


Review of the direct and indirect effects of hyperglycemia on the HPA axis in T2DM and the co-occurrence of depression

Palesa Mosili ¹, Bongeka Cassandra Mkhize,¹ Ntethelelo Hopewell Sibiya,² Phikelelani Sethu Ngubane,¹ Andile Khathi¹

To cite: Mosili P, Mkhize BC, Sibiya NH, *et al.* Review of the direct and indirect effects of hyperglycemia on the HPA axis in T2DM and the co-occurrence of depression. *BMJ Open Diab Res Care* 2024;**12**:e003218. doi:10.1136/bmjdr-2022-003218

Received 9 November 2022
Accepted 24 March 2023

ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterized by persistent hyperglycemia which is further associated with hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Several studies have shown that HPA axis hyperactivity is heightened in the chronic hyperglycemic state with severe hyperglycemic events more likely to result in a depressive disorder. The HPA axis is also regulated by the immune system. Upon stress, under homeostatic conditions, the immune system is activated via the sympatho-adrenal-medullary axis resulting in an immune response which secretes proinflammatory cytokines. These cytokines aid in the activation of the HPA axis during stress. However, in T2DM, where there is persistent hyperglycemia, the immune system is dysregulated resulting in the elevated concentrations of these cytokines. The HPA axis, already activated by the hyperglycemia, is further activated by the cytokines which all contribute to a diagnosis of depression in patients with T2DM. However, the onset of T2DM is often preceded by pre-diabetes, a reversible state of moderate hyperglycemia and insulin resistance. Complications often seen in T2DM have been reported to begin in the pre-diabetic state. While the current management strategies have been shown to ameliorate the moderate hyperglycemic state and decrease the risk of developing T2DM, research is necessary for clinical studies to profile these direct effects of moderate hyperglycemia in pre-diabetes on the HPA axis and the indirect effects moderate hyperglycemia may have on the HPA axis by investigating the components of the immune system that play a role in regulating this pathway.

INTRODUCTION

The nervous, endocrine and immune systems work together to maintain physiological homeostasis during stress challenges and inflammation.¹ The hypothalamic-pituitary-adrenal (HPA) axis is one of the physiological systems involved in several homeostatic functions such as glucose homeostasis, stress response and immune response regulation.² One of the ways the HPA axis regulates these processes is through its bidirectional communication with the immune system, where

the HPA axis plays a role in regulating the immune response.³ However, the dysregulation of the HPA axis has been at the center of the much-debated bidirectional occurrence of type 2 diabetes mellitus (T2DM) and depression.⁴⁻⁶ Disruption of glucose homeostasis resulting in hyperglycemia is the common connection between both disorders, as seen in various literature as the cause of the other coinciding.⁷⁻⁹ Nevertheless, T2DM is mainly associated with chronic hyperglycemia and has been shown to result more in the diagnosis of depression than it has been seen in depression causing T2DM.^{5 10 11}

Diabetes is currently a global health burden affecting over 537 million diagnosed and undiagnosed people worldwide.^{12 13} Various complications, such as cardiovascular and chronic kidney diseases, are widely reported and studied in T2DM, while fewer studies have reported that these complications begin in the pre-diabetic state^{12 13}. The term pre-diabetes is defined as impaired fasting glucose (IFG) concentration or impaired glucose tolerance (IGT) with an increased risk of developing T2DM.¹² It has been projected that pre-diabetes affects nearly three times the number of individuals than T2DM.¹³ There is a great need for more research on pre-diabetes and its interaction with various physiological functions that are affected in T2DM, such as the HPA axis. Furthermore, there is a need to look at other systems which regulate the HPA axis, such as the immune system, which has also been shown to be directly affected by T2DM and also indirectly contribute to the occurrence of depression in patients with diabetes.⁴

In this review, we will discuss the direct consequence of hyperglycemia on the HPA axis, as seen in T2DM, and how it results in depression. In addition, the review will also



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Human Physiology, University of KwaZulu-Natal College of Health Sciences, Durban, KwaZulu-Natal, South Africa
²Pharmacy and Pharmacology, Rhodes University, Grahamstown, Eastern Cape, South Africa

Correspondence to
Palesa Mosili;
pmosili@gmail.com

discuss the indirect effects hyperglycemia has on the immune system and the downstream consequences in the functioning of the HPA axis. Furthermore, this review will help demonstrate the need for further research on the effects of moderate hyperglycemia in pre-diabetes on the HPA axis and the immune system in this state within its role in regulating the HPA axis.

BIDIRECTIONAL RELATIONSHIP BETWEEN DIABETES AND DEPRESSION

Diabetes and depression have been shown to have a complex bidirectional relationship.¹⁴ Patients with diabetes are twice as likely to experience depression compared with the general population while diabetes increases the risk of developing depression by twofold.¹⁴ This relationship has been attributed to various biological and psychosocial factors.¹¹ Some of the psychosocial factors may be lifestyle related while others include stressful life events, poor social support and inadequate diabetes self-care.¹⁵ In individuals with diabetes, depression has been associated with higher mortality rates, increased risk of diabetic complications and poor glycemic control.¹⁵ Furthermore, chronic stress associated with diabetes management may contribute to the development of depression.¹⁶ On the other hand, engagement in unhealthy behaviors such as smoking, physical inactivity, and poor diet, which are all well-known risk factors of diabetes, was found to be more prevalent among depressed individuals.¹⁶ There are also overlapping physiological changes associated with depression and those that characterize the onset of T2DM specifically.¹⁷ Oxidative stress was shown to be elevated in individuals with both depression and T2DM.¹⁸ Oxidative stress, which is an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, may contribute to the pathophysiology of both conditions.^{18 19} Impairment of glucose metabolism and insulin resistance by depression may increase the risk of developing T2DM while chronic inflammation of T2DM may contribute to the development of depression by affecting neurotransmitter function and neural plasticity.^{6 20} However, the most common physiological change that contributes to the pathophysiology of both conditions is an altered HPA axis which will be discussed in more detail in this review.

