GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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The role of stress, sleep, and depression in obesity-related Type 2 Diabetes

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GSC Biological and Pharmaceutical Sciences, 2025, 32(01), 036-043

Publication history: Received on 25 May 2025; revised on 01 July 2025; accepted on 04 July 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.32.1.0263

Abstract

Type 2 diabetes mellitus (T2DM) affects a large population worldwide. T2DM is a complex heterogeneous group of metabolic disorders including hyperglycemia and impaired insulin action and/or insulin secretion. T2DM causes dysfunctions in multiple organs or tissues. Current theories of T2DM include a defect in insulin-mediated glucose uptake in muscle, a dysfunction of the pancreatic β-cells, a disruption of secretory function of adipocytes, and an impaired insulin action in the liver.

There is increasing scientific evidence regarding the role of obesity and overweight in type 1 diabetes. Weight gain may be considered as a complication of insulin treatment but also reveals significant pathophysiological impact on various stages of the disease. Depression and stress also plays an important role in the pathogenesis and treatment of obesity and type 2 diabetes (T2D). However, its relevance is frequently unrecognized by clinicians and researchers. The purpose of this review is to present a critical analysis of the evidence linking depression and metabolic disorders and to highlight the practical implications of this complex relationship. Evidence obtained from epidemiological, basic, clinical and controlled studies demonstrate that the association goes beyond a random phenomenon. In this review we also highlight evidence that supports the hypothesis that reduced sleep duration may be part of the behavioral modifications that played a role in the development of the current epidemic of obesity and diabetes

Keywords: Diabetes type 2; Obesity and Diabetes; Sleep disturbance; Depression; Diabetes and depression

1 Introduction

About 150 million individuals worldwide are thought to have diabetes, and in the next 20 years, this number is predicted to double[1]. Type 2 diabetes mellitus, or T2DM, accounts for 90–95% of all instances of diabetes in North America and affects 20% of people over 65 [1]. In several nations, T2DM has been funded with between 5 and 10% of the overall health care budget. Serious side effects from type 2 diabetes might include blindness, sluggish wound healing, vascular disorders, and renal failure. Here, we go over the main animal models of type 2 diabetes as well as its pathophysiology. A disturbed metabolism characterized by unusually high blood glucose levels (hyperglycemia) is commonly referred to as diabetes mellitus [2].The two most common forms of diabetes are type 1 diabetes (diminished production of insulin) and type 2 diabetes (impaired response to insulin and β-cell dysfunction). Both lead to hyperglycemia, excessive urine production, compensatory thirst, increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism.

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Insulin is the primary hormone that controls the uptake of glucose from the blood into most cells, including skeletal muscle cells and adipocytes. It is also the primary signal for the conversion of glucose to glycogen for internal storage in the liver and skeletal muscle cells. Type 2 diabetes is a complex heterogeneous group of metabolic conditions that are characterized by elevated blood glucose levels due to impairment in insulin action and/or insulin secretion [3]. Physiologically, the pancreatic β-cells continue to synthesize insulin regardless of blood glucose levels; it is stored in vacuoles and released when triggered by an elevation of blood glucose levels. A drop in the blood glucose level results in a decrease in release of insulin from the β-cells and an increase in release of glucagon from the α-cells, which stimulates the conversion of glycogen to glucose. Following an overnight fast, glucose is largely produced by glycogenolysis and gluconeogenesis. There are three key defects in the onset of hyperglycemia in T2DM: increased hepatic glucose production, diminished insulin secretion, and impaired insulin action [4].

2 Obesity and type 2 diabetes

Overweight and obesity are very strongly correlated with T2D. Obesity is the most important culprit of insulin resistance, which appears early in the disease, and is primarily compensated by hyperinsulinemia.1, [5 -6] Obese children who are overweight, tall, and have a large waist circumference are more likely to have insulin resistance. [7] Obesity is linked, among other things, to the early adiposity rebound around age three, which has been demonstrated to raise body mass index (BMI) during adolescence. 5. T2D develops when insulin insufficiency and obesity coexist. [5] Since the outset, obesity, peripheral insulin resistance, ethnic minority populations, and a family history of T2D have all been linked to the rising percentage of new onset T2D researchers. [8] According to the World Health Organization's 2002 STEPS study, the prevalence of obesity was 54.8% and T2D was 21.5%. In 2013, the same poll found that 45.8% of people had T2D. In 2030, it is estimated that 552 million people in the world could suffer from T2D.[9] The onset of T2D occurs mostly in adulthood. Among children and young adults, T2D develops most often during the second decade of life and in the middle to late puberty, [5, 10]During puberty, hormone secretion is increasing and causing physiological insulin resistance.[11]

