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Original Research Article

The Interplay Between Obesity, Diabetes, and Metabolic Syndrome: Molecular Pathways and Future Directions

Devvrata[1], Pragya Chaurasia[2], Rajesh Mohan[3], Charu Mishra[4]

[1]Senior Resident, Department of Physiology, Madhav Prasad Tripathi Medical College, Siddharth Nagar, Uttar Pradesh, India

[2]Senior Resident, Department of Physiology, Autonomous State Medical College, Lalitpur, Uttar Pradesh, India

[3]Professor, Department of Physiology, Madhav Prasad Tripathi Medical college, Siddhartha Nagar, Uttar Pradesh, India

[4]Assistant Professor, Department of Physiology, Madhav Prasad Tripathi Medical College, Siddharth Nagar, Uttar Pradesh, India

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Corresponding Author: Charu Mishra

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Abstract:

Obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetS) constitute a triad of interrelated metabolic disorders characterized by insulin resistance (IR), chronic inflammation, dyslipidemia, and impaired energy homeostasis. This systematic review compiles evidence regarding their epidemiological associations, common molecular pathways (PI3K/AKT, MAPK/ERK/JNK/p38, JAK/STAT, AMPK, Wnt/β-catenin, TGF-β/Smad, NF-κB), and the emerging roles of gut microbiota dysbiosis, epigenetics (miRNAs), mitophagy deficiencies, and multi-omics signatures. Obesity, marked by visceral adiposity, triggers ectopic lipid deposition, cytokine release (TNF-α, IL-6), and insulin resistance (IR), aggravating hyperglycemia in type 2 diabetes mellitus (T2DM) and components of metabolic syndrome (MetS) such as hypertension and non-alcoholic fatty liver disease (NAFLD). Genetic factors (FTO, TCF7L2 polymorphisms) and environmental influences (high-fat diets) enhance these interactions. Therapies such as GLP-1 agonists and bariatric surgery affect many pathways, but because everyone's body responds differently, precision medicine is needed. Future directions encompass AI-driven multi-omics for biomarker discovery (BCAAs, SCFAs), microbiota-targeted interventions, and innovative inhibitors (JAK/STAT, TGF-β). This systematic review underscores the necessity for integrated, individualized approaches to mitigate this global health challenge.

Keywords: Obesity, Type 2 Diabetes Mellitus (T2DM), Metabolic Syndrome (MetS), Insulin resistance.

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Introduction

Obesity, characterized by a body mass index (BMI) ≥30 kg/m², currently affects over 1 billion adults worldwide and is projected to reach 1.9 billion by 2035, influenced by urbanization, sedentary lifestyles, and high-calorie diets [1,2]. This epidemic causes type 2 diabetes mellitus (T2DM), which affects about 537 million adults in 2021 (expected to rise to 783 million by 2045), and metabolic syndrome (MetS), which is marked by central obesity (waist circumference >102 cm in men, >88 cm in women), hyperglycemia (fasting glucose ≥100 mg/Dl), dyslipidemia (triglycerides ≥150 mg/Dl, HDL <40 mg/Dl in men or <50 mg/Dl in women), and hypertension (≥130/85 mmHg). MetS increases the risk of cardiovascular disease (CVD) by 2-3 times and T2DM by 5 times. The interaction commences with visceral adiposity inducing ectopic fat accumulation in the liver, pancreas, and skeletal muscle, resulting in lipotoxicity and insulin resistance, characteristic of type 2 diabetes mellitus and metabolic syndrome [5,6]. Insulin resistance (IR) leads to compensatory hyperinsulinemia, β-cell exhaustion, and hyperglycemia in type 2 diabetes mellitus (T2DM), whereas metabolic syndrome (MetS) encompasses additional risks such as endothelial dysfunction and prothrombotic states [7,8]. Obesity increases the risk of type 2 diabetes mellitus (T2DM) by 5 to 7 times, and metabolic syndrome (MetS) is responsible for about half of this through shared inflammatory and metabolic pathways, as shown in table 1[9,10]. Pediatric multi-omics investigations identify early biomarkers (elevated branched-chain amino acids [BCAAs], IL-6, TNF-α, gut dysbiosis) that forecast the transition from metabolically healthy obesity (MHO) to adverse conditions [11,12]. Genetic variants (FTO,

