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Articles

The implications of chronic psychological stress in the development of diabetes mellitus type 2

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Abstract

Indroduction: Diabetes mellitus type 2 is a systemic disease with major negative effects on every organ and this is why the risk factors should be known and limited. In the past, in the majority perception, diabetes was associated especially with dietary factors, but psychological stress seems to be a factor incriminated in diabetes mellitus developement, too.

Material and Method: During the writing of this review, there were used materials selected through search engines such as Pubmed, Web of Science, and Scopus, inserting formula: (diabetes*) AND (type 2 OR type two) AND (stress). The search included articles published in last 20 years with full text in english.

Results and discussions: The complexity of the human body is distinguished through the fact that is biochemically prepared for defying every danger or risk factor by using two major physiological pathways: the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA)

Even if proinflammatory cytokines are usually synthesized as a response of the human body to a certain disease, they can also be increased when a stressor occurs, a fact previously demonstrated. Another cytokine involved in diabetes pathogeny is IL-6 of which contribution to insulin secretion has been intensely researched. Cortisol has a major impact on the stress response, a fact previously demonstrated, but is also a considerable factor in glucose metabolism: it is a hyperglycemic hormone because has a stimulating action on gluconeogenesis and glycogenolysis. Another factor that contributes to diabetes mellitus type 2 pathogeny is the higher level of homocysteine found among people who have suffered chronic psychological stress

Conclusions: The evolution of diabetes mellitus type 2 is severely affected by chronic psychological stress through modifications that occur in normal physiology, such as activation of the sympathetic nervous system, inhibition of the cholinergic pathway, synthesis of proinflammatory cytokines, or hyperproduction of homocysteine. These changes lead to hyperglycemia and insulin resistance, but they can be prevented by stress management procedures and treatment the stress-related diseases.

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1. Introduction

Diabetes mellitus type 2 is a systemic disease with major negative effects on every organ and this is why the risk factors should be known and limited. In the past, in the majority perception, diabetes was associated especially with dietary factors (Johnson et al., 2017) such as excessive intake of glucose, lipids, or obesity (Serván, 2013), leading to continuous stimulation of insulin secretion and, subsequently, to insulin resistance (Pandey et al., 2015).

Being a very complex pathology with multifactorial implications, the causes of diabetes should not be limited to diet-related aspects, but we should also analyze socio-economic factors as psychological stress (Kolb & Martin, 2017). This should be considered a solid part in diabetes pathogeny, a reason being the fact that the diagnostic rate of this disease has decreased to the medium age of forty years and appears more often in younger adults, with a nutritional status maintained in normal parameters (Novak et al., 2013). Psychological stress seems to be a factor that surpasses alimentary diet, the one that was incriminated to develop diabetes mellitus type 2 (van der Horst et al., 2019). Recent studies demonstrated the role of clinical psychological issues in the onset of chronic conditions, serving as well as factors withc count for the maintenance of pathological patterns and habits (Barchetta et al., 2021; Barone et a., 2019; Cuzzocrea et a., 2018; Di Giacomo et al., 2019; Marchini et al., 2021; Martino et al., 2019, 2021a, 2021b; Moroianu et al., 2020; Sheikh et al., 2019; Vicario et al., 2020; Vita et al., 2020). As highlighted by a consistent nranch of studies, factors as illness denial (Dimova et al., 2019; Garay-Sevilla et al., 1999; Goldbeck, 1997; Péres et al., 2007; Silva et al., 2018; Tang & Gao, 2020), chronic stress, adherence and related activational phenomena, (Anderson & Durstine, 2019; Frisone et al., 2021; Hajat & Stein, 2018; Myles & Merlo, 2022a, 2022b; Popoviciu et al., 2022), alexithymia and other relevant dynamics interfer with psychological functioning reflecting the need for interventions.

