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Research Article

### STRESS AND TYPE 2 DIABETES

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#### Abstract:

**Introduction:** Type 2 diabetes (T2D) is a group of medical diseases that are characterized by the presence of insulin insensitivity and/or a failure of pancreatic secretion of insulin to make up for this. Diabetes mellitus type 2 it is usually clinically diagnosed following the detection of increased plasma glucose concentrations, which are usually detected in association with increased weight and other metabolic abnormalities such as dyslipidemia as well as endothelial and cardiovascular diseases. The etiologies of diabetes mellitus type 2 are linked to lifestyle or genetics, both of which have been involved to varying degrees to explain racial disparities in diabetes mellitus type 2 prevalence and outcomes. There is solid evidence in the medical literature that shows the importance of conventional (non-psychosocial) predisposing factors for diabetes mellitus type 2. However, despite interventions which are based on these conventional predisposing factors, the incidence of diabetes mellitus type 2 continues to increase.

**Aim of work:** In this review, we will discuss stress and its relation to diabetes type 2.

**Methodology:** We did a systematic search for Stress and Type 2 diabetes using pubmed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

**Conclusions:** This review gives solid evidence to support the proposal that stress-related factors are an important cause of diabetes mellitus type 2 independent of behavioral factors. This review proposes that diabetes mellitus type 2 prevention research would be more effective if (a) the PSR response to psychosocial factors (especially social disparities) was recognized and (b) intervention programs assessed reduction in social disparities as part of a comprehensive approach. Research in this area could be advanced by reframing the research questions for existing datasets or designing new longitudinal studies.

**Key words:** Stress, Type 2 diabetes, Review, physiologic stress response, socioeconomic status, health inequalities, prospective studies.

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**INTRODUCTION:**

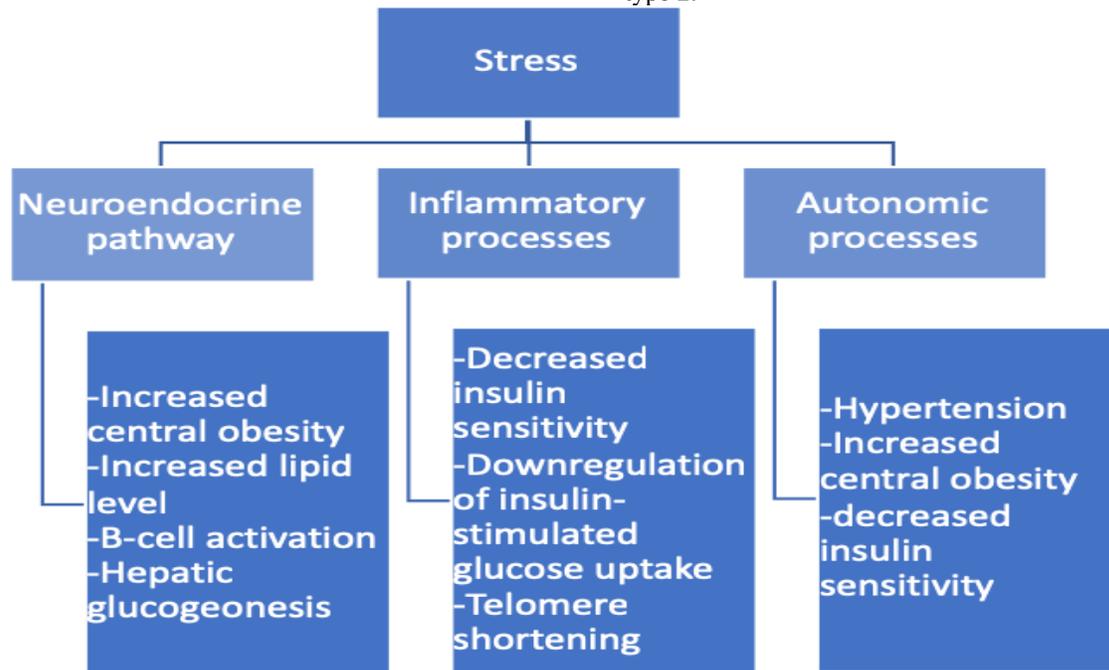
Type 2 diabetes (T2D) is a group of medical diseases that are characterized by the presence of insulin insensitivity and/or a failure of pancreatic secretion of insulin to make up for this. Diabetes mellitus type 2 it is usually clinically diagnosed following the detection of increased plasma glucose concentrations, which are usually detected in association with increased weight and other metabolic abnormalities such as dyslipidemia as well as endothelial and cardiovascular diseases. The etiologies of diabetes mellitus type 2 are linked to lifestyle or genetics, both of which have been involved to varying degrees to explain racial disparities in diabetes mellitus type 2 prevalence and outcomes. There is solid evidence in the medical literature that shows the importance of conventional (non-psychosocial) predisposing factors for diabetes mellitus type 2. However, despite interventions which are based on these conventional predisposing factors, the incidence of diabetes mellitus type 2 continues to increase.

