Insulin Resistance: To & from Diabetes Mellitus

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Obesity and overweight

- In 2022, 1 in 8 people in the world were living with obesity. Worldwide adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled.
- In 2022, 2.5 billion adults (18 years and older) were overweight. Of these, 890 million were living with obesity.
- In 2022, 43% of adults aged 18 years and over were overweight, and 16% were living with obesity.
- In 2022, 37 million children under the age of 5 were overweight.
- Over 390 million children and adolescents aged 5–19 years were overweight in 2022, including 160 million who were living with obesity (1).

Obesity is now considered a global disease as it affects over 1.9 billion people worldwide. Obesity is a state of low-grade chronic inflammation that causes an array of different metabolic disorders, including insulin resistance (IR), Type 2 Diabetes, hypertension, cardiovascular disease, dyslipidemia and even cancer (2).

Obesity and the complications associated with it can be used as a measure to estimate morbidity and mortality, while body mass index (BMI) has been used to screen overweight (BMI=25-29.9) and obese (BMI>30) individuals.

Waist circumference is the best anthropometric indicator of visceral fat and a better predictor of metabolic syndromes such as diabetes, hypertension, and dyslipidemia (3).

Adiposity

Adults with higher levels of brown fat tend to be younger in age and have a slenderer body type along with normal blood sugar levels.

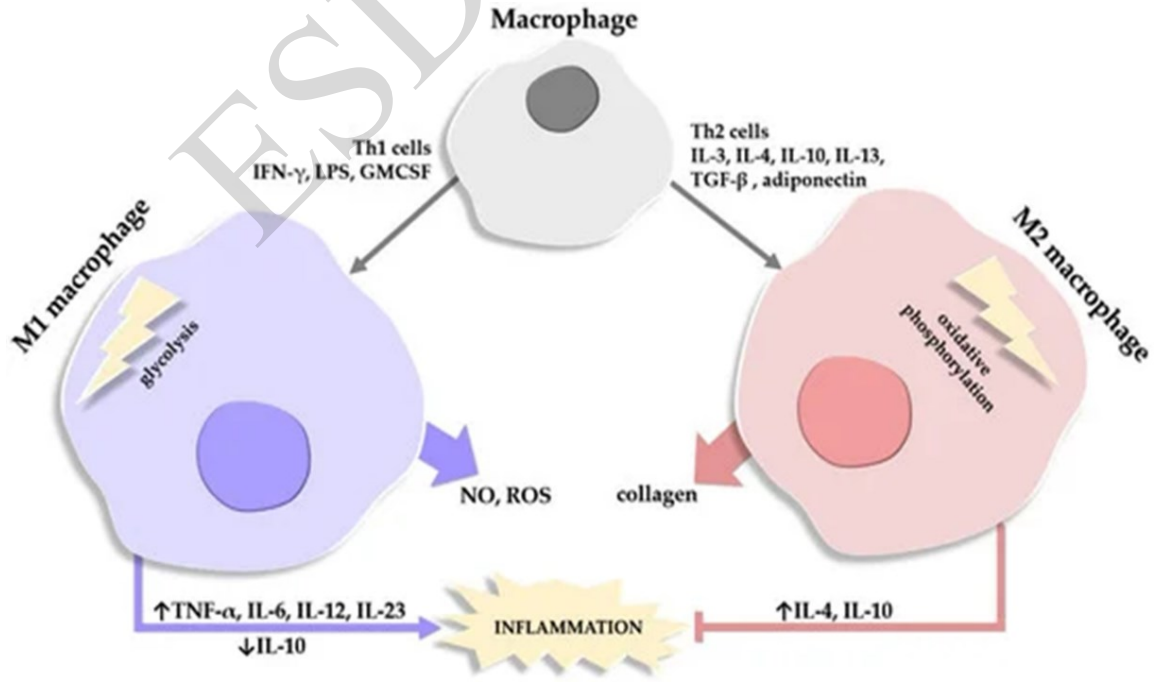

Figure (1): The Interplay between Obesity and Inflammation Life 2024, 14(7), 856; (4)

White adipose tissue (WAT) is not only an energy storage place in the body but also an important regulator of metabolic pathways, including immunity and inflammation.

Adipose tissue releases multiple pro-inflammatory and anti-inflammatory factors, such as adipokines leptin, adiponectin, resistin, and visfatin, and cytokines such as IL-6, etc.

Pro-inflammatory factors play an important role in insulin resistance and increased risk of cardiovascular diseases (CVD) associated with obesity (3).