2. Materials and Methods

During the writing of this review, there were used materials selected through search engines such as Pubmed, Web of Science, and Scopus, inserting formula: (diabetes*) AND (type 2 OR type two) AND (stress). The search included articles published in last 20 years with full text in english. The selection of the articles has taken into account: the accuracy of the data, the topic of the article, the quality of the data and the eligibility criteria presented below. After a fastidious observation, there were selected a number of 49 articles that provided the necessary data for a stringent examination of the selected theme.

2.1 Inclusion criteria

The inclusion criteria were: full English text, article available in extenso, article types: original paper, systematic review, narrative review and metanalysis,

2.2 Exclusion Criteria

The exclusion criteria: only abstract available, full text in other language then English, Clinical cases, editorials, letter to the editor.

3. Results and Discussion

3.1 The effects of psychological stress on the inflammatory system

The complexity of the human body is distinguished through the fact that is biochemically prepared for defying every danger or risk factor by using two major physiological pathways: the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis (HPA) (Irwin & Cole, 2011). Even if there is no impending danger, generally considered, as long as someone's brain perceives an event as stressing, the two pathways will activate, both of them originated from the central nervous system (Eisenberger & Cole, 2012).

The sympathetic nervous system activates immediately after exposure to a stressor (Dickerson et al., 2009) and involves releasing the catecholamines that can induce transcriptional factor NF-kB, which has the effect on immune cells to synthesize proinflammatory cytokines such as IL-6, TNF-α, IL-1β (Bierhaus et al., 2003). There are many studies that identified a major increase of those molecules in the presence of acute stress, especially IL-6, this information being selected from an article that studied a masculine cohort (Lockwood et al., 2016). The finding of S. S. Dickerson et al. shows that social stress is also relevant to the activation of the inflammatory system, a fact proved in the study by the growth of IL-6 on people who were asked to improvise a speech in front of others (Dickerson et al., 2009). The major effect of this modification on normal human physiology is the fact that IL-6 was proved to be an additional activator of the second pathway of stress response- the hypothalamic-pituitary-adrenal axis (Papanicolaou et al., 1998).

Contrastingly, there is noticed that the parasympathetic nervous system has an inhibitory activity on the synthesis of proinflammatory cytokines through the implications of acetylcholine which slows down their production (Johnston & Webster, 2009). The study of L. V. Borovikova et al. has demonstrated that chronic psychological stress inhibits the activation of the parasympathetic nervous system, leading to a small quantity of acetylcholine and an additional activation of cytokines syntesis (Borovikova et al., 2000).

The hypothalamic-pituitary-adrenal axis is the second major pathway of body response to stress and leads to corticotropin-releasing hormone (CRH) synthesis that activates the pituitary gland to synthesize ACTH, a hormone that stimulates the adrenal gland to enhance cortisol production (Gabry et al., 2002). Continuous stimulation of HPA by the stressors can lead to a greater quantity of cortisol, associated with cell resistance to this hormone (Demorrow, 2018).

Another modification on the regular human physiology that occurs with stress is noticed in homocysteine metabolism (Huang et al., 2013). There is a study that identified an association between the onset of depression, a stress-related disease, and a higher level of homocysteine in blood (Kontoangelos et al., 2015), also raised by a hostile behavior (Panagiotakos et al., n.d.).

Summing the information analyzed before, we can observe that chronic psychological stress has considerable effects on human organisms because it modifies standard parameters such as IL-6, TNF-α, IL-1β, cortisol and homocysteine, increasing their levels.

3.2 The role of inflammatory components in the pathogeny of diabetes mellitus type 2

Recent literature data provide insight into the inflammation mechanisms that underlie the pathophysiology of type 2 diabetes, obesity and cardiometabolic syndrome (Suceveanu et al, 2020). Diabetes mellitus is regarded as a proinflammatory state condition that, alongside a high intake of glucose and macronutrients and by chronic overnutrition, lead to obesity and an increase in insulin resistance (Busnatu et al, 2022). Recent studies documented the link between high body mass index (BMI) and diabetes via proinflammatory cytokines, insulin resistance, increased levels of circulating fatty acids, dysregulation of gut microbiota (Suceveanu AI et al.,2018) and impaired cellular metabolism (Dascalu et al, 2021; Serban et al, 2022).

