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REVIEW

Toxic stress, inflammation and symptomatology of chronic complications in diabetes

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Abstract

Diabetes affects at least 382 million people worldwide and the incidence is expected to reach 592 million by 2035. The incidence of diabetes in youth is skyrocketing as evidenced by a 21% increase in type 1 diabetes and a 30.5% increase in type 2 diabetes in the United States between 2001 and 2009. The effects of toxic stress, the culmination of biological and environmental interactions, on the development of diabetes complications is gaining attention. Stress impacts the hypothalamus-pituitary-adrenal axis and contributes to inflammation, a key biological contributor to the pathogenesis of diabetes and its associated complications. This review provides an overview of common diabetic complications such as neuropathy, cognitive decline, depression, nephropathy and cardiovascular disease. The review also provides a discussion of the role of inflammation and stress in the development and progression of chronic complications of diabetes, associated symptomatology and importance of early identification of symptoms of depression, fatigue, exercise intolerance and pain.

Key words: Toxic stress; Type 1 diabetes; Inflammation; Type 2 diabetes; Chronic complications; Symptomatology

Core tip: The incidence of diabetes and associated complications are increasing. Toxic stress and inflammation may be contributors to the development and progression of diabetes complications. Current evidence supports early identification of symptoms of toxic stress for preventative strategies of associated risks for diabetes complications as well as assessment of the exacerbation of symptoms related to neuropathy, cardiovascular disease and nephropathy.

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INTRODUCTION

The notion that exposure to chronic stressors predisposes individuals to developing diabetes or succumbing to worsening diabetes complications has gained

attention in recent years[1-4]. The global epidemic of both type 1 and type 2 diabetes[5-7] is occurring in an era of worldwide threats to personal, organizational and societal security due to psychosocial and economic burdens. According to the International Diabetes Federation, diabetes affects at least 382 million people worldwide, and that number is expected to reach 592 million by the year 2035[8]. Although it is well-known that type 2 diabetes comprises the largest proportion of affected individuals, the number of individuals with type 1 diabetes around the world is increasing as well. Worldwide estimates for type 1 diabetes are unknown, but are estimated to be up to 3 million in the United States[9]. A recent report on the prevalence of type 1 diabetes in youth in the United States indicated a 21 percent increase between 2001 and 2009. At the same time, rates of type 2 diabetes in youth rose 30.5%[10].

In the midst of this public health crisis, there is tremendous need to embrace the impact of "toxic stress" from biological and environmental interactions on the development of chronic complications in persons living with diabetes. Toxic stress can result from strong, frequent, or prolonged activation of the body's stress response systems, particularly in the absence of protective mechanisms through daily coping strategies and healthy interpersonal relationships[11]. The impact of toxic stress is apparent in current society and is garnering a paradigm shift regarding a more comprehensive understanding of health and disease across the lifespan[11,12]. Toxic stress can be viewed as the catalyst of a physiological memory that confers life-long risk for disease, especially due to inflammatory processes, well beyond its time of origin[13]. How individuals, institutions, and governments respond to these stressors can have an enormous effect on the collective health of a nation. Health care clinicians serve on the front line of care delivery for identifying the most vulnerable individuals for the ravages of diabetes complications through an understanding of underlying etiologies associated with toxic stress and recognition of resultant symptomatology.

With the growing numbers of individuals diagnosed with diabetes, particularly in younger cohorts, the disease burden is ever apparent, as is the importance of minimizing the role of toxic stress on associated diabetes complications. According to Shonkoff[14], the future consequences of significant adversity and chronic stress in early childhood extend beyond socioemotional and cognitive development. They also have significant implications for the pathogenesis of adult disease[15], including biological manifestations of alterations in immune function[16] and measurable increases in inflammatory markers[17,18] that are known to be associated with poor health outcomes such as cardiovascular disease[19-21], liver cancer[22], asthma[23], chronic obstructive pulmonary disease[24], autoimmune diseases[25], poor dental health[26], and depression[27-29]. Although there is no absolute evidence that chronic stress has a direct effect on the development of diabetes in adults or children, stress can influence the onset of type 2 diabetes secondary to obesity and metabolic syndrome[2].

With regard to the effects of stress on the neuroendocrine system, the hypothalamus-pituitary-adrenal (HPA) axis exerts considerable importance[30]. Upon experiencing a stressor, the hypothalamus secretes corticotropin-releasing factor, which causes the release of adrenocorticotropin (*i.e.,* ACTH). This in turn stimulates the adrenal cortex, which leads to the secretion of glucocorticoid hormones, in particular cortisol. Under normal circumstances, cortisol is secreted according to a circadian rhythm, with cortisol levels highest in the morning and lowest in the evening. However, exposures to stress stimulate the HPA axis to release additional amounts of cortisol to maintain homeostasis and reduce the effects of stress. Cortisol influences a wide range of processes, including the breakdown of carbohydrates, lipids, and proteins to provide the body with energy. Cortisol has an immunosuppressive effect and therefore plays a role in the regulation of immune and inflammatory processes.

The relationship between inflammation and the HPA axis is a complex one since pro-inflammatory cytokines also stimulate the HPA axis and contribute to stress-induced elevation in cortisol[31]. Cortisol in turn, normally plays a fundamental role in limiting the further production of pro-inflammatory cytokines *via* the important cytokine-glucocorticoid feedback cycle. This occurs through cortisol binding to glucocorticoid receptors in the white blood cells (WBCs), which once activated, leads the activated receptor [*e.g.,* Nuclear factor-κB (NF-κB)], to block intracellular cytokine signaling pathways, ultimately stopping the further production of pro-inflammatory cytokines[32] and promotion of anti-inflammatory cytokines[33]. NF-κB consists of a family of transcription factors that play critical roles in inflammatory processes, immune regulation, cell proliferation, differentiation, and survival[34].