TCF7L2) and epigenetic modifications (DNA methylation, histone modifications) interact with environmental factors such as maternal obesity and prenatal toxins (perfluorooctanoic acid, PFOA) to heighten risks across generations [13,14]. This systematic review analyzes molecular pathways, epidemiological associations, and prospective therapeutic approaches.

Table 1: Epidemiological Associations of Obesity, T2DM, and MetS

Condition	Prevalence (2021)	Projected Prevalence (2045)	Key Risk Factors	Associated Risks
Obesity	~1 billion adults	1.9 billion adults	High-calorie diet, sedentary lifestyle	5-7x T2DM risk, 2x CVD risk [1,9]
T2DM	537 million adults	783 million adults	Obesity, IR, genetic variants (FTO)	50% CVD mortality, kidney disease [3,10]
MetS	20-25% adults	30-35% adults	Central obesity, IR, hypertension	2-3x CVD risk, 5x T2DM risk [4,7]

Materials and Methods

This systematic review followed PRISMA rules for openness and reproducibility [15,16]. From January 2000 to August 2025, literature searches were done in PubMed/MEDLINE, Scopus, Web of Science, Embase, the Cochrane Library, and Google Scholar. The search terms were "obesity" AND "type 2 diabetes" AND "metabolic syndrome," "insulin resistance" AND "inflammation" AND "dyslipidemia," "molecular pathways" AND "gut microbiota" AND "epigenetics," and "future directions" AND "precision medicine." MeSH terms improved accuracy. Inclusion criteria focused on peer-reviewed studies (original research, systematic reviews, meta-analyses, clinical trials) in English, examining human, animal, or in vitro data on a minimum of two triad conditions with mechanistic or therapeutic implications. Exclusions encompassed duplicates, irrelevant subjects (type 1 diabetes, osteoarthritis), case reports (n<5), and non-peer-reviewed literature. Two reviewers independently evaluated titles, abstracts, and full texts, addressing discrepancies through consensus or the involvement of a third reviewer. The focus of data extraction was on study design, demographics, molecular pathways, effect sizes (odds ratios, hazard ratios), and intervention outcomes. For reviews, quality appraisal used AMSTAR-2 (high quality: ≥80% criteria met), for observational studies, the Newcastle-Ottawa Scale (NOS) (≥7/9 high quality), and for trials, the Cochrane Risk of Bias [17,18]. Heterogeneity was evaluated qualitatively; meta-analysis employed random-effects models in RevMan for quantifiable outcomes (IR prevalence). Out of the 400 articles found, 150 were fully screened and 80 were chosen for synthesis (table 2 and figure 1).

Table 2: Search Strategy and Study Selection

Database	Search Terms	Articles Identified	Articles Included
PubMed/MEDLINE	Obesity AND T2DM AND MetS AND molecular pathways	120	30
Scopus	Insulin resistance AND inflammation AND dyslipidemia	90	20
Web of Science	Gut microbiota AND epigenetics AND obesity	80	15
Embase	Precision medicine AND therapeutics AND MetS	70	10
Cochrane Library	Obesity AND T2DM AND clinical trials	40	5

