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Review Article

Management and interplay of Type 2 Diabetes Mellitus with obesity

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Abstract

Since T2DM is suffered by most diabetic patients (around 90–95%), this review focuses on the potential drugs acting on multi-targets involved in treating this type of diabetes. T2D is distinguished by peripheral tissue insulin resistance (IR) and pancreatic beta-cell malfunction. It is also believed that obesity alters the body's metabolism. These modifications lead to the release of fat molecules into the circulation from fat tissue, which can impact insulin-responsive cells and decrease insulin sensitivity. Furthermore, Social and cultural aspects have significance for the approach to emergency treatment and curative consequences of obesity and type 2 diabetes. Regardless of the recent advances in the therapeutic management of diabetes, there are still many obstacles to overcome: enhancing our knowledge of how diabetes and obesity are interrelated. It is helpful to explain that an agent is simply one part of a multifaceted treatment plan when prescribed for a patient with T2DM and obesity. There should be thorough counselling on the predicted benefits, adverse effects, and cessation criteria. Obesity and T2DM significantly impact early mortality, condition of life, overweight-associated concurrent illnesses, and the global healthcare sector, whether they exist alone or together as "diabesity." Knowing the therapeutic and causal interactions between these two disorders is crucial.

Keywords: Type 2 diabetes mellitus, Obesity, Insulin resistance, Antidiabetic drugs

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Introduction

Diabetes mellitus (DM) is a complex disease with many types and no clear definition. Clinical characteristics of the topic differ significantly among populations. By 2045, 629 million people worldwide will have been diagnosed with type 2 diabetes (T2DM), according to the International Diabetes Federation (IDF). In more than 80–90% of cases, the obesity pandemic has been primarily blamed for the exponential rise in prevalence. (1)

Typically, the early stages of this illness may be asymptomatic or present with very modest symptoms. As a result, it may go untreated for a long time, making it extremely difficult to estimate how many people have the disease.(2) Frequent urination, increased hunger and thirst, weariness, blurred vision, sluggish wound healing, and tingling, discomfort are among the symptoms that can be present. Since diabetes may go on for a long time without showing any signs, the diagnosis of T2DM frequently occurs alongside another condition. (3)

T2D is distinguished by peripheral tissue insulin resistance (IR) and pancreatic beta-cell malfunction. Due to impaired peripheral nutrient uptake, these changes lead to hyperglycemia due to inadequate peripheral glucose uptake, dyslipidemia, and ATP synthesis into peripheral tissues, such as skeletal muscle, due to the impaired nutrient uptake and increased glucagon production, which amplifies hyperglycemia.(4)

Furthermore, Social and cultural aspects have significance for the approach to emergency treatment and curative consequences of obesity and type 2 diabetes. Regardless of the recent advances in the therapeutic management of diabetes, there are still many obstacles to overcome: enhancing our knowledge of how diabetes and obesity are interrelated.(5)

The connection that exists between obese people and those with type 2 diabetes:

To explain the connection between type 2 diabetes and obesity, numerous theories have been proposed. The first theory suggested that obesity alters the body's metabolism. These modifications lead to the release of fatty acids into the circulation from fat tissue (adipose tissue), which can impact insulin-responsive cells and decrease insulin sensitivity. According to a second theory advanced by researchers, obesity triggers prediabetes, a metabolic disorder that almost invariably progresses to type 2 diabetes. (6) The location of fat accumulation and the level of obesity affect the impact of obesity on the risk of type 2 diabetes. Although underlying processes are unclear, increasing upper body fat, especially visceral adiposity, as seen in increased abdominal girth or waist-to-hip ratio, is linked to metabolic syndrome, type 2 diabetes, and heart disease. (1)

Adipose cells may release more glycerol, lipids, hormones, proinflammatory cytokines, and other substances that contribute to the development of insulin resistance because of alterations to the metabolic process in the body brought on by obesity.(7) Pro-inflammatory substances may be released by fat cells because of abdominal obesity. These substances can impair the activity of insulin-responding cells and their capacity to react to insulin, reducing the body's sensitivity to the insulin it generates. (8)

Investigation into the origins and problems of obesity must prioritize a better understanding of the operation of various fat cell types and depots and their involvement in metabolic equilibrium. Similar to other tissues, adipose tissue comprises various cell types. (9) Adipose tissue immune cells are likely involved in systemic metabolic functions as well. It will be crucial to consider if other adipocyte subtypes or different kinds of cells can be discovered as the research of adipose biology advances to improve our comprehension of the consequences of obesity and develop fresh approaches to prevention. (10)