HPA AXIS

The HPA axis is a stress response pathway involving three main components: the hypothalamus, the anterior pituitary gland and the adrenal gland.²¹ Though the response to stress is the primary physiological function of the pathway, it also plays a key role in circadian regulation, glucose homeostasis, and affects immune response and metabolism.^{2 21} Stress, a real or perceived threat to the natural physiological homeostasis of the body, causes an activation of the HPA axis.²² Upon stress stimuli, input from the suprachiasmatic nucleus stimulates the paraventricular nucleus (PVN) of the hypothalamus,

where the neurons found there project to the hypothalamic median eminence or hypophysiotropic neurons, which secretes corticotrophin-releasing hormone (CRH) and consequentially, arginine vasopressin (AVP).^{21 23} Though AVP is predominantly known for its antidiuretic effects when released in the posterior pituitary gland, it is secreted in concert with CRH into the hypophyseal portal blood vessels connecting the hypothalamus and the pituitary gland.^{23 24} On secretion, both hormones stimulate the corticotrophs, endocrine cells of the anterior pituitary gland, to produce and secrete adrenocorticotrophic hormone (ACTH).²¹ ACTH is released into the systemic circulation targeting the zona fasciculata layer of the adrenal cortex.²⁵ Stimulation of the cell layer by ACTH results in the synthesis and secretion of steroid hormones, glucocorticoids (GC; cortisol in humans and corticosterone (CORT) in animals).²⁵ GCs are the vital hormones produced by the HPA axis activity, which mainly mediate the stress response and facilitate various homeostatic regulations, including anti-inflammatory and immunosuppressive effects regulating metabolism.²⁶ GCs bind to glucocorticoid receptors (GR) or mineralocorticoid receptors in peripheral tissues such as the liver and skeletal muscles.^{8 27} The binding of GCs to mainly GRs in the various tissues mediates and promotes the catabolism of carbohydrates, lipids and proteins, increasing energy substrates in circulation, which are used by the different physiological processes and systems to respond to stress.^{27 28} GCs also serve a critical function in the negative feedback of their secretion, as seen in [figure 1](#).²⁹ GCs are lipid-soluble hormones; thus, they can cross the blood-brain barrier (BBB), having access to various tissues in the brain.³⁰ GC concentration in circulation is regulated via a feedback mechanism by the hypothalamus, where the elevated concentration of GCs in circulation increases GCs crossing the BBB.^{29 30} After crossing the BBB, the GCs bind to the receptors of the PVN CRH neurons of the hypothalamus, which results in the negative feedback mechanism by inhibiting CRH secretion.^{21 29} A decreased CRH concentration elicits a minimal stimulus for ACTH secretion in the anterior pituitary gland resulting in decreased ACTH concentration in the systemic circulation.²⁹ A decreased plasma ACTH concentration ultimately results in less GC production and secretion by the adrenal cortex.³¹ T2DM, evidenced by chronic hyperglycemia, has been linked to the dysregulation of the HPA axis and stress response.⁹

HPA AXIS DYSREGULATION IN T2DM AND THE CO-OCCURRENCE OF DEPRESSION

T2DM is characterized by impaired insulin secretion, impaired insulin resistance or a combination of both.³² T2DM has been reported far more common, with more than 90% of diabetes cases being T2DM compared with type 1 diabetes mellitus or gestational diabetes.³³ The metabolic phenotype of T2DM differs in individuals with the disease.^{34 35} Some individuals may have a more

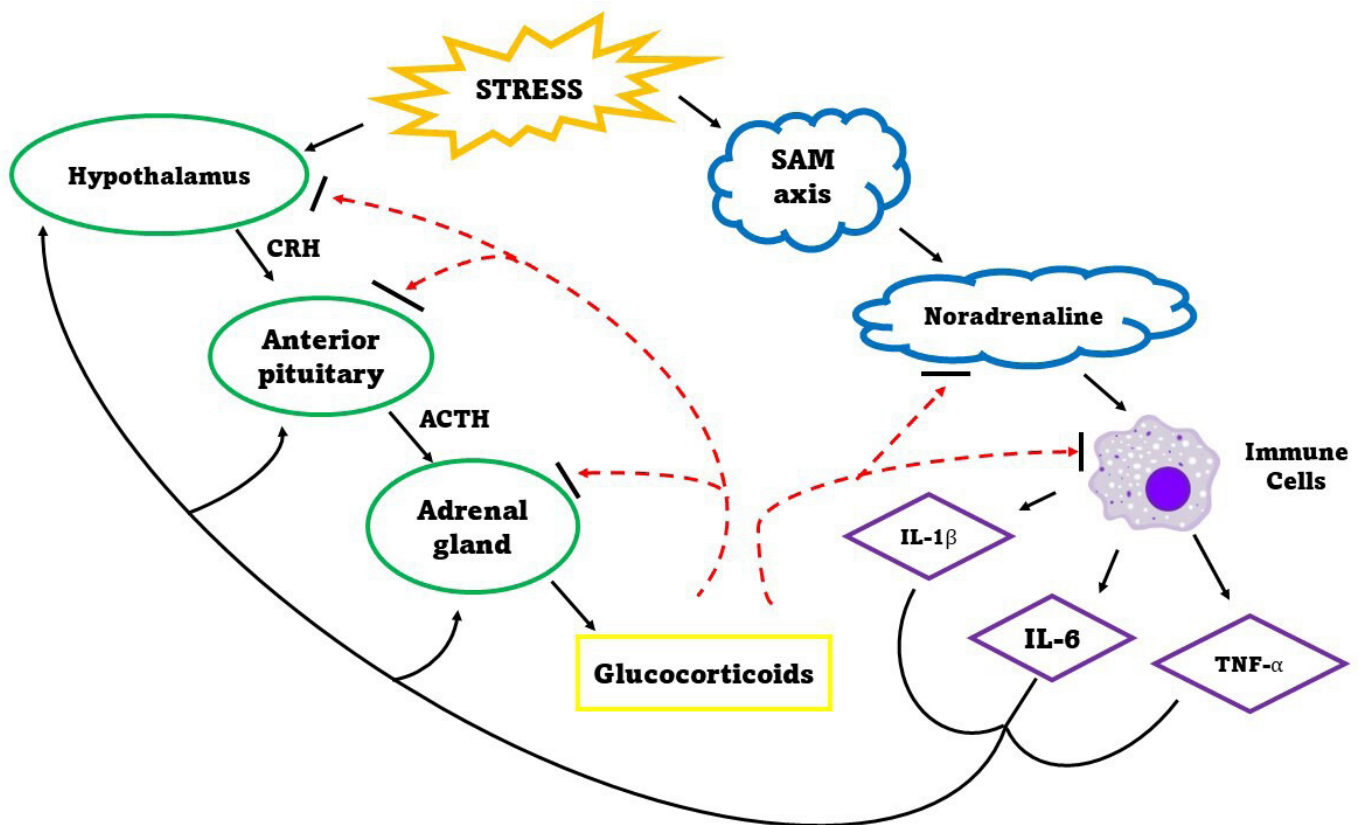


Figure 1 A diagram depicting how the hypothalamic-pituitary-adrenal (HPA) axis and immune response interact during stress: stress activates the HPA resulting in the end product, glucocorticoids (GC). Simultaneously, the sympatho-adrenal-medullary (SAM) axis is activated by stress resulting in the release of norepinephrine (NE). NE activates the innate immune cells, which release cytokines interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). The cytokines activate all three levels of the HPA, resulting in further secretion of GCs. The increase in plasma GCs causes negative feedback regulation of the HPA axis and negative feedback of NE secretion and inhibits further activation of immune cells, decreasing cytokine production and secretion. ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone.