In a meta-analysis from the United States and Europe comparing obese people and those with normal weight, obese men had a 7-fold higher risk and obese women a 12-fold higher chance to develop T2D.[9] A considerable longitudinal study from the United Kingdom was examining 369 362 participants between 2 and 15 years old.[13] Patients who had T2D were mostly obese (47.1%) compared with individuals with normal BMI (4.33%).[13] The frequency of T2D among overweight and obese people increased from 6.4 persons per 100 000 in 1994-1998 to 33.2 in 2009-2013.[13]The same observations come also from other countries: In Europe, 50.9% to 98.6% of people with T2D are obese, and in Asia—56.1% to 69.2%. In American Indian and Alaska Native adults, the percentage of obesity among T2D patients rose by 58% between 1976 and 20.In a study performed in Iraq in 2007, it was proven that among all anthropometric variables, waist circumference is the most sensitive predictor for T2D.[7]Other studies showed that the distribution of fat tissue is the crucial factor to develop insulin resistance, independently of the stage of obesity.[10, 14] The authors compared obese adolescents with a similar rate of adiposity, and those with impaired glucose tolerance (IGT) were more insulin resistant than adolescents with normal glucose tolerance. Furthermore, those with IGT had an increased intramyocellular lipid content, and dilated visceral and reduced subcutaneous fat deposition.10 Ebe D'Adamo and co-authors found that children with high proportion of visceral fat and limited abdominal subcutaneous fat are more insulin resistant and they have higher plasma glucose in the second hour of the glucose tolerance test. It has been also noticed that the ectopic fat deposition in the liver of obese patients is a very important marker of insulin resistance and glucose deregulation.[10]

3 Depression and its connection to obesity Diabetes type 2

Major depressive disorder (MDD) is among the five leading causes of years lived with disability according to the Global Burden of Disease 2017 Study [15]. It is among the twenty most common diseases regardless which world region is studied. Prevalence of depression, obesity, and type 2 diabetes has increased in parallel at an accelerating rate among children, adolescents and adults worldwide 2, 3. Globally in 2014, overweight affects about 1.9 billion adults, obesity more than 600 million [16]In 2003, Stunkard and colleagues conducted a comprehensive evaluation of the relationship between obesity and depression [17]. They understood that the association was complicated. The authors suggested a structure made up of moderators and mediators to ensure a fair evaluation. They characterize mediators as factors that serve as a link between the causal relationship between these two situations, and moderators as "variables on which the obesity-depression covariation is conditional." As moderators, they take into account factors including gender, socioeconomic position, negative childhood experiences, the degree of depression, the degree of obesity, and other gene-environment interactions.In our opinion, age is another variable to be considered in this group. In contrast, eating and physical activity, teasing, disordered eating, and stress were identified as the mediators of the association. The

interaction between moderators and mediators explains the positive [18], negative 12, 13, or, even neutral [19] results informed in cross-sectional studies for the association between depression and obesity. Longitudinal studies are the best source of information since the bidirectional relationship could be assessed. Only through the implementation of longitudinal studies with a pre-specified population stratification is possible to control the robust confounding effect of the moderators. The model proposed by Stunkard is useful to identify the areas that are potential targets for intervention Depression and obesity raise the chance of developing T2D and other chronic illnesses. Compared to those with normoglycemia, depression is twice as prevalent in T2D patients [20], and depression at baseline raises the likelihood of T2D by 37–60%. Depression affects 46–63% of Mexican T2D patients 25, 26, 27; associated characteristics include females, years of diagnosis >15, and occupation, civil state, and education [21]. According to a Mexican study, the country's social and economic transformations over the past few decades have significantly changed Mexicans' way of life. Many of the mediators that link obesity, depression and T2D are now common in low/medium income countries (i.e. migration, living in urban settings, social isolation, lower education and income, aging, low consumption of fruits and vegetables, high intake of fast food, alcohol and soft drinks, long periods of time in front of a screen, physical inactivity). Therefore, the study of the Mexican case is a potential source for reporting novel evidence to the field.