Insulin resistance

Insulin resistance is identified as the impaired biologic response of target tissues to insulin stimulation. All tissues with insulin receptors can become insulin resistant, but the tissues that primarily drive insulin resistance are the liver, skeletal muscle, and adipose tissue. Insulin resistance impairs glucose disposal, resulting in a compensatory increase in beta-cell insulin production and hyperinsulinemia (5).

The metabolic consequences of insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state. The predominant consequence of insulin resistance is type 2 diabetes(T2D). Insulin resistance is thought to precede the development of T2D by 10 to 15 years (5).

Types of people more likely to develop insulin resistance

Individuals who have hereditary factors or lifestyle-related factors are bound to have in their later life insulin resistance or prediabetes.

Hazard factors include:

- Overweight or obesity.
- Age 45 or more.
- Having a parent, sibling, or sister with diabetes.
- African American, Alaskan Native, American Indian, Asian American, Hispanic/Latino, Native Hawaiian, or Pacific Islander American ethnicity.
- Health conditions, for example, hypertension and high cholesterol levels.
- A history of gestational diabetes.
- A history of coronary illness or stroke.
- Polycystic ovary disorder, also known as PCOS.
- Individuals who have metabolic disorders—hypertension, irregular cholesterol levels, and enormous waist size—are bound to have prediabetes.
- Hormonal imbalances, for example, Cushing's disorder and acromegaly.
- Sleep issues, particularly rest apnea (6).

What is the mechanism?

Many epidemiological studies have concluded that obesity is a leading risk factor for T2DM, and reportedly, obese people are up to 80 times more likely to develop T2DM.

Furthermore, it has been shown an inverse correlation exists between plasma fatty acid concentration and insulin sensitivity in age and body mass index-matched controls.

These results and others show that excess lipid content caused by obesity is a primary cause of insulin resistance and T2DM (7).

At the molecular level, mitochondrial dysfunction is a prominent feature of T2D pathology that contributes to both β-cell defects and insulin resistance.

Mitochondrial dysfunction is manifested in several ways.

Deficient oxidative metabolism and reduced ATP generation have been described in several tissues, along with more specific defects leading to reduced or incomplete fatty acid oxidation that are implicated as causes of cellular lipid accumulation (7).

Reduced mitochondrial content and structural damage are also reported.

Defects in the function of the mitochondrial respiratory chain also cause excessive reactive oxygen species (ROS) formation, which has a clearly causative role in T2D pathophysiology.

Importantly, metabolic disorders, including obesity and T2D, are associated with altered NAD+ metabolism and generally reduced levels (7).

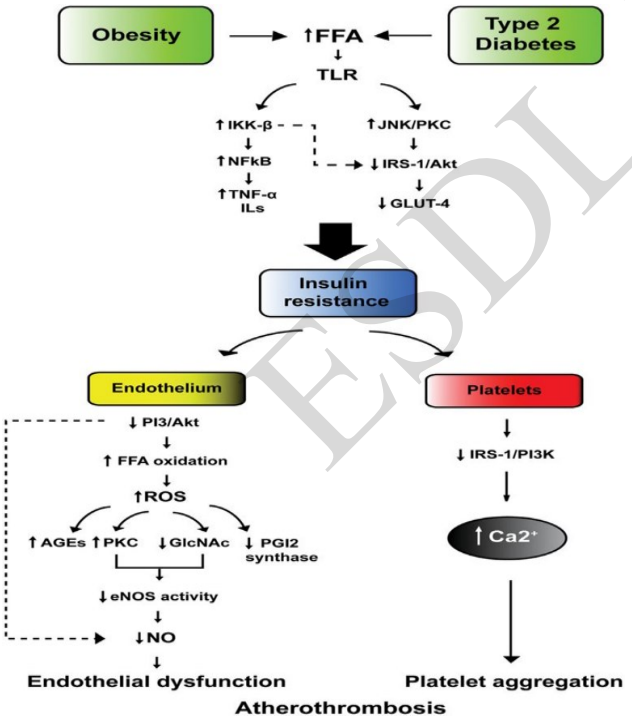

Figure (2): The Role of AGE/RAGE Signaling in Diabetes-Mediated Vascular Calcification, Journal of Diabetes Research. 2016 (8)

Obesity leads to alterations in lipid metabolism, deregulation of hormonal axes, oxidative stress, systemic inflammation, and ectopic fat distribution.