pronounced defect in insulin secretion, while others may have greater insulin resistance.³⁵ However, the individual's metabolic profile may change over time.³⁴ The chronic hyperglycemic state of T2DM causes macrovascular and microvascular damages resulting in secondary complications seen in the eyes, kidney, heart and brain, subsequently increasing the risk of several other diseases.³⁵⁻³⁶ The secondary complications include physiological changes in the functioning of the HPA axis. T2DM is associated with hyperactivity of the HPA axis. HPA axis activity is heightened, as reported in several studies in individuals with glucose intolerance or chronic hyperglycemia.³⁷⁻⁴¹ The heightened HPA axis activity due to elevated ACTH concentrations correlated with the elevated plasma cortisol concentration, which indicated an impaired negative feedback mechanism.³⁹⁻⁴¹ The elevated plasma cortisol concentration is often followed by downstream effects where gluconeogenesis is upregulated, worsening the hyperglycemic state.³⁸ Furthermore, the presence of chronic complications, such as hyperinsulinemia, exaggerates the HPA axis hyperactivity resulting in a dysregulated stress response system, which is further associated with mental disorders, specifically depression, as also seen in T2DM cases.⁴²

Depression is a neurological disorder with symptoms manifested at the psychological, behavioral and physiological levels.⁴³ The pathophysiology of depression is multifaceted, with the dysregulation of the HPA axis being one of the causes of the disorder.⁴⁴ The dysregulation of the HPA axis is limited to depression and is associated with other neurological disorders, such as post-traumatic stress disorder and anxiety, which is sometimes coupled with depression.⁴⁵⁻⁴⁶ The persistent activation of the HPA axis due to chronic stress, a traumatic episode such as neglect, loss of a loved one or even abuse, such as sexual, physical and emotional abuse, can cause impairment of the negative feedback system of the HPA axis.⁴⁷ Impaired negative feedback regulation of HPA axis function is a hallmark of major depression which is reflected by decreased responsiveness to GCs (or GC resistance) as manifested by increased cortisol concentrations seen in various studies.⁴⁸⁻⁴⁹ Chronic hyperglycemia seen in patients with T2DM has been shown to increase the risk and result in the eventual occurrence of a depressive disorder.⁵⁻⁶⁻¹¹ A study showed that individuals who had not experienced severe hyperglycemic events and had not been diagnosed with depression were reported to receive a diagnosis of a depressive disorder

after a severe hyperglycemic event.⁶ Hyperglycemia in T2DM has also been shown to cause dysregulation of the immune response, which is associated with HPA axis dysregulation.⁹

HPA AXIS AND IMMUNE SYSTEM

The nervous and immune systems communicate extensively to regulate the body's homeostasis.^{50 51} One of the ways they communicate is through the HPA axis, with the primary hormone, cortisol/CORT, being the link between the two systems.⁵² The limbic system, mainly the amygdala, forms part of the nervous system that perceives stress and sends the message to the HPA axis, causing its activation.^{46 53} The perceived stress also causes activation of the immune system in preparation for attacking the stressor.⁵⁴ The HPA axis activation increases CORT concentration in circulation. Most cells in the body express GR, including immune cells.⁵⁵ Increased CORT in circulation during a stress response increases the expression of GRs of the different cells of the body, including the immune cells resulting in increased GC-GR binding, thus triggering various responses such as inhibition of the synthesis and secretion of inflammatory cytokines, inhibition of inflammation, and suppression of proinflammatory cytokine expression.^{28 54} As previously discussed, the HPA axis is self-regulatory, with its activity curtailed via a negative feedback mechanism.²⁹ However, the immune system also regulates HPA axis activity via cytokines.⁵⁶ The proinflammatory cytokines, such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), stimulate CORT release by acting at all three levels of the HPA axis.^{56 57} On the other hand, the HPA axis also plays a role in regulating the immune system via GCs by suppressing the further synthesis and release of proinflammatory cytokines.^{56 57}

Immune response during stress

In response to stress, the immune system prepares and protects itself from challenges such as wounds or infection from a stressor that may include injury or pathogen invasion.⁵⁴ The driving force in immune activation due to stress involves the combined effects of the HPA axis, the sympatho-adrenal-medullary (SAM) axis and the parasympathetic nervous system.^{49 54} Stress activates the SAM axis resulting in the release of catecholamines, specifically norepinephrine.⁵⁸ The release of catecholamines causes the stimulation of β 2-adrenoreceptor of the immune cells, which results in the activation of the innate immune response, the body's first line of defense.^{49 58} The role of the innate immune cells is to detect the pathogen and activate an inflammatory response. Activation of the inflammatory response recruits more innate immune cells, including neutrophils and macrophages, which encounter a foreign antigen or pathogen-associated molecular pathogen and respond by producing a variety of cytokines, including IL-1 β , IL-6, and IL-12 along with TNF- α .⁵⁴ The inflammatory response is further

strengthened with the dendritic cell maturation process, followed by antigen presentation and supplementary cytokine production.⁵⁹ Under pathogen invasion, the activation of the inflammatory response elicits the more specific and memory-forming adaptive immune response.^{49 54} Lymphocytes, the key effector cells of the adaptive immune response, are activated.⁵⁹ However, in acute stress, there is an underlying assumption that only the innate immune response is required and capable of effective immunoprotection on a short time scale and that suppressing adaptive immune function would result in more energy available to the innate immune system.⁶⁰ Apart from eliciting an inflammatory response, the cytokines, IL-1 β , IL-6 and TNF- α , act on all three levels of the HPA axis to increase the secretion of CORT.^{23 54} When plasma CORT increases, this results in negative feedback regulation of the immune system by decreasing all three-cytokine production and ultimately exerting an immunosuppressive response to regulate the immune system homeostasis.^{49 54}