All three conditions have a polygenic nature. Contrary to the multiple associations reported for obesity and T2D, few positive findings have been reported for depression. Some of the genetic variants associated with obesity or T2D are shared with other clinical outcomes including depression. Twelve percent of the variants linked to obesity have been associated also with depression in case controls studies [22]

Another approach to explore the common genetic background between depression and metabolic disorders is to search for gene × environment interactions (GXE). This approach was proposed by Caspi and coworkers [23]. They reported that a polymorphism in the promoter of the serotonin transporter gene SLC6A4 modulates the incidence of depression in subjects exposed to stressful life events.

As described in the following paragraphs, serotonin is a major determinant of satiety. Although the interaction between the polymorphisms in SLC6A4 and depression is still under debate, these findings suggest that serotonergic pathways may play a role both in depression and feeding behavior.

Serotonin is a neurotransmitter implicated in several mechanisms in which depression, T2D, and obesity converge: mood regulation, satiety, insulin and leptin action, carbohydrate metabolism and inflammatory cytokines. A decreased serotonergic tone is present in both depression and metabolic disorders. Serotonin has an inverse relationship with food intake [24].

The interaction between depression and the obesity-related complications (i.e T2D) has raised the attention of multiple research groups. Depression is linked with poorer behavioral management of diabetes (i.e., greater BMI and waist circumference, less physical activity) and poorer glycemic control (i.e., higher fasting glucose, HbA1c) [25] Depression is associated lower insulin sensitivity (M value: 1.8 ± 0.9) in comparison to healthy controls (M value: 3.4 ± 1.7). This abnormality is partially reverted when depression is treated [26]. In a group of 277 Peruvians with T2D, depression increased the probability of having poor glycemic control (HbA1c > 7-vs. >7%) (Prevalence ratio (PR) = 1.32; 95% CI 1.15–1.51) [27]. In a retrospective one year follow up cohort study from Colombia, depression was associated with poor metabolic glycemic control (OR 4.2, 95%CI 1.08–16.4) [28]. In another study, Mexican patients with early onset T2D, depression scores correlated positively with fasting glucose and HbA1c levels [29] The Pathways Epidemiologic Follow-Up Study is a prospective cohort study aiming to determine the impact of depression in patients with T2D in primary care. Results showed that severity of depression was associated with increased risk of retinopathy (OR 1.03, 95% CI 1.002–1.051) [30] In addition, an association between depression and incident diabetic foot ulcers (adjusted HR 2.00, 95% CI 1.24–3.25) has been reported [31]. Several studies confirm the association with macrovascular complications as well. Patients with major depressive disorder (MDD) and T2D were at 82% increased risk for myocardial infarction (HR 1.82 [95% CI 1.69–1.97]) compared with patients without depression . In a systematic review of 16 studies, it was concluded that depression is associated with ∼1.5 fold increased the risk of any cause of mortality. Depression increased the risk of cardiovascular mortality by 39% (HR = 1.39, 95% CI = 1.11–1.73) in patients with T2D ([32].

Physical activity plays a significant role in T2D, obesity, and depression. Inactivity increases insulin resistance, which increases T2D risk . Inactivity is a representation of a self-neglect behavior. Depression incidence is higher among inactive subjects (16.5%) compared with active subjects (10.6%) in a Mexican sample [33]. Recently, physical activity has been highlighted as a major contributor in the relationship between stress, depression, and obesity in women, the most vulnerable group [34]. Exercise is one of the few interventions that have a positive effect in both depression and obesity.

Physical activity is important for T2D, obesity, and depression; inactivity raises insulin resistance, which raises the risk for T2D; inactivity is a sign of self-neglect; in a Mexican sample, the incidence of depression was higher among inactive subjects (16.5%) than among active subjects (10.6%); in the relationship between stress, depression, and obesity in women, the most vulnerable group, in recent years, physical activity has been identified as a major contributor [33], and exercise is one of the few interventions that has a positive effect on both depression and obesity.