We suggest that chronic activation of the physiologic stress response (PSR) elevates the risk of developing diabetes mellitus type 2. The amount of medical literature examining this relationship is still limited and, conceptually, the association is still largely debated; However, putting more attention on the role of chronic stress factors in the development of diabetes mellitus type 2 can help researchers and physicians develop greater insights and potential new

avenues for management and treatment of diabetes mellitus type 2.

The prevalence of diabetes mellitus type 2, similar to that of heart diseases, elevates significantly with less social position. In the case of heart diseases, solid evidence is present indicating that neither genetic factors nor lifestyle factors could completely explain the presence of socioeconomic status (SES) variations and racial disparities in the disease prevalence and incidence within a certain country or explain variations between different countries <sup>1</sup>. In addition, although heart diseases and diabetes mellitus type 2 have many mutual predisposing factors, only for heart diseases is there important research on the role that stress-related exposure has in the development of this condition. Although there is still some debate of the mechanisms by which difficult life circumstances (associated for example to low socioeconomic status) could impact the health, the most important theories suggest mechanisms such as cumulative exposure to stressors (allostatic load) <sup>2</sup>, perceived lack of control <sup>3</sup>, and stress-related consequences arising from unfavorable social comparisons <sup>4</sup>.

Much of present research explains the mechanisms occurring due to “stress,” but the terminology is not consistent <sup>5</sup>. In this review, we will discuss the most recent evidence regarding stress and its relation to diabetes type 2.



**Figure 1:** Summary of possible effects of stress causing type 2 diabetes

**METHODOLOGY:**

We did a systematic search for Stress and Type 2 diabetes using pubmed search engine (<http://www.ncbi.nlm.nih.gov/>) and Google Scholar search engine (<https://scholar.google.com>). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Stress, Type 2 diabetes, Review, physiologic stress response, socioeconomic status, health inequalities, prospective studies.

**Stress Terminology:** Stress is generally considered <sup>6</sup> as a significant etiology of ill-health and is usually cited as an important contributor to socioeconomic variations in healthcare systems<sup>7</sup>. A general problem is the terminology that is usually used in research. As an example, the term “stress” has been long used to describe “the stimuli that cause a certain state, the subjective feelings of discomfort in this certain state and the responses that occur in an organism to this certain state”<sup>8</sup>; as Cohen and colleagues describe it, stress might have environmental roles, psychological roles and/or biological roles in the development of diseases.

In this review, the term “stressor” will be used to refer to objective events or circumstances that are usually agreed to be stressful (like traumatic life events); “distress” will be used to refer to subjective feelings of discomfort; and PSR will be used to refer to the physiological responses that will occur within an organism that is exposed to stressors. Here we are particularly focused on the PSR and whether it provides a testable hypothesis to associated psychosocial predisposing factors with the occurrence of diabetes mellitus type 2.

**The Stress Mechanism Hypothesis:** As in the case of heart diseases, the original models for the development of diabetes mellitus type 2 were mainly behavioral and posited that, specifically, bad diet and lack of physical activity were primarily responsible for diabetes mellitus type 2. The development of heart disease, however, has been demonstrated to be independently correlated with a variety of stress-related predisposing factors, which include control (meaning the feelings of control of one’s life), hostility, and a history of traumatic life events<sup>9</sup>. Such stress-related predisposing factors, that have been shown to be essential for the development of heart diseases, might also be essential for the development of diabetes mellitus type 2. Many may argue that stress-related predisposing factors can act through behavioral predisposing factors, and indeed most of

the evidence reviewed here uses this explanation. However, as we will discuss later, most of the studies in this review controlled the statistical analyses for many or most of the behavioral risk factors and still detected an impact from stress-related factors. As an example, few studies have demonstrated that risk is significantly higher for those of low socioeconomic<sup>10</sup> or ethnic minority status, proposing pathways that go above the behavioral.

The immediate PSR is not thought to be the main issue affecting health; rather, chronic activation of the PSR is thought to be the main key. The role of the PSR is to keep physiologic homeostasis in normal levels; it consists of an interactive response from the sympathetic adrenomedullary system (SAM) and the hypo-thalamic pituitary adrenal axis (HPA). Initially, the sympathetic adrenomedullary system secretes epinephrine and norepinephrine; if the stressor is sustained, the hypo-thalamic pituitary adrenal axis comes into play. The development of abdominal obesity, an essential risk factor for the development of diabetes, is a major step in the evolution of the condition.