Obesity is characterized by an imbalance between brown and white adipose tissue (WAT and BAT). The rate of obesity worldwide is increasing, which implies that there is a chronic mismatch between calorie intake and the consumption of energy.(11) Currently, 712 million individuals (or 10% of the world's population) are obese, making up around 2.2 billion overweight people worldwide, or nearly one-third of the population. Systemic glucose homeostasis is significantly impacted by obesity, which also has significant effects on cellular insulin sensitivity. (12)

Pathophysiological Causes Promoting T2DM:

1-Dietary elements:

Large amounts of lipids and carbs in high-calorie diets cause blood sugar levels to rise—reactive oxygen species (ROS) concentrations increase, which triggers the aberrant production of inflammatory chemicals. The steady-state amounts of ROS have been steadily rising, which has profoundly impacted the pathophysiology of T2DM and IR. Consequently, a pro-oxidant environment causes ER stress, NADPH oxidase activation, and mitochondrial failure.(13) An increasing body of evidence indicates that IR and aberrant lipid profiles are closely related. In addition to T2DM, IR is a critical factor in several other metabolic diseases. For instance, a high level of low-density lipoprotein (LDL), high levels of serum triglycerides (TG), and a low amount of high-density lipoprotein (HDL) have all been linked to IR. As a result, practically all follow-up programs for T2DM point out the lipid profile, which is a significant risk factor .(14)

1- <u>Physical Activity:</u>

Exercise increases the body's ability to use insulin, which results in weight loss and higher quality of life. It also lowers blood pressure, controls blood sugar and lipid levels, and improves the cardiovascular system's function .(15) Obesity and T2DM are linked by decreased exercise and raised sedentary behaviors, linked to elevated indicators of persistent moderate systemic inflammatory conditions. Interleukin 6 (IL-6), C-Reactive Protein

(CRP), tumour necrosis factoralpha (TNF-α), or IL-1 are examples of proinflammatory chemicals released into the circulation that cause metabolic, inflam-matory processes. According to prior studies, reducing inflammation could increase insulin sensitivity and delay the onset of T2DM in people with obesity and prediabetes.[16] Irisin is a myokine rele-ased by skeletal muscles and fat when subjected to physical exertion and enhances glucose tolerance. Compared to control people, T2DM patients were found to have reduced levels of irisin in their blood.[17]

2- Gut Dysbiosis:

Gut commensal microbes produce numerous metabolites, supporting healthy people's physiology. However, alterations brought on by inherited and acquired factors, including age, dietary habits, way of life, genetic background, or underlying disorders, can have an impact on the proportion of metabolites generated by the gut microbiota, which can cause metabolic abnormalities that can eventually result in disease.[18] Additionally, intestinal dysbiosis can lessen the production of short-chain fatty acids, which support the integrity of the gut barrier, pancreas cell proliferation, and insulin manufacturing. [19] The transfer of bacterial toxins to different body parts because of a rise in intestinal permeability in patients with diabetes is a rapidly developing research topic in DM. Acting indirectly, a healthy gut microbiota will reduce the nervous system's sensitivity to stress. In contrast, dysbiosis will increase the hypothalamic–pituitary–adrenal (HPA) 's response to stress, which will exacerbate barrier dysfunction by causing the breakdown of the gut's extracellular matrix (ECM). [20] Moreover, it is hypothesized that endotoxin components of the bacterial cell wall can stimulate immune cells within the gut or elsewhere to release these cytokines, which consequently influence the parts of the central nervous system involved in regulating the HPA axis response. [21]

3- Reduced mitochondrial function:

Previous studies have suggested that mitochondrial malfunction may impact diseases like obesity and diabetes because of these organelles' role in metabolism and general health. Mitochondria use fat to produce energy, and a decline in mitochondrial activity is linked to an increase in ectopic fat and IR .[22] When analyzed alongside insulin-sensitive people, the amount of ATP produced at rest in muscle cells is lower in insulin-resistant people involved, suggesting that mitochondrial dysfunction contributes to IR .[23] The effects of oxidative stress and mitochondria dysfunction are intimately related and have been linked to IR and T2D. Reactive oxygen species (ROS), such as superoxide anion and hydrogen peroxide (H2O2), are produced mainly by mitochondria. Their excessive synthesis reflects oxidative stress. In a vicious loop, excessive ROS production damages the health of mitochondria and then creates even more ROS. [24] Additionally, it has been discovered that individuals with T2DM have downregulated peroxisome proliferator-activated receptor co-activator 1 α (PGC 1α)-regulated genes that are important in oxidative metabolism.[25] One such method of enhancing mitochondrial and metabolic health may be exercise. Obese mice do not appear to have an apparent mitochondrial path-way failure, and the muscles seem to respond and adapt effectively to new stress, whether that stress comes from exercise or a high-fat diet. This implies that exercise may have a similar positive impact on obese people. The researchers want to duplicate their results with human subje-cts in the future .[26]