Even if proinflammatory cytokines are usually synthesized as a response of the human body to a certain disease, they can also be increased when a stressor occurs, a fact previously demonstrated (Evans & Whicher, 1993). This aspect is even more dangerous for the normal physiology of the human organism because episodes of psychological stress appear more often and, in certain cases, they can have a continuous character, for longer periods of time, which implies a long-term growth of cytokines levels and stronger damage on organs (Anisman et al., 2008). For example, IL-1β inhibits the function of β-cells, which are responsible for insulin secretion through Fas gene activation. This gene induces cellular apoptosis, causing a reduced quantity of hypolipemiant hormone, resulting in a decreased adaptability to glucose (Donath et al., 2008).

Another cytokine involved in diabetes pathogeny is IL-6 of which contribution to insulin secretion has been intensely researched (Akbari & Hassan-Zadeh, 2018). The study of Suzuki

et al. has demonstrated that IL-6 can stimulate insulin secretion by activating L-pancreatic cell and α-cell to synthesize glucagon-like peptide 1, but also by intensifying the phospholipase C signaling pathway (Suzuki et al., 2011). Additionally, there is noted an intercommunication between a higher level of IL-6 and the patients with insulin resistance (K. Rehman et al., 2017). The possible causes may be the inhibitory effect of IL-6 on the hepatic synthesis of glycogen and the stimulatory action on the glycogen phosphorylase and the lipolysis, resulting in a higher level of blood glucose (Senn et al., 2002).

Cortisol has a major impact on the stress response, a fact previously demonstrated, but is also a considerable factor in glucose metabolism: it is a hyperglycemic hormone because has a stimulating action on gluconeogenesis and glycogenolysis (de Weerth et al., 2003). Cortisol has a direct effect on pancreatic β-cells through the inhibition of insulin secretion, which inevitably leads to an increased blood glucose (Lambillotte et al., 1997). As well, this is accompanied by higher levels of free fatty acids caused by the gluconeogenesis intensification in adipose cells, followed by the lipolysis (Vargatu, 2016). Cortisol can also generate abdominal obesity, especially with visceral manifestations, which is associated with a dysmetabolic syndrome and feedback dysfunction of the hypothalamic-pituitary-adrenal axis (Anagnostis et al., 2009). Due to the fact that psychological stress has a persistent character, hyperstimulation of cortisol synthesis can cause hypercortisolism (Mezuk et al., 2008) and abnormal secretion of corticotropin releasing factor (CRH) (Gragnoli, 2012). CRH is synthesized by the parvocellular neurons from the paraventricular nucleus (PVN) which can be found in the hypothalamus (Aguilera & Liu, 2012). When CRH reaches the pituitary gland through blood flow, it binds the Corticotropin-releasing hormone receptor 1 (CRHR 1) and stimulates ACTH secretion, which leads to cortisol synthesis intensification (Vargatu, 2016). There is a study published in 2002 that demonstrated that CRHR 1 can additionally be found in pancreatic β-cells and has a direct contribution to the amplification of insulin secretion (Bale et al., 2002). Being a continuous stimulation, it can produce further cell resistance to insulin, a fact that makes them ineffective for subsequent spontaneous increases in blood glucose (Saltiel, 2000).

