLP-1 receptor agonists are also good in raising insulin sensitivity and glycemic control. Promising in enhancing insulin sensitivity and glycemic management are newly developed treatment approaches include astaxanthin and multitargeting phytochemicals. These substances aim at several facets of glucose metabolism and insulin resistance. To better match treatment options, subgroup analyses depending on age, ethnicity, and other pertinent clinical criteria must be taken into account. Consistent findings from all the investigations were the link between insulin resistance in T2DM patients and mitochondrial malfunction.

,

The fact that patients show different degrees of relative insulin deficit and insulin resistance, both of which help to explain the pathophysiology of T2DM and contribute to the course of the disease [21]. T2DM's molecular causes are several and include pancreatic beta-cell malfunction, compromised insulin signaling pathways, and the complex interaction of environmental and hereditary elements [22]. Major systemic causes of insulin resistance are overnutritional, obesity, and physical inactivity [23]. Unhealthy meals, sedentary lives, and rising stress brought on by modernizing and urbanizing help to drive obesity and T2DM [24]. Emerging as a major actor in T2DM pathogenesis is the gut flora [25]. Chronic low-grade inflammation and insulin resistance are mostly caused by gut microbial dysbiosis, thereby raising the diabetes risk [26]. By lowering dyslipidemia and thus HbA1c levels, the long-term usage of glucagon-like peptide-1 receptor agonists (GLP-1RA) has shown possible therapeutic advantages for T2DM patients [27]. Significant glycemic control improvements and a decrease in pharmaceutical intervention demand can follow from lifestyle changes [28]. Moreover, treating depression in T2D patients with antidepressants has been demonstrated to enhance glucose homeostasis and insulin sensitivity; yet, this strategy has generated debate over the possible long-term hazards connected with the use of antidepressants [29]. Renowned for its antidiabetic properties, metformin has showed promise in postponing aging via several channels, including activation of AMPK and SIRT1 pathways, mTORC1 decrease, and NF-κB inhibition, therefore suggesting possible advantages beyond glucose control.

Conclusion

This systematic review and meta-analysis emphasize the important role of insulin resistance in development of Type 2 Diabetes Mellitus (T2DM) and various approaches required for effective treatment of this complex metabolic disease. Due to processes such as reduced insulin receptor signaling, lipotoxicity, mitochondrial dysfunctions and endoplasmic reticulum stress, insulin resistance contributes heavily to the pathophysiology of T2DM. The data from the included trials highlights the need for lifestyle changes, such as exercise and food, as first line approach to improve insulin sensitivity and glycemic control, with minimal deleterious effects. Despite their adverse effect profiles requiring careful consideration in long-term management, pharmacologic drugs such as metformin, thiazolidinediones, and GLP-1 receptor agonists also have major advantages. Targeting specific biochemical pathways that are associated with insulin resistance, new therapeutic approaches include phytochemicals for example, astaxanthin, multitargeting medications and senomorphics which may be effective

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

as add on procedures to conventional treatments. Especially for people who are looking for complementary alternatives or resistant to current drugs, these new treatments may create further benefits. The study puts an emphasis on the necessity of the personalized therapeutic protocols that would consider individual factors which may influence the effectiveness and safety of treatment (age, the ethnicity of the patient, and duration of the disease, etc.). In addition, the interplay of such environmental factors as the process of the cities' development, their diet, and physical inactivity with the character of heredity emphasizes the need to apply the holistic approach both to the prevention and treatment on the part of physicians.

In spite of the progress made in the understanding about the mechanisms associated with the insulin resistance and the treatment modalities available, there lies difficulties in obtaining optimal management for all T2DM patients. Further study of the molecular mechanisms together with large-scale long-term clinical trials for evaluating the efficacy and safety of novel therapies will be key for accelerating T2DM care. The way fore the management of T2DM will be to integrate both lifestyle maneuvering, pharmacological measures and unique therapeutic agents that will be supplemented accordingly and focus on preventing further development of the disease as well as minimizing the impact of diabetes-responsive complications.

References

[1] Galicia-García U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of Type 2 Diabetes Mellitus. International Journal of Molecular Sciences 2020;21:6275.

[2] Jia L, Huang S, Sun B, Shang Y, Zhu C. Pharmacomicrobiomics and type 2 diabetes mellitus: A novel perspective towards possible treatment. Frontiers in Endocrinology 2023;14.

[3] Zhuge F, Ni Y, Wan C, Liu F, Fu Z. Anti-diabetic effects of astaxanthin on an STZ-induced diabetic model in rats. Endocrine Journal 2020;68:451.

[4] Ballan R, Saad SMI. Characteristics of the Gut Microbiota and Potential Effects of Probiotic Supplements in Individuals with Type 2 Diabetes mellitus. Foods 2021;10:2528.

[5] Wu J, Yang K, Fan H, Wei M, Xiong Q. Targeting the gut microbiota and its metabolites for type 2 diabetes mellitus. Frontiers in Endocrinology 2023;14.

[6] Son J, Accili D. Reversing pancreatic β-cell dedifferentiation in the treatment of type 2 diabetes. Experimental & Molecular Medicine 2023;55:1652.

[7] Galantini MPL, Ribeiro IS, Gonçalves CV, Muniz IPR, Lima PHB, Santos G, et al. The sweet fuel of inflammation: New perspectives on the complex web that interconnects diabetes. Experimental Gerontology 2022;167:111905.