4 Stress and its relation to Diabetes type 2

The hypothalamic-pituitary-adrenal (HPA) axis is one of the main systems which, in concert with the sympathetic nervous system (SNS), is activated in acute stress situations and is thus defined as the stress axis [35].

When chronically activated or dysregulated at central or peripheral level, it can affect the individual's health. In fact, through its action on the neuroendocrine, metabolic and immune systems, chronic stress can contribute, especially in vulnerable individuals, to the development of several diseases, including obesity (OB) and diabetes (DM) [36].Long-term stress exposure and the glucocorticoid (GC) release that follows can alter the expression of several genes related to cellular pathways that are essential for the body's intermediate metabolism. Adiposity, insulin resistance, lean mass loss, and coagulation problems that lead to hypercoagulability, dyslipidemia, hypertension, and an increase in the production of inflammatory cytokines are all linked to these changes [36]. Subjects with abdominal OB, metabolic syndrome (MS), or type 2 diabetes (T2DM), as well as those with depression and alcoholism—the so-called "pseudo-Cushing's" conditions—are frequently described by the Cushingoid phenotype, which aptly captures these changes [37–38]. It should be mentioned that persistent hypercortisolism may not be the primary factor influencing the Cushingoid phenotype brought on by chronic stress, but also by changes in corticosteroid-binding globulin levels, GC receptor sensitivity in peripheral tissues and by the activity of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), a key enzyme in the peripheral GC metabolism [37-38]. These alterations are also associated with a kind of 'genetic programming' of the HPA axis that occurs in the fetal and perinatal period , influencing the activity of this axis in adulthood and promoting the onset of OB and MS [39].

The relationship between stress, inflammation and AT has been a growing subject of interest in recent years. Considerable data indicate a potential role of inflammation and increased levels of cytokines, produced by both immune cells and adipocytes, in the pathogenesis of MS and T2DM [40], Furthermore, acute and chronic stress can exacerbate or worsen metabolic conditions by supporting an inflammatory state.

AT has traditionally been divided into two types, white AT (WAT) and brown AT (BAT), based on tissue color, though cytological, biochemical and functional differences also exist. A third type of adipocyte, beige or brite adipocyte, has similar characteristics to BAT, although it differs in developmental origins and body distribution [41].

If AT becomes insulin resistant, the capacity of insulin to suppress adipocyte lipolysis and reduce serum levels of FA and glycerol is impaired. This results in a sustained exposure of liver and muscle to high levels of FA and a further ectopic uptake and storage of lipids in these tissues. Ectopic lipids impair insulin signaling, and thus insulin resistance in adipocytes through increased lipolysis may play a major role in whole-body insulin resistance [42].

A relationship between IL-6 and insulin resistance has been described in OB and MS, although data are not consistent. Circulating concentrations of IL-6 and PCR are increased in subjects with OB and are predictive of T2DM in predisposed subjects. IL-6 production from liver and tissue correlates with and promotes insulin resistance, while IL-6 produced by skeletal muscle has a protective effect [44]. Hyperglycaemia is known to trigger an inflammatory process in pancreatic insulae and to facilitate β-cell apoptosis. This pro-apoptotic mechanism is up-regulated by the glucose-induced increase in IL-1β through its stimulating effect on the 11β-HSD1 enzyme [45].

Repeated stress induces increased levels of IL-1b and other inflammatory cytokines in subcutaneous WAT. This impaires its regular lipogenesis and adipogenesis functions, thus resulting in impaired insulin signalling and a shift of circulating lipids toward visceral adipose tissue with subsequent development of visceral obesity [45].

5 Sleep problems in patients with Diabetes type 2

Lack of sleep is associated with a wide range of adverse health outcomes, including obesity, cardiovascular disease, depression, poor academic achievement and reduced quality of life/well-being. [46]

The mechanisms that underlie these associations are not fully The mechanisms that underlie these associations are not fully understood; however, insufficient sleep is associated with insulin resistance, increased food intake and impaired glucose tolerance.[50] The mechanisms underlying the association between long sleep duration and increased T2D risk are more speculative and may be associated with other health problems

As for obesity risk, there is evidence for associations of both short sleep and long sleep with an increased risk of T2DM . Very different mechanisms are likely to be involved and the present review will focus on short sleep only and on the recent and best-documented studies.