Adipose tissue is an active source of inflammatory mediators and free fatty acids (FFAs).

In obesity, there is ↓ in adiponectin and there is ↑ in leptin→ leptin resistance.

Obesity induces a phenotypic switch in adipose tissue from anti-inflammatory (M2) to pro-inflammatory (M1) macrophages.

There is also ↑fibrinogen, thrombin, fibrin & ↓TPA & ↑PAI1 (8).

Why is there an increase in FFA?

Fat cells are resistant to insulin's antilipolytic effect, leading to day-long elevation in the plasma FFA concentration. Chronically increased plasma FFA levels stimulate gluconeogenesis, induce hepatic/muscle insulin resistance, and impair insulin secretion. Dysfunctional fat cells produce proinflammatory cytokines & adipokines & downregulate the insulin-sensitizing adipocytokines such as adiponectin. Enlarged fat cells are insulin-resistant and have diminished capacity to store fat (9).

Insulin resistance in liver and adipose tissue.

In the fasted state, the liver secretes hepatic glucose production (HGP), and involves the breakdown of hepatic glycogen (glycogenolysis) and de novo synthesis of glucose (gluconeogenesis) using fatty acids and glycerol derived from adipose tissues.

After food intake, insulin secreted by pancreatic β-cells promotes anabolism and suppresses catabolic programs.

In addition, insulin suppresses HGP by inhibiting the expression of gluconeogenic genes and lipolysis in adipose tissue.

Insulin also suppresses glucagon secretion from pancreatic α-cells and reduces appetite via the central nervous system.

In T2DM patients, insulin cannot regulate hepatic glycogen synthesis or glucose production, and increased hepatic gluconeogenesis is the primary cause of fasting hyperglycemia in T2DM.

Defective suppression of hepatic gluconeogenesis in insulin resistance is largely associated with lipolysis defects in adipose tissue and the de-suppression of FOXO1 transcription factor in the liver.

{FOXO1 is a transcription factor that plays important roles in the regulation of gluconeogenesis and glycogenolysis by insulin signaling, and is also central to the decision for a preadipocyte to commit to adipogenesis.}

Hepatic insulin resistance reduces the amplitude of hepatic glycogen metabolism induced by fasting and feeding.

In the case of hepatic insulin resistance, insulin fails to suppress HGP but stimulates lipogenesis, which results in hyperglycemia, hyperlipidemia, and hepatic steatosis (7).

Insulin resistance in skeletal muscles

A defect in the insulin signaling cascade at the level of IRS-1 is likely the primary defect that leads to insulin resistance in skeletal muscle.

In insulin-resistant individuals with overt hyperglycemia, for example, T2DM, a number of post-binding defects have been demonstrated, including reduced insulin receptor tyrosine kinase activity and altered insulin signal transduction, decreased glucose transport, diminished glucose phosphorylation, and impaired glycogen synthase activity. Impaired glycogen synthesis represents the major pathway responsible for the insulin resistance and this defect is present long before the onset of overt diabetes, that is, in normal glucose-tolerant, insulin-resistant prediabetic subjects, and in individuals with IGT.

It is likely due to a defect in the ability of insulin to phosphorylate IRS-1, which leads to increased intramyocellar fat content and fatty acid metabolites (10).

How does DM occur?

Type 2 diabetes (T2D) occurs when insulin-producing β cells of pancreatic islets are unable to produce and/or release sufficient insulin to overcome peripheral insulin resistance, resulting in hyperglycemia (11).

Autopsy studies in various populations have reported significant reductions in the number of pancreatic β-cells in patients with type 2 diabetes compared with non-diabetic individuals. It is suggested that the decline in B-cell mass precedes the onset of diabetes by almost a decade. Those studies show that at the time of diagnosis, diabetic patients seem to have already lost about 50% of their pancreatic B cells. The range can be from 20% to 65%. There is also evidence for a B-cell defect in prediabetic individuals with impaired fasting glucose (12).

Normally islet β cells respond to insulin resistance by Increased insulin secretion & Expansion of β cell mass. Insulin resistance→ compensatory increase in insulin secretion.

Compensation involves a heightened response to the normal physiological processes affecting B cell function & mass.

It is the progressive exposure to the extra fuel surfeit (both the level & duration of exposure) &/or genetic predisposition with the increased glucotoxicity & lipotoxicity that causes mitochondrial dysfunction & B cell failure (13).