Among all the different cytokines and proinflammatory markers, IL-1 β , IL-6 and TNF- α have the most modulating effects on the HPA axis activation associated with an immune response, as seen in [figure 1](#) and summarized in [table 1](#).⁴

Interleukin-1 β

Cytokines are soluble mediators of the immune system aiding in cell-to-cell communication during an immune response.⁶¹ ILs, specifically, are cytokines that interact with leukocytes.⁶¹ IL-1 β , a proinflammatory cytokine, is a major mediator of innate immune response and its actions are tightly balanced.⁶² It is produced by various immune cells, including mononuclear phagocytes, neutrophils, endothelial cells, and microglia in the brain.⁵⁴ On recognition of bacterial endotoxins and pathogenic agents by pathogen recognition receptors, IL-1 β is synthesized and secreted. The production of IL-1 β has a vital role in the induction and maintenance of the adaptive immune response by promoting increased expression of IL-2 receptors and IL-2 secretion, which impacts T cell differentiation and B cell activation.⁶³ During stress stimulation, IL-1 β interacts with neurotransmitters and neuropeptide regulatory systems, making IL-1 β a critical mediator of the adaptive stress response.⁶⁴ IL-1 β has also been shown to directly affect the adrenal gland, influencing the release of GC.⁶⁵

Interleukin-6

IL-6 is a multifunctional proinflammatory cytokine that plays vital roles in immune regulation, hematopoiesis, oncogenesis and regulation of the HPA axis.⁶⁶ In response to injury or infections, IL-6 is rapidly synthesized and secreted by innate immune cells such as macrophages, dendritic cells as well as mast cells, and activates the immune response.^{61 67 68} Its role in the immune response stimulates B cell differentiation into immunoglobulin-producing plasma cells during the innate immune

Table 1 Summary of the immune cytokine function in the HPA and its contribution in T2DM and depression

Cytokine	Target on the HPA axis	Effect on the HPA axis	Contribution in T2DM and depression
Interleukin-1 β (IL-1 β)	Adrenal gland	Influence the release of GC.	Destruction and loss-of-function insulin-producing β cells of the pancreas. Critical mediator of the adaptive stress response where overproduction dysregulates, causing maladaptive sickness response.
Interleukin-6 (IL-6)	IL-6 receptors in the hypothalamus	Regulate CRH production and stimulate corticotrophs and ACTH release in CRH deficiency.	Involved in brain signaling, resulting in maladaptive sickness response causes depressive symptoms.
	IL-6 receptors of the adrenal gland	Promote glucocorticoid secretion.	Induce insulin resistance.
Tumor necrosis factor-alpha (TNF- α)	Mainly the hypothalamus	Depending on CRH, it affects ACTH secretion.	Induce insulin resistance.

ACTH, adrenocorticotrophic hormone; CRH, corticotrophin-releasing hormone; GC, glucocorticoid; HPA, hypothalamic-pituitary-adrenal; T2DM, type 2 diabetes mellitus.

response.⁶⁷ IL-6 also plays a role in the differentiation of naïve CD4+ T cells into effector cells during the adaptive immune response.⁶⁷ IL-6 has been reported to have a role in immune-mediated HPA axis activation and thus plays a role in stress response induction via direct interaction with IL-6 receptors in the PVN of the hypothalamus.⁵⁴ IL-6 has been shown to regulate CRH production by binding to IL-6 receptors in the hypothalamus. A study has demonstrated that in the presence of IL-6, the cytokine can stimulate the HPA axis in the absence of CRH by stimulating the corticotrophs and ACTH release, compensating for CRH deficiency in an inflammatory response.⁶⁹ Furthermore, IL-6 was shown to also promote GC secretion by binding to IL-6 receptors of the adrenocortical cells of the adrenal gland.⁶⁹

Tumor necrosis factor-alpha

TNF- α is a multifunctional cytokine that plays a central role in mediating host defense against intracellular pathogens and bacterial endotoxin.^{54 70} Like IL-6 and IL-1 β , TNF- α is produced by various cell types such as activated macrophages, T lymphocytes and natural killer cells.⁷⁰ TNF- α plays a critical role in the inflammatory response by promoting inflammation via the stimulated expression of IL-1 β and IL-6 in association with promoting lymphocyte proliferation.⁵⁴ Several reports on the effects of TNF- α on ACTH secretion have shown that the main actions of TNF- α are on the hypothalamus and depend on CRH.⁶⁹

EFFECTS OF IMMUNE SYSTEM DYSREGULATION DUE TO HYPERGLYCEMIA ON THE HPA AXIS

The persistent state of hyperglycemia in T2DM affects the immune system by disrupting the immune response,

which increases the susceptibility to infections of patients with diabetes.⁷¹ The cytokines of interest are implicit in the development and exacerbation of T2DM.⁷² Impairment of cytokine production is reported in studies with diabetic individuals, and this has been evidenced by varying levels of TNF- α , IL-6 and IL-1 β .^{71 73} Irregular production and long-term exposure to these cytokines lead to persistent inflammation, which induces insulin resistance.^{74 75} Insulin-producing β cells of the pancreas have been shown to be prone to destruction and loss of function from macrophage-derived IL-1 β .⁷⁶ Overexcretion of remaining β cells increases insulin production resulting in hyperinsulinemia and eventual β cell exhaustion resulting in decreased insulin production as seen in overt T2DM.⁷⁶

The disrupted immune response seen in T2DM, which is evidenced by varying levels of TNF- α , IL-6 and IL-1 β , is shown to contribute to the etiology of depression.⁷⁷ According to the cytokine hypothesis, depression may result from a stress-related increased production of proinflammatory cytokines, which induce oxidative and nitrosative brain damage, resulting in the impairment of the serotonin (5-HT) system and subsequently contributing to GC resistance.^{78 79} IL-1 β , IL-6, and TNF- α are of significant potential in the etiology of depression concerning immune response.⁷⁷ Proinflammatory cytokine IL-6, along with prolonged activation of the IL-1 β and TNF- α in circulation, has shown to be involved in brain signaling, resulting in maladaptive sickness response, which is an adaptive response to illness or injury that leads to behavioral changes such as reduced appetite, altered sleep pattern and decreased activity which are seen as depressive symptoms.⁸⁰ Additionally, the proinflammatory marker C reactive protein has been shown to