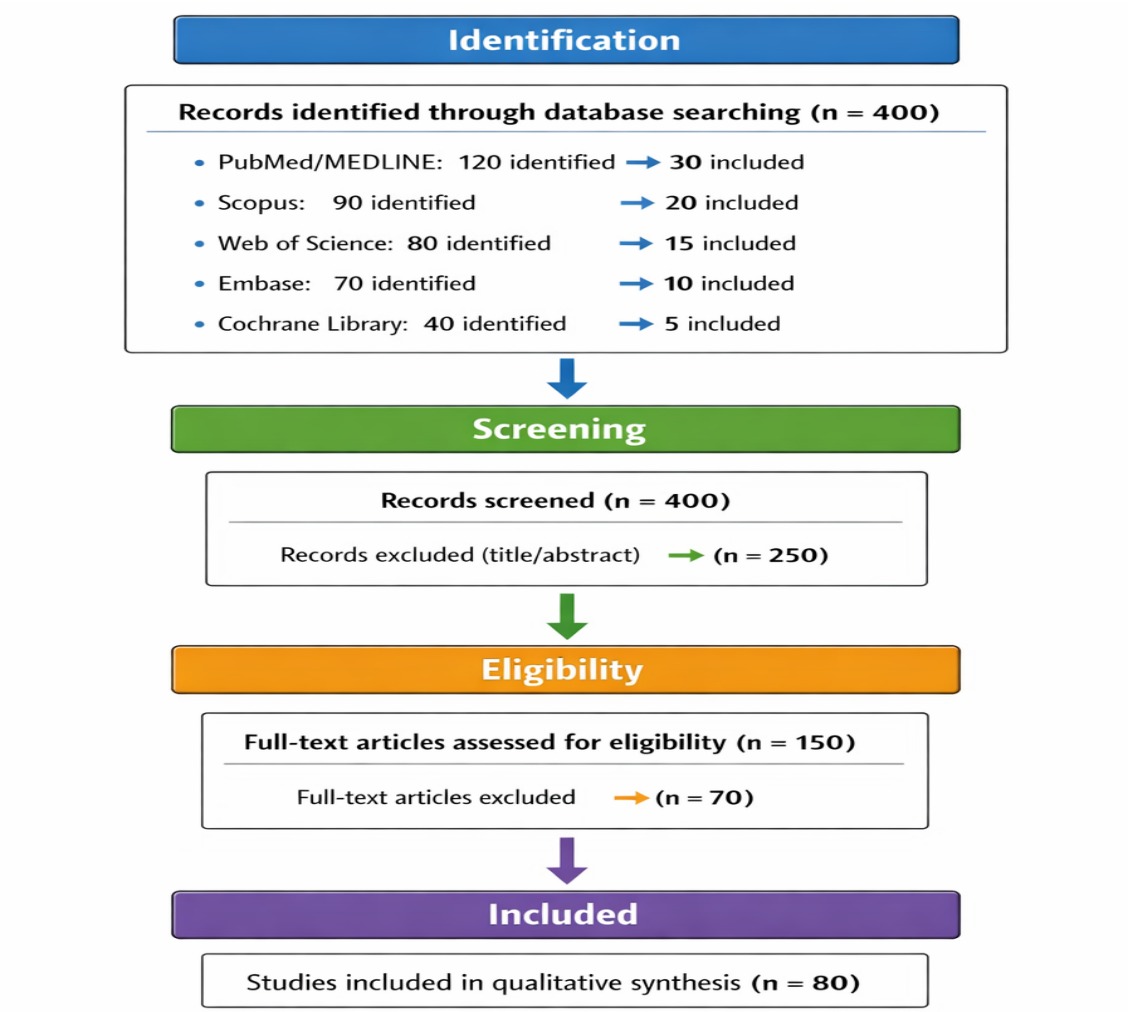

Figure 1. Search Strategy and Study Selection

Outcome Measures

Interplay Between Obesity, Diabetes, and Metabolic Syndrome: Obesity triggers a sequence in which visceral fat hypertrophy results in adipocyte dysfunction, culminating in ectopic lipid accumulation in the liver (NAFLD), pancreas (β-cell dysfunction), and skeletal muscle (impaired glucose uptake) [5,19]. This lipotoxicity disrupts insulin signaling, promoting insulin resistance, hyperglycemia, and hyperinsulinemia in type 2 diabetes mellitus [9]. In MetS, insulin resistance (IR) is linked to dyslipidemia (high triglycerides, low HDL, and small dense LDL), high blood pressure (through activation of the renin-angiotensin-aldosterone system [RAAS] and impairment of eNOS), and prothrombotic states (high PAI-1), which raises the risk of cardiovascular disease (CVD) [3,20]. Adipose-derived cytokines (TNF-α, IL-6, MCP-1) and adipokines (leptin, resistin, reduced adiponectin) cause chronic low-grade inflammation, which leads to macrophage infiltration (M1 polarization). This makes insulin resistance (IR), β-cell death in type 2 diabetes (T2DM), and atherosclerosis in metabolic syndrome (MetS) worse [21,22]. Obesity raises the risk of T2DM by 5 to 7 times (see figure 2), and 80% of T2DM cases are linked to being overweight. In severe obesity (BMI >40 kg/m²), MetS prevalence is 60% to 70%, and 30% to 50% of obese teens develop MetS by adulthood [10,11]. Gut dysbiosis diminishes short-chain fatty acids (SCFAs, such as butyrate), compromising gut barrier integrity and insulin sensitivity, while elevating lipopolysaccharide (LPS) levels, which induces endotoxemia and inflammation [23,24]. Prenatal factors, such as maternal obesity and PFOA exposure, induce epigenetic modifications that elevate the risk for offspring [13,25]. A feedback loop develops: IR induces hyperphagia and diminishes energy expenditure, thereby sustaining obesity, T2DM, and MetS [26].

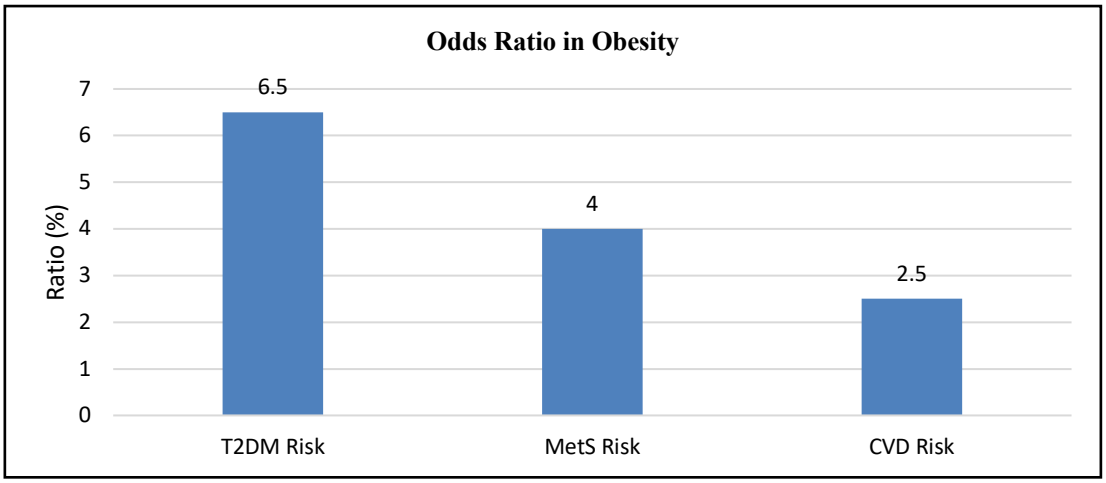

Figure 2: Risk Associations of Obesity with T2DM and MetS

Molecular Pathways

Key pathways facilitate the obesity-T2DM-MetS connection illustrated in table 3, focusing on insulin resistance and inflammation:

- **PI3K/AKT/mTOR Pathway:** Increased free fatty acids (FFAs) in obesity lead to IRS-1/2 serine phosphorylation, which inhibits PI3K-AKT, decreases GLUT4 translocation, and results in hyperglycemia in T2DM [1,2]. Hyperactivation of mTORC1 in visceral fat stimulates lipogenesis and insulin resistance; in β-cell dysfunction; in metabolic syndrome, it enhances SREBP-1c expression, worsening dyslipidemia [27,28].
- **MAPK Pathways (ERK, JNK, p38):** Cytokines produced by obesity activate JNK, which phosphorylates IRS-1 at Ser307, leading to IR and β-cell apoptosis in T2DM [1,29]. ERK/p38 control the growth of fat cells and inflammation. In MetS, JNK causes fat buildup in the liver and high blood pressure through AP-1 [30,31]. p38 increases glucose uptake in muscle but encourages NAFLD fibrosis [11].
- **JAK/STAT Pathway**: When leptin resistance occurs, STAT3 is activated, SOCS3 is upregulated, IRS-1 is inhibited, and IR gets worse [1]. Hepatic STAT3 facilitates gluconeogenesis and non-alcoholic fatty liver disease (NAFLD); its deficiency exacerbates metabolic syndrome (MetS) steatosis [27]. It facilitates cytokine-induced vascular complications in T2DM [32].
- **AMPK Pathway:** In obese hypothalamus, it is suppressed, leading to hyperphagia; on the other hand, AMPK activation inhibits acetyl-CoA carboxylase (ACC), which lowers lipogenesis and raises fatty acid oxidation, which helps with IR and dyslipidemia [1,33]. Metformin acts on AMPK [34].
- **Wnt/β-Catenin and TGF-β/Smad:** Wnt stops fat cell formation but starts JNK inflammation; TGF-β/Smad3 stops PGC-1α, which lowers mitochondrial biogenesis and insulin sensitivity in T2DM/MetS [1,27]. TGF-β plays a role in fibrosis and high blood pressure in NAFLD [20].
- **NF-κB and ER Stress:** ER stress caused by obesity activates NF-κB/JNK through the unfolded protein response (UPR), which leads to the release of cytokines and the death of β-cells in T2DM [21,35]. Multi-omics demonstrate elevated NF-κB levels in severe MetS [11].
- **Gut Microbiota and Metabolomics:** Dysbiosis elevates Firmicutes/Bacteroidetes, decreases SCFAs, and increases LPS, thereby activating TLR4/NF-κB and disrupting insulin signaling [23,36]. Dysregulated BCAA catabolism and arginine/proline metabolism are associated with insulin resistance (IR) and non-alcoholic fatty liver disease (NAFLD) [34,37].
- **Epigenetics and Mitophagy:** miRNAs (miR-34a, miR-155) hinder β-cell function; impaired mitophagy elevates reactive oxygen species (ROS), exacerbating insulin resistance (IR) [13,38]. DNA methylation at the FTO/TCF7L2 loci influences susceptibility [13].

Table 3: Key Molecular Pathways in Obesity, T2DM, and MetS

Pathway	Role in Obesity	Impact on T2DM	Impact on MetS
PI3K/AKT/mTOR	Inhibits GLUT4 via IRS-1 phosphorylation	Hyperglycemia, β-cell dysfunction	Dyslipidemia via SREBP-1c [1,27]
MAPK (JNK/ERK/p38)	Promotes inflammation, IR	β-cell apoptosis, hyperglycemia	Hepatic steatosis, hypertension [29,30]
JAK/STAT	Leptin resistance, SOCS3 upregulation	IR, gluconeogenesis	NAFLD, vascular complications [1,32]
AMPK	Suppressed, causing hyperphagia	Reduced insulin sensitivity	Dyslipidemia, reduced fatty acid oxidation [33,34]
Wnt/β-Catenin	Inhibits adipogenesis, activates JNK	Reduced insulin sensitivity	Fibrosis in NAFLD [1,20]
NF-κB/ER Stress	Cytokine release, inflammation	β-cell apoptosis	Atherosclerosis, inflammation [21,35]
Gut Microbiota	Dysbiosis, reduced SCFAs, high LPS	IR, endotoxemia	NAFLD, systemic inflammation [23,36]