In T2D, increased metabolic stress due to hyperglycemia and peripheral insulin resistance can induce mitochondrial dysfunction, leading to the production of reactive oxygen species (ROS). It is believed that at a basic level, ROS can serve as physiological signals (11).

Increased ROS downregulates respiratory chain proteins and reduces mitochondrial ATP production, which can also impair insulin secretion.

These reactive species can substantially damage cell components, including the mitochondria, via lipid peroxidation, protein oxidation, and DNA mutation (12).

Autophagy is the basic catabolic mechanism to degrade dysfunctional proteins as well as defective cellular components.

However, persistent metabolic stress on β cells under hyperglycemic conditions leads to dysregulation of autophagy, which can ultimately aggravate β cell function or result in β cell demise (11).

The ER is the site of insulin biosynthesis

In the pre-diabetic stage, two processes occur: insulin resistance and an overexpression of proinsulin and unfolded protein species in the ER lumen.

The accumulation of misfolded proteins is believed to lead to the ERS of B cells and is associated with an inability to clear misfolded proteins or dysfunctional autophagy.

This process is associated with a substantial generation of ROS, apoptosis and B cell death (12).

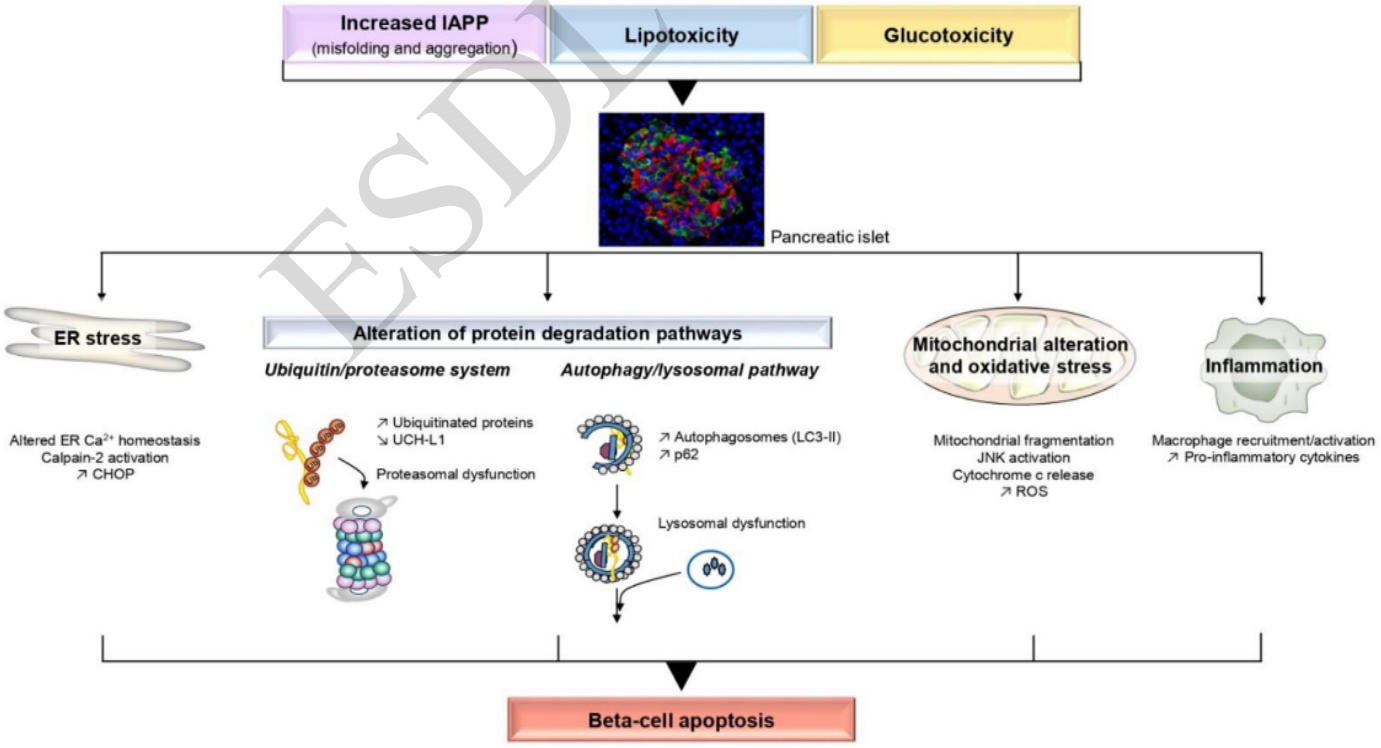

Figure (3): Pharmacologic Treatment of Overweight and Obesity in Adults. [Updated 2024] (14)

Islet amyloid is a pathological lesion found in the pancreas of more than 90% of individuals with T2D. Islet amyloid is formed mainly by the abnormal aggregation of the β-cell hormone islet amyloid polypeptide. Increased islet amyloid deposition correlates with decreased β-cell mass and insulin production via multiple mechanisms, including promotion of islet inflammation and activation of apoptotic pathways (11).