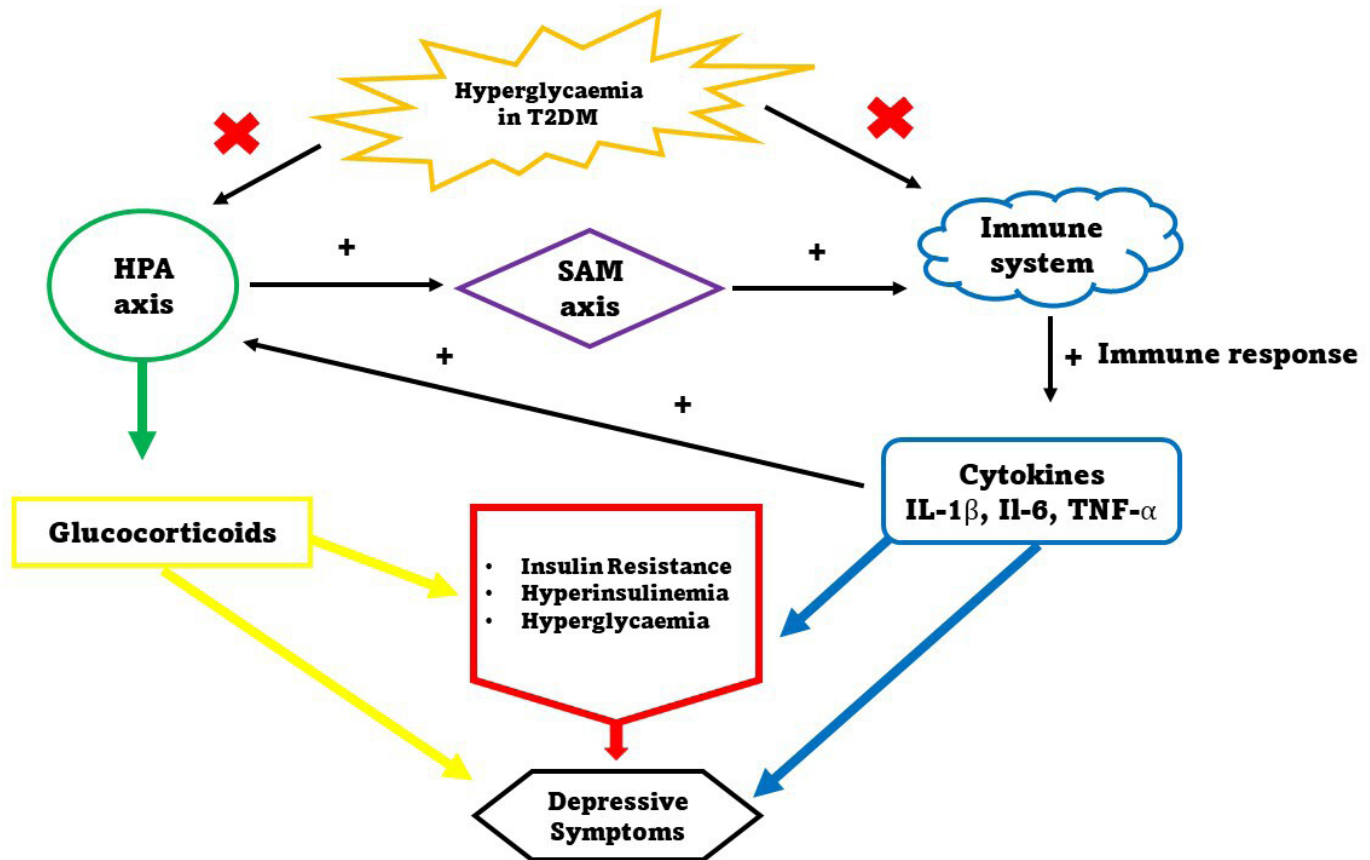


Figure 2 A diagram depicting the direct and indirect effects of hyperglycemia in type 2 diabetes mellitus (T2DM) on the hypothalamic-pituitary-adrenal (HPA) axis: hyperglycemia in T2DM dysregulates the HPA axis, which activates the sympatho-adrenal-medullary (SAM) axis resulting in an immune response. Hyperglycemia also dysregulates the immune system, which activates an immune response. Activation from the SAM axis and the dysregulated immune system cause an increase in immune cells secreting cytokines, especially interleukin-1 β (IL-1 β), IL-6 and tumor necrosis factor-alpha (TNF- α). Increased levels of these cytokines contribute to the dysregulation of the HPA axis, which results in increased glucocorticoids. The elevated glucocorticoids and cytokines exacerbate the hyperglycemic state in T2DM by further causing insulin resistance, hyperinsulinemia, and hyperglycemia. All these further contribute to depressive symptoms such as anhedonia, altered sleep pattern and reduced appetite.

be associated with the development of depression, where increased concentrations correlate to greater severity of depressive symptoms, as seen in several population-based studies among individuals without clinical depression.⁸¹

The HPA axis and immune response are connected (figure 1), and given how each system is affected individually in T2DM and depression, taken together, the combination of both the HPA axis and immune response dysregulation in T2DM from the chronic hyperglycemic state can result in the further diagnosis of depression in patients with diabetes which can be seen in figure 2.⁴² The activation of the HPA axis due to hyperglycemia results in the activation of the SAM axis.⁸² Subsequently, the activation of the SAM axis simultaneously activates the immune systems resulting in an immune response releasing the three cytokines discussed above.³ Simultaneously, the activation of the immune system in the presence of hyperglycemia results in the release of these cytokines due to chronic low-grade inflammation, activating the HPA axis.⁷⁷ This leads to increased production of GCs, triggering

GC resistance and hyperactivity of the HPA axis.⁷⁷ The elevation of GCs and cytokines exacerbates the hyperglycemic state by either causing insulin resistance, hyperinsulinemia, or hyperglycemia.^{3 42 82} Furthermore, maladaptive sicknesses such as decreased activity, altered sleep patterns, and reduced appetite may be seen, which are symptoms of depression.⁸⁰

However, the onset of T2DM is often preceded by pre-diabetes, a reversible state of moderate hyperglycemia and insulin resistance.⁸³ Complications often seen in T2DM have been reported to begin in the pre-diabetic state, while the current management strategies have been shown to ameliorate the moderate hyperglycemic state and decrease the risk of developing T2DM.¹² However, further research is necessary to investigate whether moderate hyperglycemia, as seen in pre-diabetes, can cause similar changes in seen chronic hyperglycemia in T2DM by directly and indirectly dysregulating the HPA axis and increasing the risk of depression.