Discussion

Obesity induces insulin resistance, integrating type 2 diabetes mellitus and metabolic syndrome via inflammation (TNF-α, IL-6), dysregulated signaling pathways (PI3K/AKT, MAPK), and metabolic disturbances (BCAAs, lipids) [3,27]. Genetic-epigenetic factors (FTO, TCF7L2, miRNAs) influence susceptibility, while visceral fat enhances effects through adipokines and FFAs [13,28]. Pediatric multi-omics indicate early inflammatory (Toll-like receptor, NF-κB) and metabolic alterations (BCAAs, ceramides), forecasting adult disease and emphasizing the necessity for prenatal interventions [11,15]. Figure 3 shows the therapeutic outcomes for T2DM and MetS. Current treatments, such as GLP-1 agonists (semaglutide), can help people lose weight (15–20%) and put T2DM into remission in 50–70% of cases by targeting IR and inflammation. However, differences in microbiota make these treatments less effective [1,2]. SGLT2 inhibitors enhance glycemic regulation and cardiovascular disease outcomes, especially in metabolic syndrome [39]. Bariatric surgery results in a 70-80% remission rate of type 2 diabetes mellitus (T2DM) through alterations in gut hormones (GLP-1, PYY) and shifts in microbiota; however, challenges include accessibility, cost, and long-term adherence [2,40]. Limitations encompass study heterogeneity, insufficient representation of non-Western populations, and dependence on animal models, which may not entirely extrapolate to humans [17,41]. Mitophagy defects, gut dysbiosis, and epigenetic changes could all lead to better results, but this will need long-term, diverse trials [23,38].

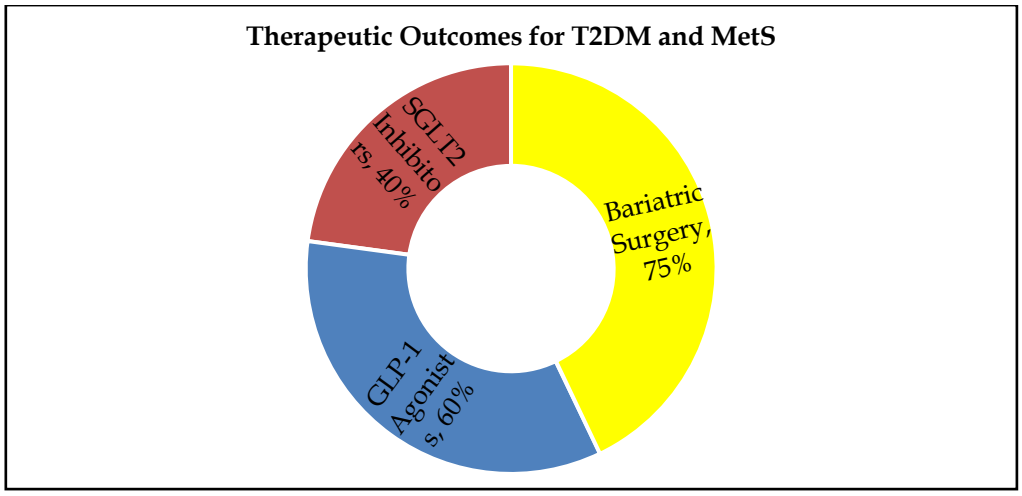

Figure 3: Therapeutic Outcomes for T2DM and MetS

Future Directions

For precision medicine to work, AI-integrated multi-omics (genomics, transcriptomics, proteomics, and metabolomics) must be able to group patients based on their molecular signatures (high BCAA/IR clusters) and guess how they will respond to treatment [3,10,11]. Table 4 shows that probiotics, prebiotics, or fecal microbiota transplantation (FMT) can change the microbiota in a way that