Epidemiology of DM

537 million adults (20-79 years) are living with diabetes - 1 in 10. This number is predicted to rise to 643 million by 2030 and 783 million by 2045.

Over 3 in 4 adults with diabetes live in low- and middle-income countries. Diabetes is responsible for 6.7 million deaths in 2021-1 every 5 seconds.

541 million adults have Impaired Glucose Tolerance (IGT), which places them at high risk of type 2 diabetes (15).

The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014. Prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries. Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.

Between 2000 and 2019, there was a 3% increase in diabetes mortality rates by age.

A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type 2 diabetes (1).

The number of people diagnosed with DM earlier in life is increasing, including adults aged 18 to 39 years. They now represent 15 to 20% of the adults with type 2 DM (16).

The incretin effect

It refers to the enhanced insulin secretion in response to oral or enteric glucose. The incretin effect is due to hormones secreted from the intestine, the most important ones being glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both these hormones stimulate pancreatic insulin secretion (17).

Assessment of insulin sensitivity/resistance

Homeostasis model assessment (HOMA) was developed in 1985 to study the interaction between glucose and insulin.

Its application was later expanded to measure insulin resistance and β-cell function.

Glucose concentration depends on the insulin-dependent HGP, whereas insulin levels depend on the response of β cell to glucose-stimulated insulin secretion.

Computer simulations have been used to generate a nomogram from mathematical transformations of fasting glucose and insulin data from individual subjects.

The model assumes a feedback loop between the liver and the pancreatic β cell.

This helps in determining insulin sensitivity, SI (HOMA%S) and β-cell function (HOMA%B).

The homeostasis model of insulin resistance (HOMA-IR) is calculated as follows:

HOMA1-IR= {Fasting plasma insulin(μU/ml) ×fasting glucose(mmol/L)} ÷22.5

Or HOMA1-IR= {Fasting insulin(μU/ml) ×fasting glucose(mg/dl)} ÷405

The denominator 22.5 is the normalizing factor, derived from the product of normal fasting plasma insulin (5 μU/mL) and normal fasting plasma glucose (4.5 mmol/L). Therefore, a normal healthy individual should have an HOMA-IR of 1 (18).

Management of insulin resistance

The most important step in management is obesity and weight management.

It decreases insulin resistance and hyperinsulinemia, hence delay or prevent progression to prediabetes and diabetes.

Obesity and Weight Management

Nutrition, Physical Activity, and Behavioral Therapy

The associations between obesity, central obesity (increased waist circumference, especially intra-abdominal/visceral fat) and the risks for cardiometabolic diseases as well as obstructive sleep apnea, asthma, and nonalcoholic fatty liver disease (NAFLD) are well established.

Cytokines secreted from visceral adipocytes, including interleukin-6, tumor necrosis factor alpha, resistin, and plasminogen activation inhibitor-1, have been implicated in the pathogenesis of these diseases, in part by promoting local and systemic states of inflammation and thrombosis.

A reduction in body weight of 5-10% significantly lowers inflammatory and pro-thrombotic markers, as well as chronic disease incidence (19).

- Role of integrative medicine
- Role of acupuncture
- Role of homeotherapy
- Role of energy therapy
- Role Naturopathy: Naturopathic products that work include those made with grapefruit seed extract, oregano oil & others.
- Role of lymphatic massage therapy, power plate & jumping over a trampoline.

In Europe, patients often receive a special massage called lymph therapy or lymph drainage before undergoing surgery.
On an everyday basis, regular lymph massage (particularly around the abdomen, axillary nodes, and breast) can be great preventive health maintenance. For patients who have failed to achieve clinically significant weight loss, defined as ≥ 5% of baseline weight after 6 months of lifestyle interventions, professional organizations, including The Obesity Society, the Endocrine Society, and the American Association of Clinical Endocrinologists, recommend AOMs for individuals with BMI ≥ 30 kg/m2 or BMI ≥ 27 kg/m2 with comorbidities (19).