Another factor that contributes to diabetes mellitus type 2 pathogeny is the higher level of homocysteine found among people who have suffered chronic psychological stress. Even if the mechanism is still uncertain, there are studies that statistically demonstrated the correlation between those two components and found out that 82,8% of patients diagnosed with diabetes mellitus type 2 have hyperhomocysteinemia, as well (Devrajani et al., n.d.). For all that, homocysteine is more likely a marker for diabetes severity and its vascular complications such as diabetic neuropathy, retinopathy, and nephropathy (T. Rehman et al., 2020). Macro and microangiopathy are considerable consequences of diabetes because can modify the normal

morphology of vessels by smooth muscle proliferation and vascular matrix degradation caused by oxidative stress and free radicals production which leads to cellular apoptosis of endothelial cells (Welch & Loscalzo, 2009). Among macrovascular complications of diabetes, there is atherosclerosis caused by the metabolization of homocysteine in homocysteine thiolactone, which interacts with low-density-lipoproteins (LDL) and forms aggregates, integrated into atheroma plaque (Packard, 2006). Nephropathy and retinopathy are the most common microvascular complications of diabetes mellitus type 2 and, even if the mechanism is not completely discovered (Ardeleanu et al.,2020), the actual theories are based on endothelial dysfunction caused by the hydrogen peroxidase activated by the increased copper which accumulates after an oxygen-dependent reaction from homocysteine metabolism (Starkebaum & Harlan, 1986).

3.3 The correlation between diabetes and stress-dependent mental disorders

Depression is a multifactorial disease and among its causes is chronic psychological stress (Guze, 2006). The correlation between this illness and diabetes mellitus type 2 is based on the hypothalamic-pituitary-adrenal axis modifications such as cortisol hypersecretion (Katon et al., n.d.). Even though it is difficult to concretely demonstrate the fact that depression induces diabetes, the study of Lloyd et al. confirmed a correlation between them. This statistical analysis showed that 10,6% of diabetic patients had been diagnosed with major depression and 17% with moderate depression (Lloyd et al., 2018). Furthermore, depression treatment seems to surprisingly meliorate the evolution of diabetes by normalizing or decreasing the level of glycated hemoglobin, which is a positive prognosis of this endocrine pathology (van der Feltz-Cornelis et al., 2021), (Pantea Stoian A et al.,2018). There is a similar evolution among patients diagnosed with posttraumatic stress, a disease caused by extended exposure to stressors, because they can additionally be afflicted with diabetes mellitus type 2, but indirectly developed through predisposition to obesity (Scherrer & Lustman, 2019).

3.4 Stress management and diabetes evolution

If previously was demonstrated that chronic psychological stress leads to type 2 diabetes, now we need to analyze how the resolution of stress-related disease can contribute to the evolution of diabetes mellitus. Stress management training has the primary role to increase the quality of life, but also has benefits of reducing the severity of diabetes and preventing its consequences through more efficient control of glycemia (Soo & Lam, 2009). These results are explained by increasing patient's motivation to change their negative behaviors such as smoking and alcohol consumption, to be more cooperative with their pharmaceutical treatment (Zugravu et al, 2012)

, and adopting a more active lifestyle (McGinnis et al., 2005). The study of Scherrer et al. shows that the treatment of depression, stress-related disease, is correlated with a lower glycemic index and an improved resistance to insulin (Scherrer et al., 2019), a fact confirmed statistically by measuring the glycated hemoglobin (Lustman & Clouse, 2002).

4. Conclusion

Even if the risk factors and pathological elements that lead to the occurrence of diabetes mellitus type 2 are known, new data is emerging regarding the influence of psychological issues on this frequent pathology. The evolution of diabetes mellitus type 2 is severely affected by chronic psychological stress through modifications that occur in normal physiology, such as activation of the sympathetic nervous system, inhibition of the cholinergic pathway, synthesis of proinflammatory cytokines, or hyperproduction of homocysteine. These changes lead to hyperglycemia and insulin resistance, but they can be prevented by stress management procedures and treatment the stress-related diseases. In the pathophysiological chain of diabetes mellitus, we have explained the effects of psychological stress on the inflammatory system, the role of inflammatory components in the pathogeny of diabetes mellitus type 2, the correlation between diabetes and stress-dependent mental disorders and the link between stress management and diabetes evolution. In conclusion the data we have gathered suggest the need of new studies that can help in the prevention of some of the cases of diabetes due to psychologic disorders.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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