PRE-DIABETES: CAN MODERATE HYPERGLYCEMIA HAVE THE SAME EFFECT IN HPA AXIS DYSREGULATION?

Pre-diabetes is characterized by reduced insulin sensitivity, impaired glucose and increased glycated hemoglobin.⁸³ Furthermore, it is defined as an intermediary state of moderate hyperglycemia with blood glucose concentration above normal but below the diabetes threshold.⁸³ The WHO defines pre-diabetes with the following two parameters: IFG which is defined as fasting plasma glucose of 6.1–6.9 mmol/L, and IGT which is defined as postprandial or 2-hour plasma glucose of 7.8–11.0 mmol/L after ingestion of 75 g of oral glucose load or a combination of both based on a 2-hour oral glucose tolerance test.⁸⁴ The American Diabetes Association has an additional hemoglobin A1c (HbA1c)-based criteria of a level of 5.7–6.4% in defining pre-diabetes and lower cut-off levels for IFG with the parameter being 5.6–6.9 mmol/L.^{36 83}

Our laboratory has established a pre-diabetic rat model that mimics the human condition. Using this model, we investigated changes in the activity of the cardiovascular system, the functioning of organs such as the kidney and liver, and physiological systems such as renin-angiotensin-aldosterone system in the pre-diabetic state.^{85–88} The HPA axis and immune systems have also been observed in the pre-diabetic state.^{89 90} In a study by Mosili and colleagues, hyperactivity of the HPA axis was observed in the pre-diabetic state.⁹⁰ This study further showed impairment of the negative feedback mechanism as evidenced by elevated GC concentration with no directly proportional increase in ACTH.⁹⁰ Additionally, the stress response was also measured and reported to have been dysregulated on stress induction which was evidenced by behavioral and biochemical changes.⁹⁰ The changes in immune cell concentration were also studied along with some of the cytokines that are secreted, specifically TNF- α and IL-6.⁸⁹ The study showed an increase in immune cells that secreted these cytokines due to moderate hyperglycemia.⁸⁹ The immune cells would secrete these cytokines and target inflamed areas in the body due to moderate hyperglycemia.⁸⁹

CONCLUSION

The studies provide evidence that the pre-diabetic state in the animal model setting correlates to the changes in the HPA axis and immune system. Furthermore, the studies show the risk of what potentially happens in a clinical setting when moderate hyperglycemia occurs. However, research is still necessary for clinical studies to profile these direct effects of moderate hyperglycemia in pre-diabetes on the HPA axis and the indirect effects moderate hyperglycemia may have on the HPA axis by investigating the components of the immune system that play a role in regulating this pathway. A view and thorough study into this will increase more knowledge of the

dangers of the pre-diabetic state and the importance of a normoglycemic state, eventually decreasing the risk of T2DM and subsequently decreasing the risk of hyperglycemic-related depression.

Contributors PM, BCM and AK conceptualized and wrote the first draft of the review paper. NHS and PSN edited the first draft, reviewed, verified and added references useful for the review paper. PM and BCM edited the final review paper for the publication.

Funding The study was funded by the National Research Fund (NRF), South Africa.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Palesa Mosili <http://orcid.org/0000-0001-9971-1854>

REFERENCES

- Kariagina A, Romanenko D, Ren S-G, *et al*. Hypothalamic-pituitary cytokine network. *Endocrinology* 2004;145:104–12.
- Dickmeis T, Weger BD, Weger M. The circadian clock and glucocorticoids—interactions across many time scales. *Mol Cell Endocrinol* 2013;380:2–15.
- Malek H, Ebadzadeh MM, Safabakhsh R, *et al*. Dynamics of the HPA axis and inflammatory Cytokines: insights from mathematical modeling. *Comput Biol Med* 2015;67:1–12.
- Champaneri S, Wand GS, Malhotra SS, *et al*. Biological basis of depression in adults with diabetes. *Curr Diab Rep* 2010;10:396–405.
- Chen P-C, Chan Y-T, Chen H-F, *et al*. Population-based cohort analyses of the Bidirectional relationship between type 2 diabetes and depression. *Diabetes Care* 2013;36:376–82.
- Gilsanz P, Karter AJ, Beerli MS, *et al*. The Bidirectional association between depression and severe Hypoglycemic and Hyperglycemic events in type 1 diabetes. *Diabetes Care* 2018;41:446–52.
- Chiodini I, Adda G, Scillitani A, *et al*. Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications. *Diabetes Care* 2007;30:83–8.
- Di Dalmazi G, Pagotto U, Pasquali R, *et al*. Glucocorticoids and type 2 diabetes: from physiology to pathology. *J Nutr Metab* 2012;2012:525093.
- Gragnoletti C. Depression and type 2 diabetes: Cortisol pathway implication and investigational needs. *Journal Cellular Physiology* 2012;227:2318–22. 10.1002/jcp.23012 Available: <https://onlinelibrary.wiley.com/doi/10.1002/jcp.23012>
- Bogner HR, Morales KH, Post EP, *et al*. Diabetes, depression, and death: a randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT). *Diabetes Care* 2007;30:3005–10.
- Semenkovich K, Brown ME, Svrakic DM, *et al*. Depression in type 2 diabetes mellitus: prevalence, impact, and treatment. *Drugs* 2015;75:577–87.
- Beulens JWW, Rutters F, Rydén L, *et al*. Risk and management of pre-diabetes. *Eur J Prev Cardiol* 2019;26:47–54.
- Control CfD, Prevention. *National diabetes statistics report: estimates of diabetes and its burden in the United States, 2014*. Atlanta, GA: US Department of Health and Human Services, 2014.
- Bădescu SV, Tătaru C, Kobylinska L, *et al*. The association between diabetes mellitus and depression. *J Med Life* 2016;9:120–5.
- Schmitt A, Bendig E, Baumeister H, *et al*. Associations of depression and diabetes distress with self-management behavior and Glycemic control. *Health Psychol* 2021;40:113–24.
- Schmitt A, Reimer A, Hermanns N, *et al*. Depression is linked to Hyperglycaemia via suboptimal diabetes self-management: a cross-sectional mediation analysis. *J Psychosom Res* 2017;94:17–23.
- Tabák AG, Akbaraly TN, Batty GD, *et al*. Depression and type 2 diabetes: a causal Association *The Lancet Diabetes & Endocrinology* 2014;2:236–45.