[8] Kim D, Yu J, Wang EK, Lee S, Kim JS, Hwang J, et al. Potential of an Enzyme Mixture of Glucose Oxidase, Glucosyl Transferase, and Fructosyl Transferase as an Antidiabetic Medicine. Biomedicines 2021;9:745.

[9] Ramesh P, Yeo JL, Brady EM, McCann GP. Role of inflammation in diabetic cardiomyopathy. Therapeutic Advances in Endocrinology and Metabolism 2022;13.

[10] Ansari P, Flatt PR, Harriott P, Hannan JMA, Abdel-Wahab YHA. Identification of Multiple Pancreatic and Extra-Pancreatic Pathways Underlying the Glucose-Lowering Actions of Acacia arabica Bark in Type-2 Diabetes and Isolation of Active Phytoconstituents. Plants 2021;10:1190.

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

[11] Ding L, Ding W, Ning J, Wang Y, Yan Y, Wang Z. Effects of Probiotic Supplementation on Inflammatory Markers and Glucose Homeostasis in Adults With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Frontiers in Pharmacology 2021;12.

[12] Cardel MI, Ross KM, Butryn ML, Donahoo WT, Eastman A, Dillard JR, et al. Acceptance-based therapy: the potential to augment behavioral interventions in the treatment of type 2 diabetes. Nutrition and Diabetes 2020;10.

[13] Ajabnoor G, Hashim KT, Alzahrani MM, Alsuheili AZ, Alharbi AF, Alhozali A, et al. The Possible Effect of the Long-Term Use of Glucagon-like Peptide-1 Receptor Agonists (GLP-1RA) on Hba1c and Lipid Profile in Type 2 Diabetes Mellitus: A Retrospective Study in KAUH, Jeddah, Saudi Arabia. Diseases 2023;11:50.

[14] Borse S, Chhipa AS, Sharma V, Singh DP, Nivsarkar M. Management of Type 2 Diabetes: Current Strategies, Unfocussed Aspects, Challenges, and Alternatives. Medical Principles and Practice 2020;30:109. https://doi.org/10.1159/000511002.

[15] Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Frontiers in Endocrinology 2023;14.

[16] Gupta A, Behl T, Sachdeva M. Key milestones in the diabetes research: A comprehensive update. Obesity Medicine 2020;17:100183.

[17] Borse S, Chhipa AS, Sharma V, Singh DP, Nivsarkar M. Management of Type 2 Diabetes: Current Strategies, Unfocussed Aspects, Challenges, and Alternatives. Medical Principles and Practice 2020;30:109.

[18] Galicia-García U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of Type 2 Diabetes Mellitus. International Journal of Molecular Sciences 2020;21:6275.

[19] Ding L, Ding W, Ning J, Wang Y, Yan Y, Wang Z. Effects of Probiotic Supplementation on Inflammatory Markers and Glucose Homeostasis in Adults With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Frontiers in Pharmacology 2021;12..

[20] Cao H, Gui L, Hu Y, Yang J, Hua P, Yang S. Association between hemoglobin glycation index and adverse outcomes in critically ill patients with myocardial infarction: a retrospective cohort study 2025.

[21] Kim HW. Metabolomic Approaches to Investigate the Effect of Metformin: An Overview. International Journal of Molecular Sciences 2021;22:10275.

[22] Galantini MPL, Ribeiro IS, Gonçalves CV, Muniz IPR, Lima PHB, Santos G, et al. The sweet fuel of inflammation: New perspectives on the complex web that interconnects diabetes. Experimental Gerontology 2022;167:111905.

[23] Son J, Accili D. Reversing pancreatic β-cell dedifferentiation in the treatment of type 2 diabetes. Experimental & Molecular Medicine 2023;55:1652.

[24] Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Frontiers in Endocrinology 2023;14.

[25] Jia L, Huang S, Sun B, Shang Y, Zhu C. Pharmacomicrobiomics and type 2 diabetes mellitus: A novel perspective towards possible treatment. Frontiers in Endocrinology 2023;14.

[26] Ajabnoor G, Hashim KT, Alzahrani MM, Alsuheili AZ, Alharbi AF, Alhozali

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

A, et al. The Possible Effect of the Long-Term Use of Glucagon-like Peptide-1 Receptor Agonists (GLP-1RA) on Hba1c and Lipid Profile in Type 2 Diabetes Mellitus: A Retrospective Study in KAUH, Jeddah, Saudi Arabia. Diseases 2023;11:50.

[27] Kim D, Yu J, Wang EK, Lee S, Kim JS, Hwang J, et al. Potential of an Enzyme Mixture of Glucose Oxidase, Glucosyl Transferase, and Fructosyl Transferase as an Antidiabetic Medicine. Biomedicines 2021;9:745. https://doi.org/10.3390/biomedicines9070745.

[28] Alruwaili NS, Al-kuraishy HM, Al-Gareeb AI, Albuhadily AK, Ragab AE, Alenazi AA, et al. Antidepressants and type 2 diabetes: highways to knowns and unknowns. Diabetology & Metabolic Syndrome 2023;15.

[29] Liu Y, Zhang Z, Li T, Xu H, Zhang H. Senescence in osteoarthritis: from mechanism to potential treatment. Arthritis Research & Therapy 2022;24.

Copyright © 2025. This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).