In November 2022, the American Society of Metabolic and Bariatric Surgery (ASMBS) and the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) issued updates to the 1991 National Institutes of Health (NIH) guidelines for bariatric surgery.

Recommendations included the following:

- Metabolic and bariatric surgery (MBS) is recommended for all individuals with a body

mass index (BMI) higher than 35 kg/m 2, regardless of the presence, absence, or severity of comorbid conditions.

- MBS should be considered for individuals who have metabolic disease and a BMI between 30 and 34.9 kg/m 2.
- In the Asian population, BMI thresholds should be adjusted so that a BMI exceeding 25 kg/m 2 suggests clinical obesity. MBS should be offered to Asian individuals with BMIs higher than 27.5 kg/m 2.
- Long-term results of MBS consistently demonstrate safety and efficacy.
- MBS should be considered for appropriately selected children and adolescents.

Drugs used in the management of insulin resistance

1. Metformin

The American Diabetes Association recommends metformin as the initial pharmacological option for most people with type 2 diabetes.

It has a strong record of safety and efficacy, as well as a favorable effect on weight (20).

Metformin is a complex drug with multiple sites of action and multiple molecular mechanisms.

Physiologically, metformin acts directly or indirectly on the liver to lower glucose production, and acts on the gut to increase glucose utilization, increase GLP-1 and alter the microbiome.

At the molecular level, metformin inhibits the mitochondrial respiratory chain in the liver,

Drug (trade name)	Approval FDA/EMA (year)	Mechanism of action	Adverse events[a]	Contraindications[b]
Orlistat (Xenical, Alli)	FDA 1999 EMA 1998	Gastric and pancreatic lipase inhibitor	Oily rectal leakage, abdominal distress, abdominal pain, flatulence with discharge, fecal urgency, steatorrhea, fecal incontinence, increased defecation	Patients with chronic malabsorption syndrome or cholestasis, pregnancy
Phentermine/ Topiramate (Qsymia)	FDA 2012	NE agonist/GABA agonist, glutamate antagonist	Elevation in heart rate, mood and sleep disorders, cognitive impairment, metabolic acidosis, paresthesia, dry mouth	Glaucoma, hyperthyroidism, during or within 14 days following the administration of monoamine oxidase inhibitors, hypersensitivity to sympathomimetic amines, pregnancy
Naltrexone/ Bupropion (Contrave/ Mysimba)	FDA 2014 EMA 2015	Opioid receptor antagonist/DA and NE reuptake inhibitor	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, diarrhea, sleep disorder	Chronic opioid use, acute opioid withdrawal, uncontrolled hypertension, seizure disorder, bulimia or anorexia nervosa, abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiseizure drugs; concomitant use of MAOIs, patient receiving linezolid or IV methylene blue, pregnancy
Liraglutide (Saxenda)	FDA 2014 EMA 2015	GLP-1 analogue	Increased heart rate, hypoglycemia, constipation, diarrhea, nausea, vomiting, headache	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy
Semaglutide (Wegovy)	FDA 2021 EMA 2021	GLP-1 analogue	Nausea, vomiting, diarrhea, abdominal pain, constipation, headache	Personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2, pregnancy
Setmelanotide (Imcivree)	FDA 2020 EMA 2021	MC4R agonist	Injection site reactions, hyperpigmentation, nausea, headache, diarrhea, vomiting, abdominal pain	None
Tirzepatide[c]	Under consideration by FDA	GIP/GLP-1 dual agonist	Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, known serious hypersensitivity to tirzepatide or any of the excipients

Abbreviations: DA, dopamine; EMA, European Medicines Agency; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; IV, intravenous; MAOIs, monoamine oxidase inhibitors; MC4R: melanocortin-4 receptor; NE, norepinephrine. [a]Adverse events presented here are those that are present in more than 10% of the population, based on the FDA approval leaflet. [b]Contraindications are based on the FDA approval leaflet. [c]Under exped[illegible]

Table 1: **Anti-obesity medications: approval, mechanism of action, adverse events, and contraindications.**

Figure (4): ASMBS/IFSO Guidelines for Metabolic and Bariatric Surgery Clin Diabetes. 2016 (20)

leading to activation of AMPK, enhancing insulin sensitivity (via effects on fat metabolism) and lowering cAMP, thus reducing the expression of gluconeogenic enzymes.

Metformin also has AMPK-independent effects on the liver that may include inhibition of fructose-1,6-bisphosphatase by AMP (20).