- 18 Pascoe MC, Thompson DR, Jenkins ZM, *et al.* Mindfulness mediates the physiological markers of stress: systematic review and meta-analysis. *J Psychiatr Res* 2017;95:156–78.
- 19 Shivavedi N, Kumar M, Tej G, *et al.* Metformin and Ascorbic acid combination therapy ameliorates type 2 diabetes mellitus and comorbid depression in rats. *Brain Res* 2017;1674:1–9.
- 20 Dong G-Z, Zhang Q-Y, Jiao Y-W, *et al.* The contribution of type 2 diabetes mellitus to hypothalamic inflammation and depressive disorders in young patients with obesity. *Ann Transl Med* 2022;10:134.
- 21 Spencer RL, Deak T. A users guide to HPA axis research. *Physiology & Behavior* 2017;178:43–65.
- 22 Bose M, Oliván B, Laferrère B. Stress and obesity: the role of the hypothalamic–pituitary–adrenal axis in metabolic disease. *Curr Opin Endocrinol Diabetes Obes* 2009;16:340–6.
- 23 Nezi M, Mastorakos G, Mouslech Z. Corticotropin releasing hormone and the immune/inflammatory response. 2015.
- 24 Beurel E, Nemeroff CB. n.d. Interaction of stress, corticotropin-releasing factor, arginine vasopressin and behaviour. *Behavioral Neurobiology of Stress-Related Disorders*;2014:67–80.
- 25 Spiga F, Lightman SL. Dynamics of adrenal glucocorticoid Steroidogenesis in health and disease. *Mol Cell Endocrinol* 2015;408:227–34.
- 26 Oppong E, Cato AC. n.d. Effects of glucocorticoids in the immune system. *Glucocorticoid Signaling*;2015:217–33.
- 27 Caratti G, Matthews L, Poolman T, *et al.* Glucocorticoid receptor function in health and disease. *Clin Endocrinol (Oxf)* 2015;83:441–8.
- 28 Desmet SJ, De Bosscher K. Glucocorticoid receptors: finding the middle ground. *J Clin Invest* 2017;127:88886:1136–45..
- 29 Herman JP, McKlveen JM, Solomon MB, *et al.* Neural regulation of the stress response: glucocorticoid feedback mechanisms. *Braz J Med Biol Res* 2012;45:292–8.
- 30 Salvador E, Shityakov S, Förster C. Glucocorticoids and endothelial cell barrier function. *Cell Tissue Res* 2014;355:597–605.
- 31 Gjerstad JK, Lightman SL, Spiga F. Role of glucocorticoid negative feedback in the regulation of HPA axis Pulsatility. *Stress* 2018;21:403–16.
- 32 DeFronzo RA, Ferrannini E, Groop L, *et al.* Type 2 diabetes mellitus. *Nat Rev Dis Primers* 2015;1:15019.
- 33 Sun H, Saeedi P, Karuranga S, *et al.* IDF diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2022;183:109119.
- 34 Kohei K. Pathophysiology of type 2 diabetes and its treatment policy. *JMAJ* 2010;53:41–6.
- 35 Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *The Lancet* 2011;378:169–81.
- 36 Association AD. Classification and diagnosis of diabetes. *Diabetes Care* 2015;38:S8–16.
- 37 Bruehl H, Rueger M, Dziobek I, *et al.* Hypothalamic-pituitary-adrenal axis dysregulation and memory impairments in type 2 diabetes. *J Clin Endocrinol Metab* 2007;92:2439–45.
- 38 Lee ZS, Chan JC, Yeung VT, *et al.* Plasma insulin, growth hormone, Cortisol, and central obesity among young Chinese type 2 diabetic patients. *Diabetes Care* 1999;22:1450–7.
- 39 Liu H, Bravata DM, Cabaccan J, *et al.* Elevated Late-Night salivary Cortisol levels in elderly male type 2 diabetic veterans. *Clin Endocrinol* 2005;63:642–9.
- 40 Reynolds RM, Labad J, Strachan MWJ, *et al.* Elevated fasting plasma Cortisol is associated with ischemic heart disease and its risk factors in people with type 2 diabetes: the Edinburgh type 2 diabetes study. *J Clin Endocrinol Metab* 2010;95:1602–8.
- 41 Reynolds RM, Strachan MWJ, Labad J, *et al.* Morning Cortisol levels and cognitive abilities in people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care* 2010;33:714–20.
- 42 Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *The Lancet Diabetes & Endocrinology* 2015;3:461–71.
- 43 Cryan JF, Mombereau C. In search of a depressed Mouse: utility of models for studying depression-related behavior in genetically modified mice. *Mol Psychiatry* 2004;9:326–57.
- 44 Keller J, Gomez R, Williams G, *et al.* HPA axis in major depression: Cortisol, clinical Symptomatology and genetic variation predict cognition. *Mol Psychiatry* 2017;22:527–36.
- 45 Dunlop BW, Wong A. The hypothalamic-pituitary-adrenal axis in PTSD: pathophysiology and treatment interventions. *Prog Neuropsychopharmacol Biol Psychiatry* 2019;89:361–79.
- 46 Faravelli C, Lo Sauro C, Godini L, *et al.* Childhood stressful events, HPA axis and anxiety disorders. *World J Psychiatry* 2012;2:13–25.
- 47 Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci* 2008;31:464–8.
- 48 Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry* 2001;49:391–404.
- 49 Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of Cytokines in the pathophysiology of major depression. *Biological Psychiatry* 2009;65:732–41.
- 50 Tracey KJ. The inflammatory reflex. *Nature* 2002;420:853–9.
- 51 Flierl MA, Rittirsch D, Huber-Lang M, *et al.* Catecholamines—crafty weapons in the inflammatory arsenal of immune/inflammatory cells or opening Pandora's box *Mol Med* 2008;14:195–204.
- 52 Berczi I. n.d. The influence of pituitary-adrenal axis on the immune system. *Pituitary Function and Immunity*;2019:49–132.
- 53 Seo D, Rabinowitz AG, Douglas RJ, *et al.* Limbic response to stress linking life trauma and hypothalamus-pituitary-adrenal axis function. *Psychoneuroendocrinology* 2019;99:38–46.
- 54 Hughes MM, Connor TJ, Harkin A. Stress-related immune markers in depression: implications for treatment. *Int J Neuropsychopharmacol* 2016;19:pyw001.
- 55 Baschant U, Tuckermann J. The role of the glucocorticoid receptor in inflammation and immunity. *J Steroid Biochem Mol Biol* 2010;120:69–75.
- 56 Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci* 2012;1261:55–63.
- 57 Silverman MN, Pearce BD, Miller AH. Cytokines and HPA axis regulation. *Cytokines and Mental Health: Springer* 2003:85–122.
- 58 Dragoş D, Tănăsescu MD. The effect of stress on the defense systems. *J Med Life* 2010;3:10–8.
- 59 Hoebe K, Janssen E, Beutler B. The interface between innate and adaptive immunity. *Nat Immunol* 2004;5:971–4.
- 60 Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res* 2014;58:193–210.
- 61 Tanaka T, Kishimoto T. The biology and medical implications of Interleukin-6. *Cancer Immunol Res* 2014;2:288–94.
- 62 Weber A, Wasiliew P, Kracht M. Interleukin-1 (IL-1) pathway. *Sci Signal* 2010;3:105.
- 63 Mandrup-Poulsen T, Pickersgill L, Donath MY. Blockade of interleukin 1 in type 1 diabetes mellitus. *Nat Rev Endocrinol* 2010;6:158–66.
- 64 Gałek-Michalska A, Tadeusz J, Rachwalska P, *et al.* Effect of prior stress on Interleukin-1B and HPA axis responses to acute stress. *Pharmacol Rep* 2011;63:1393–403.
- 65 Engström L, Rosén K, Angel A, *et al.* Systemic immune challenge activates an intrinsically regulated local inflammatory circuit in the adrenal gland. *Endocrinology* 2008;149:1436–50.
- 66 Guo Y, Xu F, Lu T, *et al.* Interleukin-6 signaling pathway in targeted therapy for cancer. *Cancer Treat Rev* 2012;38:904–10.
- 67 Rincon M. Interleukin-6: from an inflammatory marker to a target for inflammatory diseases. *Trends Immunol* 2012;33:571–7.
- 68 Hirano T. Interleukin 6 and its receptor: ten years later. *International Reviews of Immunology* 1998;16:249–84.
- 69 Bethin KE, Vogt SK, Muglia LJ. Interleukin-6 is an essential, corticotropin-releasing hormone-independent Stimulator of the adrenal axis during immune system activation. *Proc Natl Acad Sci USA* 2000;97:9317–22.
- 70 Josephs SF, Ichim TE, Prince SM, *et al.* Unleashing endogenous TNF-alpha as a cancer Immunotherapeutic. *J Transl Med* 2018;16:242:242..
- 71 Berbudi A, Rahmadika N, Tjahjadi AI, *et al.* Type 2 diabetes and its impact on the immune system. *Curr Diabetes Rev* 2020;16:442–9.
- 72 Pradhan AD, Manson JE, Rifai N, *et al.* C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286:327–34.
- 73 Ye J. Regulation of PPAR γ function by TNF-A. *Biochemical and Biophysical Research Communications* 2008;374:405–8.
- 74 Ye J. Emerging role of Adipose tissue hypoxia in obesity and insulin resistance. *Int J Obes* 2009;33:54–66.
- 75 Rehman K, Akash MSH, Liaqat A, *et al.* Role of Interleukin-6 in development of insulin resistance and type 2 diabetes mellitus. *Crit Rev Eukaryot Gene Expr* 2017;27:229–36.
- 76 Maedler K, Dharmadhikari G, Schumann DM, *et al.* Interleukin-1 beta targeted therapy for type 2 diabetes. *Expert Opin Biol Ther* 2009;9:1177–88.
- 77 Valkanova V, Ebmeier KP, Allan CL. IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord* 2013;150:736–44.