During the early 1990s, Bjorntorp and Rosmond suggested that “neuroendocrine responses to stress-related pressures” may elevate the accumulation of abdominal fat. Their final model suggested that the hypo-thalamic pituitary adrenal axis undergoes reprogramming following chronic stress exposure. The main key is that the stressor exposure may be of enough magnitude or duration to reprogram the hypothalamic pituitary adrenal axis. With the current recognition that diabetes mellitus type 2 is an inflammatory medical condition, the suggested pathophysiology could shift from a behavioral model to a model of repeated episodes of acute or chronic PSR, that stimulates a chronic inflammatory process that produces inflammatory diseases<sup>11</sup>.

Animal models have demonstrated that stress exposures precede the development of chronic subclinical inflammatory reactions. The animals were found to develop central obesity, insulin resistance, dyslipidemia, increased blood pressure, and clinical depression; and they continue to later develop diabetes mellitus type 2, metabolic syndrome, and/or coronary artery disease. In humans, on the other hand, prospective work has demonstrated that higher concentrations of inflammatory markers can predict the development of diabetes mellitus type 2, and even subclinical increases have been demonstrated to be able to predict the development of diabetes mellitus type 2 in the Atherosclerosis Risk in Communities

(ARIC) study cohort <sup>12</sup>, specifically within the first three years <sup>13</sup>.

Cross-sectional studies have demonstrated that patients with diabetes mellitus type 2, when compared to individuals who do not have diabetes mellitus type 2, have generally poorer mental health, are more likely to be depressed, to be alcohol abusers, and to have post-traumatic stress disorder (PTSD). diabetes mellitus type 2 patients report more chronic stressors, higher work distress, and exposure to a higher number of stressful life events. There is a socioeconomic gradient in diabetes mellitus type 2 such that the lower the socioeconomic status, the greater the prevalence of diabetes mellitus type 2 <sup>14</sup>. Above and beyond the socioeconomic status effects, disadvantaged minority populations are generally at greater risk of developing diabetes mellitus type 2 <sup>15</sup>. Most these cross-sectional analyses controlled for the behavioral risk factors for diabetes mellitus type 2 such as obesity, family history, bad diet, and absence of physical activity. However, cross-sectional studies could not be used to detect the direction of causality among variables. It may be, for example, that coping with diabetes mellitus type 2 can make people depressed and less likely to keep necessary health behaviors such as adhering to their diet. They might also tend to view the world negatively and to be more affected by, and likely to report, stressors.

Two longitudinal studies have evaluated the relationship between T2DM incidence and self-reported mental stress levels. One study, assessing only females, detected no association after adjusting for general mental health, where, on the other hand, the other study detected a significant correlation only in men. Because human's ability to accurately describe their personal stress burden has been questioned, some researchers prefer to rely on more objective measures, such as inventories of life events that are generally acknowledged as traumatic or life changing. Moderate-to-severe childhood abuse has been demonstrated to elevate the risk of developing T2DM in a dose response fashion even after adjusting for the conventional risk factors. The US National Comorbidity Study has also shown a significant relationship between childhood neglect and midlife diabetes onset following adjustment for age, sex, race, and socioeconomic status.<sup>16</sup>

Stressful working conditions, objectively assessed from questions about specific stressful characteristics of work, have been associated with a higher risk of later heart diseases. However, there have been very few attempts to extend this work to T2DM. The Japanese have used their system of annual medical

check-ups in large occupational cohorts to assess several aspects of work that are supposed to be stressful. For example, these routinely collected data have demonstrated a higher risk for the development of T2DM in those who worked for extensive overtime and those who found the introduction of new technology stressful. In those studies, the correlations remained even after adjusting for an extensive list of behavioral predisposing factors for T2DM. In the overtime study, the researchers also detected a non-significantly higher risk of T2DM in shift workers when compared with white-collar (non-shift) workers, that might be due to either shift work itself or to the social position associated with it within the occupational hierarchy. Alternating shift work (along with age, body mass index, liver enzymes levels, and absence of physical activity) was linked to a greater risk of T2DM in another Japanese study. A study of the British Civil Service concluded the presence of a two-fold increase of the risk for T2DM in females but not in males exposed to job strain (a measure of work stress).<sup>17</sup>

Overall, objective measures of stressor exposure are linked to a higher risk of developing diabetes mellitus type 2, but sex differences might be present. The limited amount of research into distress (perceived stress) does not propose a higher risk for those perceiving their lives as more stressful.