2. Thiazolidinediones

Thiazolidinediones (TZDs) improve insulin sensitivity by increasing insulin-dependent glucose disposal and decreasing hepatic glucose output (21).

TZDs exert their antidiabetic effects through a mechanism that involves activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR gamma), a nuclear receptor.

TZD-induced activation of PPAR gamma alters the transcription of several genes involved in glucose and lipid metabolism and energy balance, including those that code for lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl-CoA synthase, malic enzyme, glucokinase and the GLUT4 glucose transporter.

TZDs reduce insulin resistance in adipose tissue, muscle and the liver (21).

3. Glimins

Imeglimin's dual mechanism of action.

This includes the reversal of β-cell dysfunction via amplification of glucose-stimulated insulin secretion (GSIS) and augmentation of insulin action in liver and skeletal muscle.

Underlying these effects are improvements in mitochondrial function that have been shown in multiple cell types.

In addition, Imeglimin induces an increase in the cellular NAD+ pool (in islets) that has also been linked to Ca++ mobilization and enhanced GSIS (25).

Imeglimin is a novel oral agent for the treatment of type 2 diabetes (T2D).

Imeglimin's mechanism of action has dual effects:

A. Increased glucose-stimulated insulin secretion and preservation of β-cell mass; and

B. Enhanced insulin action, including the potential for inhibiting hepatic glucose output and improving insulin signaling both in the liver and skeletal muscle, resulting in decreased insulin resistance (22).

Key Features of Mitochondrial Dysfunction

1. Impaired Energy Production
ATP production is reduced due to problems in oxidative phosphorylation, the process by which mitochondria convert nutrients into energy.
This often results from defects in the electron transport chain (ETC) complexes or enzymes. Increased Reactive

2. Oxygen Species (ROS):
Mitochondria are a major source of ROS, byproducts of oxidative phosphorylation.

Dysfunction can lead to excessive ROS production, causing oxidative stress and damage to cellular components like DNA, proteins, and lipids.

3. Calcium Dysregulation

Mitochondria help regulate intracellular calcium levels, essential for cell signaling and energy production.

Dysfunction can lead to calcium overload, which may trigger cell death pathways.

4. Altered Apoptosis

Mitochondria release pro-apoptotic factors (e.g., cytochrome c) that initiate programmed cell death.

Dysregulation of this process can result in excessive cell death or failure to eliminate damaged cells, contributing to disease.

5. Metabolic Abnormalities

Mitochondrial dysfunction can disrupt metabolic pathways, including the Krebs cycle and fatty acid oxidation.

This can lead to the accumulation of toxic intermediates and an energy imbalance (22).

Possible benefits of these mechanisms to improve glucose homeostasis include increasing insulin sensitivity, decreasing gluconeogenesis, increasing β-cell function, increasing mitochondrial function, and decreasing oxidative stress.

Imeglimin has several documented effects on mitochondrial function. It has been found to enhance the generation of adenosine triphosphate (ATP) and increase the ATP/adenosine diphosphate ratio, resulting in improvement of mitochondrial function.

In addition, imeglimin amplifies glucose-stimulated insulin secretion. It improves B-cell function by increasing nicotinamide phosphoribosyltransferase(NAMPT), which leads to increased nicotinamide adenine dinucleotide(NAD) and ultimately contributes to calcium mobilization in the insulin secretion amplification pathway.Enhanced insulin effects can be seen in both the liver and skeletal muscle.

Recently, imeglimin was found to prevent endothelial cell death in human cells by inhibiting the opening of the mitochondrial permeability transition pore without inhibiting mitochondrial respiration (22).