Several prospective studies have investigated the link between short sleep duration (SSD) and the development of type 2 diabetes mellitus (T2DM). A meta-analysis by Cappuccio et al. (2010), which included ten studies published between 2003 and 2007, found that short sleep was associated with a higher risk of incident diabetes, with a pooled odds ratio (OR) of 1.28 (95% CI: 1.03–1.6). Importantly, there was a significant sex difference: men had an OR of 2.07 (1.16–3.72), while women had an OR of 1.07 (0.90–1.28). Difficulty initiating and maintaining sleep also predicted diabetes onset.[51]

Since that meta-analysis, additional prospective studies have expanded the evidence base. Chaput et al. (2009) studied 276 participants from the Quebec Family Study over six years, using oral glucose tolerance tests (OGTT) to detect impaired glucose tolerance (IGT) and T2DM. They found that those sleeping ≤6 hours per night had an adjusted relative risk (RR) of 2.78 (1.61–4.12) compared to those sleeping 7–8 hours. Although adjusting for BMI and other obesity measures weakened the association, the risk remained significant, suggesting that obesity partially mediates the link between short sleep and diabetes.[51] Similarly, the Western New York Health Follow-up Study observed about 900 nondiabetic participants over six years. This nested case-control study compared 91 individuals who developed impaired fasting glucose (IFG) to 273 matched controls. Short sleepers (<6 hours) had a threefold increased risk of developing IFG. However, when insulin resistance (measured by HOMA-IR) was factored into the analysis, the association between short sleep and IFG was no longer significant, implying that insulin resistance partly explains the relationship.[51]

The NIH-AARP Diet and Health Study included 164,399 nondiabetic participants and 10,143 who developed diabetes after 2000. It found that both SSD (<5 hours) and daytime napping (≥1 hour) were independently associated with an increased risk of T2DM, even after adjusting for various health, behavioral, and socioeconomic factors. Notably, longer daytime napping was linked to higher diabetes risk in a dose-response manner across different night sleep durations. Although adjusting for BMI and physical activity weakened the association, the risk remained noteworthy. This study was among the first to prospectively identify daytime napping as an independent risk factor for T2DM, whereas earlier cross-sectional studies could not establish causality. The researchers suggested that napping might reflect poor sleep quality or conditions like obstructive sleep apnea (OSA) and depression, both associated with higher diabetes risk. Ethnic differences in sleep duration and diabetes risk have also been explored. In the Insulin Resistance Atherosclerosis Study (IRAS), Beihl et al. examined African-Americans (AAs), Hispanics, and non-Hispanic whites (NHWs). NHWs had the longest average sleep duration (7.1 hours), followed by Hispanics (6.8 hours), and AAs (6.3 hours). A significant interaction between short sleep and race/ethnicity was found: short sleep predicted diabetes in NHWs and Hispanics but not in AAs, even after adjusting for multiple variables.[51]

An Italian study involving 1,282 patients over six years examined predictors of obesity and fasting hyperglycemia (including IFG and diabetes). Among 979 participants with normal fasting glucose at baseline, sleep duration predicted the incidence of obesity but not fasting hyperglycemia after adjusting for various confounders. The authors noted that sleep restriction appears to impact post-challenge glucose levels more than fasting glucose, based on consistent findings from laboratory studies.

In summary, SSD and poor sleep quality are consistently associated with an increased risk of developing T2DM and related conditions like IGT and IFG. Obesity and insulin resistance appear to mediate these relationships to varying degrees. Additionally, daytime napping, race/ethnicity, and sex differences play significant roles in modifying this risk. These findings highlight the complexity of the relationship between sleep patterns and diabetes risk and suggest the importance of considering sleep habits as part of diabetes prevention strategies.[51]

6 Conclusion

In fact, through its effects on the neuroendocrine, metabolic, and immune systems, chronic stress can contribute, especially in vulnerable individuals, to an altered biological and behavioral condition, characterized by epigenetic changes in cellular pathways crucial to the body's glucose and lipid metabolism and a release of inflammatory cytokines.

Prolonged depression, stress, and/or inadequate regulation of stress can result in a condition of chronic hypercortisolism or, in some cases, an inadequate cortisol response to stress, which increases adiposity, insulin resistance, and type 2 diabetes

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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