Brown and white adipose tissue's role in obesity and type 2 diabetes

White and brown adipocytes are thought to develop from different embryonic origins. The mobilization and storage of lipids is a specialty of white adipocytes. White adipocytes use lipolysis of fat and the breakdown of fatty acids to offer persistent metabolic fuel during caloric necessity.[27] Brown adipocytes, on the contrary, are adept at burning calories and use chemical power for thermogenesis, which is essential for regulating the body's core temperature. Uncoupling protein 1 (UCP1), a particular protein found only in brown adipocytes, is abundant in the mitochondria of these cells.[28] Brown adipocytes also exhibit multilocular lipid

droplets. UCP1, a key regulator of thermogenesis in the inner membrane of the mitochondria, dissociates ATP synthesis from mitochondrial respiration, causing thermogenesis. [29]

Only a minor portion of BAT's energy originates from glucose metabolism; instead, the majority comes from the -oxidation of fatty acids. However, because of BAT's high glucose uptake rate following activation compared to other metabolically functioning tissues, it has an essential effect on glucose homeostasis in vivo.[30] One of the most tissues sensitive to insulin is the BAT. Insulin increases the BAT's ability to absorb glucose, and the anaerobic breakdown of glucose that occurs in the BAT's cytoplasm can lead to ATP production .[31] It can be used to activate free fatty acids (FFA) before they enter mitochondria for -oxidation, and it can also be utilized to prevent ATP shortage brought on by the uncoupling of oxidative phosphorylation that occurs in mitochondria.[32] Insulin sensitivity and glucose absorption rate under cold temperatures and stimulation with insulin were reduced in obese individuals than in lean participants, indicating that obesity significantly blunts the results of cold temperatures and insulin on BAT function .[33] However, mice with age-dependent interscapular brown fat loss when the insulin receptor of brown adipocytes was knocked out revealed higher expression of UCP1 and UCP2 instead. Due to their innate thermogenic activity and propensity to enhance glucose metabolism, brown and white adipose tissues are promising therapeutic targets to treat obesity and T2DM. The adipose tissues that are brown and beige have defensive properties. [34]

Managing type 2 diabetes and its possible connection with obesity

The suggested initial strategy for T2DM therapy combines pharmacological medications with effective lifestyle modifications. It is a method for achieving effective metabolic management .[35] A balanced diet and regular exercise are the two essential lifestyle adjustments. Focusing on its primary pathophysiological abnormalities, pharmacological treatment is also available for insulin resistance and manifest diabetes mellitus.[36] Treatment should aim to achieve glycemic control and prevent or decrease weight gain. [37]

1. **Insulin Sensitizers:** can reduce insulin resistance in people with T2DM. Years before hyperglycemia and the clinical genesis of diabetes, the T2DM period's early defect, poor insulin responsiveness (leading to insulin resistance), began. In addition to increasing insulin sensitivity, insulin sensitizers benefit metabolic abnormalities linked to type 2 diabetes (T2DM), such as poor lipid metabolism and dangerous atherosclerotic vascular processes.

- One of the most often prescribed oral antihyperglycemic drugs is biguanides Metformin (dimethyl biguanide) is the most common biguanide used to treat non-insulin-dependent T2DM. Metformin's effects are linked to decreased hepatic glucose synthesis, enhanced sensitivity to insulin in peripheral tissues, and lowered fasting insulin levels.[38] The mitochondrial regulation of hepatic gluconeogenesis causes lower cell energy levels and gluconeogenesis. According to theory, metformin's positive effects on insulin receptor expression and tyrosine kinase activity can reduce insulin resistance .[39] New research indicates that the hypothalamus appetite-regulating centers are modulated in metformin-associated weight loss.[40]