### **Mental Health and the Development of Type 2**

**Diabetes:** We suggest that severe, rather than mild, mental health problems are a chronic stressor. It is well established that clinical depression and T2DM are comorbid conditions with a bidirectional relationship. Three systematic reviews have found an overall mild, but statistically significant elevation of the risk of developing T2DM in patients with depression. As we think the mental health status has to be severe enough to activate the PSR. We reexamined the nature of the mental health measure. It is important to notice that in one of published reviews the quality of the T2DM diagnosis was assessed, whereas the quality of the depression diagnosis was not. Assessing the evidence cited in published reviews, we noticed that the more clinically robust the instrument used to classify the depression was, the higher likelihood the study was to detect a statistically significant association between T2DM and a previous diagnosis of clinical depression or depressive manifestations. The studies that defined depression on the basis of depressive clinical manifestations collected within a general mental health scale were less likely to detect a statistically significant increased risk, although some

did. These findings need to be re-assessed in a full systematic review.<sup>18</sup>

Interactions with socioeconomic status and sex were noted in these studies of depression. Two studies detected an association between the education level (low educational levels) and depression for the higher risk of developing T2DM when compared to those with more education and depression and those with neither risk factor. Again, two studies also found sex differences, reporting an association of T2DM with depression in men but not in women.<sup>19</sup>

In conclusion, there is enough evidence from prospective studies to say that depression can lead to T2DM, with only a small risk of the reverse (T2DM elevating the risk for developing depression). Additionally, our review proposes that mild mental health problems are less likely to be linked to an elevation in T2DM risk than more severe mental health problems. The relationship between positive mental health measures and T2DM occurrence requires conducting further thorough investigations.<sup>18</sup>

#### **Effects of Position in the Social Status Hierarchy:**

It is well known that living in poor economic conditions can impact people's health, but it is only within the recent few decades that we have come to know that there is a social gradient in health to the extent that middle-class people have more medical conditions and shorter life expectancies than do people just one step higher in the social hierarchy. Socioeconomic index is the most studied measure of social position. In developed countries, it is classically measured as educational level, annual income, and/or occupational prestige. It has been demonstrated that the prevalence of health-adverse events increases with declining social position. It has also been demonstrated that the latter is linked to higher exposure to stressors like poor social circumstances and psychological challenges. For example, Canadian data have concluded that self-reported chronic stressors ranging from marital issues to neighborhood, job, financial, and life stressors were all more common as income was less.<sup>20</sup>

It has been repeatedly shown in cross-sectional studies that diabetes mellitus type 2 rates are higher with less socioeconomic positions; but it has also been debated, without clear evidence, that having diabetes mellitus type 2 can affect a person's ability to maintain a high social standing. There is a need for conducting of longitudinal studies that shows that having diabetes mellitus type 2 changes a person's

socioeconomic index to provide evidence that supports this view.

The high prevalence and incidence of T2DM in racial minority groups is often attributed to having a poorer lifestyle and lower socioeconomic status. However, several studies have reported higher risk for minorities that have higher educational levels and annual income, and there has been a call to focus more on the stress-related risks of minorities rather than just on their health behaviors. The thrifty-gene hypothesis proposes that some racial groups who have a history of famine have developed a gene that elevates their risk of developing T2DM when present in a non-famine environment. This proposed gene could allow them to fatten more rapidly in times of food abundance, but in modern society this prepares them for a food scarcity that no longer occurs. This hypothesis continues to be used to explain higher rates of T2DM in minority groups, in spite of other researchers' findings that low socioeconomic status can explain most of the relationship in some populations and the fact that many groups at risk have no history of famine or starvation (like Pacific Islanders). Socioeconomic status during childhood has also been associated with the development of T2DM in midlife. A recent systematic review of the effects of early childhood socioeconomic index has found evidence that childhood neglect, trauma, or deprivation elevates the future risk of developing T2DM. As an example, using data from the 1958 birth study, researchers tried to distinguish the impact on T2DM risk of: (a) stressful emotional childhood adversities or experience of neglect; (b) other childhood events, such as material disadvantage; (c) adult health behaviors (tobacco, alcohol abuse, diet, and exercise); and (d) adult socioeconomic status. In a multivariate analysis, only poor-quality parenting was found to be linked, neglect and early childhood adversity was significantly associated with the development of T2DM.<sup>21, 22</sup>

#### **CONCLUSION:**

This review gives solid evidence to support the proposal that stress-related factors are an important cause of diabetes mellitus type 2 independent of behavioral factors. This review proposes that diabetes mellitus type 2 prevention research would be more effective if (a) the PSR response to psychosocial factors (especially social disparities) was recognized and (b) intervention programs assessed reduction in social disparities as part of a comprehensive approach. Research in this area could be advanced by reframing the research questions for existing datasets or designing new longitudinal studies.

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