brings back SCFAs and lowers LPS-driven inflammation. Trials show that this can lower HbA1c levels by 10–20% in people with T2DM [23,34]. New drugs that block the JAK/STAT (baricitinib), TGF-β, or NF-κB pathways have been shown to work in phase II trials for NAFLD/MetS [1,27]. Epigenetic therapies (HDAC inhibitors) and mitophagy enhancers (urolithin A) have the potential to reverse initial modifications [13,38]. Single-cell RNA sequencing will clarify tissue-specific mechanisms, while non-invasive diagnostics (MRI-PDFF for NAFLD, wearable biosensors for metabolomics) facilitate early detection [17]. Longitudinal studies across varied cohorts, integrating gene-environment interactions (such as climate effects on obesity), are essential for global relevance [11,13]. Public health strategies focused on prenatal exposures and childhood obesity may avert long-term metabolic repercussions [14].

Table 4: Emerging Therapeutic Targets

Target	Intervention	Mechanism	Potential Outcome
Gut Microbiota	Probiotics, FMT	Restore SCFAs, reduce LPS	10-20% HbA1c reduction, improved IR [23,34]
JAK/STAT	Baricitinib	Inhibit SOCS3, reduce inflammation	Reduced NAFLD, IR [1,27]
TGF-β/Smad	TGF-β inhibitors	Enhance PGC-1α, mitochondrial function	Improved insulin sensitivity, less fibrosis [1,20]
Epigenetics	HDAC inhibitors	Reverse miRNA dysregulation	Enhanced β-cell function [13,38]
Mitophagy	Urolithin A	Reduce ROS, enhance mitochondrial clearance	Reduced IR, oxidative stress [13,38]

Conclusion

The intricate interaction among obesity, T2DM, and MetS, influenced by insulin resistance, inflammation, microbiota dysbiosis, and epigenetics, requires comprehensive interventions. Multi-omics, AI-driven personalization, and targeted therapies (microbiota modulation, JAK/STAT inhibitors) show promise for slowing the progression of CVD and lowering its burden, which would improve health outcomes around the world [3,10,34].

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References

1. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119. doi:10.1016/j.diabres.2021.109119. https://doi.org/10.1016/j.diabres.2021.109119 (or https://www.sciencedirect.com/science/article/pii/S0168822721004782).
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627-2642. doi:10.1016/S0140-6736(17)32129-3. https://doi.org/10.1016/S0140-6736(17)32129-3 (or https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32129-3/fulltext).
3. Huang X, et al. Global, regional, and national burden of type 2 diabetes mellitus caused by high BMI from 1990 to 2021, and forecasts to 2045: analysis from the Global Burden of Disease Study 2021. Front Public Health. 2025;13:1515797. doi:10.3389/fpubh.2025.1515797. https://doi.org/10.3389/fpubh.2025.1515797
4. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.
5. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell. 2012;148(5):852-871. (Ectopic lipid deposition, lipotoxicity, IR in liver/muscle/pancreas). [DOI: 10.1016/j.cell.2012.02.017
6. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840-846. (DOI: 10.1038/nature05482).
7. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol

Metab. 2007;92(2):399-404. (DOI: 10.1210/jc.2006-1711).
8. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444(7121):881-887. (DOI: 10.1038/nature05488).
9. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. Diabetes Res Clin Pract. 2010;89(3):309-319. (DOI: 10.1016/j.diabres.2010.04.012).
10. Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on three definitions among adults in the U.S. J Diabetes. 2010;2(1):37-48. (DOI: 10.1111/j.1753-0407.2009.00051.x).
11. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009;9(4):311-326. (DOI: 10.1016/j.cmet.2009.02.002).
12. Lynch CJ, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance. Nat Rev Endocrinol. 2014;10(12):723-736. (DOI: 10.1038/nrendo.2014.171).
13. Ling C, Rönn T. Epigenetics in Human Obesity and Type 2 Diabetes. Cell Metab. 2019;29(5):1028-1044. (DOI: 10.1016/j.cmet.2019.03.009).
14. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359(1):61-73. (DOI: 10.1056/NEJMra0708473).
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71. https://doi.org/10.1136/bmj.n71.
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097. https://doi.org/10.1371/journal.pmed.1000097.
17. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. doi:10.1136/bmj.j4008. https://doi.org/10.1136/bmj.j4008.
18. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute; 2011. [Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp].
19. Samuel VT, Shulman GI. Nonalcoholic fatty liver disease as a nexus of metabolic and hepatic diseases. Cell Metab. 2018;27(1):22-41. (DOI: 10.1016/j.cmet.2017.11.021).
20. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177-185. (DOI: 10.1038/nature21363).
21. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011;11(2):98-107. (DOI: 10.1038/nri2925).
22. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol. 2010;72:219-246. (DOI: 10.1146/annurev-physiol-021909-135846).
23. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. Diabetes. 2008;57(6):1470-1481. (DOI:10.2337/db07-1403).
24. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027-1031. (DOI: 10.1038/nature05414).
25. Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. Mol Cell Endocrinol. 2009;304(1-2):90-96. (DOI: 10.1016/j.mce.2009.02.025).
26. Morton GJ, Cummings DE, Baskin DG, et al. Central nervous system control of food intake and body weight. Nature. 2006;443(7109):289-295. (DOI: 10.1038/nature05026).
27. Huang X, Liu G, Guo J, Su Z. The PI3K/AKT pathway in obesity and type 2 diabetes. Int J Biol Sci. 2018;14(11):1483-1496. doi:10.7150/ijbs.27173. https://doi.org/10.7150/ijbs.27173. (PI3K/AKT details).
28. Manning BD, Toker A. AKT/PKB Signaling: Navigating the Network. Cell. 2017;169(3):381-405. (DOI: 10.1016/j.cell.2017.04.001).
29. Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002;420(6913):333-336. (DOI: 10.1038/nature01137).
30. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005;115(5):1111-1119. (DOI: 10.1172/JCI25102).
31. Hotamisligil GS, Davis RJ. Cell signalling and stress responses. Cold Spring Harb Perspect Biol. 2016;8(10):a006072. (DOI: 10.1101/cshperspect.a006072).

32. Dodington DW, Desai HR, Woo M. JAK/STAT - Emerging Players in Metabolism. Trends Endocrinol Metab. 2018;29(1):55-65. (DOI: 10.1016/j.tem.2017.11.001).
33. Steinberg GR, Kemp BE. AMPK in Health and Disease. Physiol Rev. 2009;89(3):1025-1078. (DOI: 10.1152/physrev.00011.2008).
34. Foretz M, Guigas B, Bertrand L, et al. Metformin: from mechanisms of action to therapies. Cell Metab. 2014;20(6):953-966. (DOI: 10.1016/j.cmet.2014.09.018).
35. Ozcan U, Cao Q, Yilmaz E, et al. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science. 2004;306(5695):457-461. (DOI: 10.1126/science.1103160).
36. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature. 2012;490(7418):55-60. (DOI: 10.1038/nature11450).
37. Pedersen HK, Gudmundsdottir V, Nielsen HB, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature. 2016;535(7612):376-381. (DOI: 10.1038/nature18646).
38. Liesa M, Shirihai OS. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab. 2013;17(4):491-506. (DOI: 10.1016/j.cmet.2013.03.006).
39. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720. https://doi.org/10.1056/NEJMoa1504720.
40. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes — 5-year outcomes. N Engl J Med. 2017;376(7):641-651. doi:10.1056/NEJMoa1600869. https://doi.org/10.1056/NEJMoa1600869.