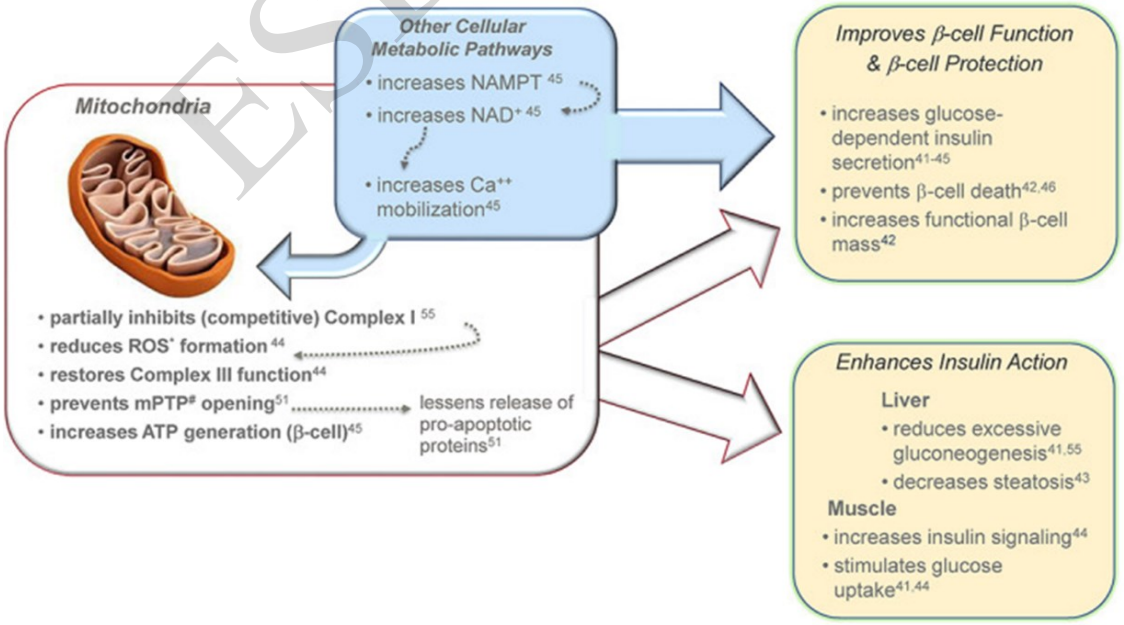

Figure (5): Mitochondrial modulation enhances β-cell function and insulin action (22)

Imeglimin	Metformin
In vivo (clinical)	
Glucose-stimulated insulin secretion (hyperglycaemic clamp)[39]	No reported effect on insulin secretion[39,71]
Evidence of insulin sensitivity - QUICKI[a], Stumvoll[a]	No clear increase in insulin sensitivity[71,72]
In vivo (preclinical)	
Glucose-stimulated insulin secretion (GTT)[44]; hyperglycaemic clamp[41,43]	No effect on insulin secretion[71]
Glucose disposal; insulin sensitivity (Figure 3); insulin signalling[41,44]	± Insulin sensitization[71,72]
Cell and organ	
Glucose-stimulated insulin secretion (islets/perfused pancreas)[41,43,45]	No effect on glucose-stimulated insulin secretion[71,73]
Islet β-cell protection; preserved β-cell mass[41,42]	In vitro β-cell protection[74,75]; no known in vivo effects on β-cell mass[71]
Muscle glucose uptake[41]	± Muscle glucose uptake[71]
Gluconeogenesis (hepatocytes)[41]	Gluconeogenesis (hepatocytes)[71]
Intracellular	
Competitive/partial mitochondrial Complex I inhibition; no decrease in mitochondrial respiration; decreased ROS[b] formation[44,51,55]	Uncompetitive mitochondrial Complex I inhibition; decreased respiration[55,71]; decreased ROS formation[76,77]
No effect on mitochondrial glycerophosphate[a]	Mitochondrial glycerophosphate dehydrogenase[58]
Increased NAD^+ synthesis; potentially via NAMPT[c]; increased glucose-responsive intracellular Ca^{++}[45]	No increase in Ca^{++};[73] no effect on NAD^+ reported[3]

Figure (6): Imeglimin's mode of action is distinct versus metformin. Diabetes, Obesity and Metabolism 2025;(3):1498-1506(22)

Conclusion:

Obesity became a global pandemic, increasing in recent era, especially in children and adolescents.

Insulin resistance is an ultimate consequence of obesity, increasing cardiovascular morbidity and mortality.

The metabolic consequences of insulin resistance can result in hyperglycemia, hypertension, dyslipidemia, hyperuricemia, elevated inflammatory markers, endothelial dysfunction, and a prothrombotic state.

Management of obesity and insulin resistance can delay or prevent type 2 DM, decreasing cardiovascular morbidity & mortality.

Lifestyle modifications & healthy lifestyle is a top management standard followed by anti-obesity drugs, bariatric surgery & insulin sensitizers.

Imeglimin is a novel oral agent for the treatment of type 2 diabetes (T2D) with dual effects by increasing glucose-stimulated insulin secretion, preservation of β-cell mass and enhanced insulin action, including the potential for inhibiting hepatic glucose output and improving insulin signaling both in the liver and skeletal muscle.

Underlying these effects are improvements in mitochondrial function that have been shown in multiple cell types.

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