- 78 Catena-Dell'Osso M, Bellantuono C, Consoli G, *et al.* Inflammatory and neurodegenerative pathways in depression: a new Avenue for antidepressant development *Curr Med Chem* 2011;18:245–55.
- 79 Stepanichev M, Dygalo NN, Grigoryan G, *et al.* Rodent models of depression: Neurotrophic and Neuroinflammatory biomarkers. *Biomed Res Int* 2014;2014:932757.
- 80 Dantzer R, O'Connor JC, Freund GG, *et al.* From inflammation to sickness and depression: when the immune system Subjugates the brain. *Nat Rev Neurosci* 2008;9:46–56.
- 81 Köhler-Forsberg O, Buttenschön HN, Tansey KE, *et al.* Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. *Brain Behav Immun* 2017;62:344–50.
- 82 Marik PE, Bellomo R. Stress hyperglycemia: an essential survival response *Crit Care* 2013;17:305.
- 83 Bansal N. Prediabetes diagnosis and treatment: A review. *World J Diabetes* 2015;6:296–303.
- 84 Organization WH. Definition and diagnosis of diabetes mellitus and intermediate Hyperglycaemia: report of a WHO/IDF consultation; 2006.
- 85 Mkhize BC, Mosili P, Ngubane PS, *et al.* Diet-Induced Prediabetes: effects on the activity of the Renin-Angiotensin-Aldosterone system (RAAS) in selected organs. *J Diabetes Investig* 2021.
- 86 Khathi A, Luvuno M, Mabandla M. Diet-induced Prediabetes: effects on oxidative stress and inflammatory biomarkers as agents for vascular complications in renal function. *PONTE* 2019;75.
- 87 Luvuno M, Khathi A, Mabandla MV. Diet-induced Prediabetes: effects of exercise treatment on risk factors for cardiovascular complications. *Nutr Metab* 2021;18:45:45..
- 88 Gamede M, Mabuza L, Ngubane P, *et al.* Plant-derived Oleanolic acid ameliorates markers associated with non-alcoholic fatty liver disease in a diet-induced pre-diabetes rat model. *Diabetes Metab Syndr Obes* 2019;12:1953–62.
- 89 Mzimela NC, Ngubane PS, Khathi A. The changes in immune cell concentration during the progression of pre-diabetes to type 2 diabetes in a high-fat high-carbohydrate diet-induced pre-diabetic rat model. *Autoimmunity* 2019;52:27–36.
- 90 Mosili P, Mkhize BC, Ngubane P, *et al.* The dysregulation of the hypothalamic–pituitary–adrenal axis in diet-induced Prediabetic male Sprague Dawley rats. *Nutr Metab* 2020;17:104.