- Another oral antihyperglycemic drug is Thiazolidinediones, which lower blood sugar levels, enhance beta-cell function, and reduce insulin resistance (particularly in adipose and liver tissues). Additionally, the use of these substances has been linked to decreased levels of circulating free fatty acids, anti-inflammatory properties, and a reduced risk of cardiovascular illnesses.[41] The nuclear transcription factor PPAR, which is mainly present in adipose tissue and is involved in metabolizing glucose, lipids, and proteins, activates these benefits. Weight gain is yet another well-known adverse consequence. Disturbances in the distribution of adipose tissue are thought to be a possible cause of weight gain .[42]

2. **Insulin Secretagogues:**

- Sulphonylureas are sulphonamide derivatives with an affinity for the sulphonylurea receptor on pancreatic cells. Without relying on glucose, they

directly affect cells that trigger insulin release. In the most advanced stage of T2DM, however, individuals most likely do not manufacture insulin from the malfunctioning pancreas .(43) Sulphonylureas bind to the transmembrane sulphonylurea receptor (SUR-1), a regulatory subunit of ATP-sensitive K+ channels, which causes the channels to close and release pre-formed insulin. Elderly adults, people using several drugs, people with poor renal function, and people with liver illness are more likely to experience hypoglycemia. Additional adverse effects include weight increase (1-4 kg during six months). (44)

- Glinides have a quick onset but a brief activity period. They bind to the pancreatic receptor and control the closing of K+ channels in these cells as sulphonylureas. They do not bind as strongly to the sulphonylurea receptor 1 binding site as sulphonylureas do, and they dissociate from this receptor more quickly. Glinides, commonly known as "short-acting type insulin secreta-gogues," primarily regulate blood sugar levels after meals. Weight increase with glitinide therapy is consistent with that from sulphon-ylurea therapy .(45)

3. **Incretin Therapies:** proglucagon hormones produced by small intestine cells**.** By interacting with the highly expressed G-protein-coupled receptors on islet cells and blocking ATP-sensitive K+ channels, one can induce insulin release from pancreatic -cells. They also promote neogenesis and cell proliferation in various ways while lowering apoptosis. They also prevent pancreatic cells from secreting glucagon. Several substances, mainly glucose and carbs, can impact how incretins work. Due to their widespread expression in several cells and tissues, GLP-1 and GIP receptors have indirect metabolic effects. (46)

*(GLP-1R) GLP-1 receptor One of the medications affecting the endogenous incretin hormone, GLP-1, is an agonist. These drugs can also alter cell dysfunction, prolong stomach emptying, and promote satiety. They can also suppress the sec-retion of glucagon and hepatic glucose synthesis. The initial blood glucose level can impact the reduction in blood sugar that GLP-1 receptor agonists cause. (47) Emerging new combination anti-obesity drugs that target GLP-1 agonism serve as a baseline for future pharmacyological treatments for obesity. (48)

* Orally used incretin mimics are called dipeptidyl peptidase-4 inhibitors. They stop the process that degrades GLP-1, known as Dipeptidyl peptidase (DPP)-4, bringing GLP-1 back to physiological levels .(49) In addition to delaying stomach emptying, increasing levels of active GLP-1, lowering levels of postprandial glucagon, and decreasing food intake, DPP-4 inhibitors are glucose-lowering medications. They imitate many of GLP-1's functions, including maintaining cell mass .(50) DPP-4 inhibitors typically do not affect weight, while they have been associated with a small amount of weight loss .(51)

4. **SGLT2 Inhibitors:** A class of medications used to decrease blood sugar called sodium-glucose cotransporter 2 (SGLT2) inhibitors prevent the reabsorption of glucose by the kidneys (52) The renal tubules reabsorb all filtered glucose, and SGLT2 is responsible for more than 90% of this process. The reabsorption process is inhibited by SGLT2 inhibitors, which cause an increase in the excretion of glucose through the urine .(53) These medications can normalize the lipid profile, minimize renal problems, improve cardiova-scular system performance, and control blood glucose levels. They could be utilized by T2DM patients alone or in addition to other antidiabetic medications (particularly metformin).(54) If sufficiently significant lifestyle adjustments are made and closely monitored in the T2D population using SGLT2 inhibitors, better weight control may be attained. (55)

Conclusion

Even though T2DM is a complex disease, a positive energy balance, mainly brought on by increased energy intake and decreased physical activity, which leads to overweight and obesity, is the main risk factor for T2DM. Obesity and T2DM significantly impact early mortality, condition of life, associated

persistent vascular problems (in the case of T2DM), overweight-associated concurrent illnesses, and the global healthcare sector, whether they exist alone or together as "diabesity." Knowing the therapeutic and causal interactions between these two disorders is crucial.

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