With toxic stress, chronic exposure of the WBCs to high cortisol leads to down regulation of the glucocorticoid receptors, resulting in their resistance to cortisol. This stops the cytokine-glucocorticoid feedback cycle, leading to dysregulated cytokine production and chronically elevated cortisol; two states known to worsen disease outcomes. Thus, toxic stress has been associated with inflammation due to glucocorticoid receptor resistance, a mechanism of dysfunctional inflammation regulation that allows proinflammatory mediators to be uncontrolled, adding to stress-related morbidity[35].

ROLE OF INFLAMMATION IN THE PHYSIOLOGY OF DIABETIC COMPLICATIONS

Chronic inflammation contributes to diabetes and its

complications. Features of chronic inflammation include an up-regulation of proinflammatory cytokines, such as TNF-α, interleukin (IL)-1, IL-6, IL-8, monocyte chemo attractant protein-1, and C-reactive protein that are produced by activated immune cells, resident macrophages and adipocytes[36]. Production of these proinflammatory cytokines functions to amplify the immune response. It is recognized that a chronic, low-grade inflammatory response that occurs with an activated immune system is involved in the pathogenesis of obesity-related insulin resistance and type 2 diabetes[37].

Markers of systemic inflammation correlate with risk for the development of diabetes related macrovascular complications[38]. For example, in obesity-related type 2 diabetes, adipose tissue, liver, muscle and pancreatic tissues are sites of inflammation. There is an infiltration of macrophages and other immune cells coupled with a shift in cell population from anti-inflammatory to a pro-inflammatory profile. The shift in the inflammatory profile promotes insulin dysfunction leading to hyperglycemia[39].

One complication of hyperglycemia is the formation and accumulation of advanced glycation endproducts (AGEs), ubiquitous irreversible end products of protein glycation which are formed from Amadori protein products[40]. AGEs crosslink proteins to form stable complexes that are resistant to enzymatic degradation. In addition to hyperglycemia, oxidative stress appears to increase AGE formation. AGEs ligate with their receptor, RAGE, to amplify and perpetuate the inflammatory response through nuclear factor κβ (NF-κβ), cAMP regulated element binding protein (CREB), and activator protein-1 (AP-1) signaling pathways. RAGE is a promiscuous receptor and has multiple ligands including lipopolysaccharide, S100/calcium binding proteins, High Mobility Group Box Protein 1 (HMGB1) and Amyloid-βpeptide (Aβ), as well as many others[40,41]. Data from multiple studies demonstrate that AGEs and their receptor, RAGE, are important contributors to the development of diabetes related complications[40,42].

Oxidative stress, an alteration in redox regulation and control, occurs in response to excessive reactive species production that overwhelms antioxidant defenses[43]. Reactive species may modify glucose, free fatty acids, oxysterols or lipids through oxidation-reduction reactions. For example, oxidize glucose is involved in the formation of AGEs. AGEs ligate with their receptor RAGE to promote an inflammatory response; modification of lipids has been shown to affect mitochondrial metabolic pathways leading to mitochondrial damage[44,45]. Inflammation and mitochondrial damage result in oxidative stress thereby producing an autocrine feedback pathway to perpetuate inflammation and oxidative stress[46]. This pathway has been described in the macrovasculature as well as in peripheral neurons and is recognized as a contributor to the complications of diabetes[47,48].

Vascular dysfunction characterized by an activated endothelium that is primed to facilitate immune cell migration into tissue also occurs in diabetes. Indeed vascular dysfunction is a key contributor of neuropathy, impaired cognition, nephropathy and cardiovascular diseases (*e.g.,* atherosclerosis, cardiomyopathy, *etc.*) that underlie complications of diabetes.

DIABETIC NEUROPATHY

Peripheral neuropathy (PN) affects up to 50% of people with diabetes and the diffuse peripheral neuropathies (distal sensori-motor polyneuropathy and autonomic neuropathy) are major risk factors for foot ulceration and amputation[49]. The etiology of PN is complex; however, studies show that altered blood flow, hyperglycemia and alterations in metabolics (oxidative/nitrative stress, advanced glycation end products and a pro-inflammatory response) are involved.

In animal models of diabetes, evidence of reduced blood flow to the nerve is seen within the first few days of the induction of diabetes with a chemical agent such as streptozosin (STZ). These changes often precede changes in nerve conduction velocity[50-52]. However, the loss of blood flow results in neuronal hypoxia sufficient to compromise nerve function and initiate neurodegeneration[53]. This effect has also been described in autonomic ganglia, dorsal root ganglia and in the hippocampus[54-56].

Hypoxia also induces the expression of numerous pro-angiogenic and pro-inflammatory genes in macrophages[57]. Alterations in the microvasculature effect associated peripheral nerves[58]. Indeed capillary occlusion induces ischemia to the nerve producing ischemic nerve fiber damage and perineural capillary luminal occlusion (due to endothelial cell hypertrophy and hyperplasia)[59]. In rats, hypoxic conditions reduced nerve velocity conduction, and within the context of hyperglycemic hypoxia, blockade of potassium channels leads to intra-axonal acidification by anaerobic glycolysis. This suggests that hypoxia induced neuronal changes may play a role in the development of neuropathy[60,61]. However, reversal of hypoxia in the ischemic limbs of individuals with diabetes does not improve nerve function[62].

Hyperglycemia appears to contribute to the pathogenesis of diabetic neuropathy. Within the first month of inducing diabetes in rats, hyperglycemia resulted in slowing of sensory[63-65] and motor[66,67] nerve conduction velocity coupled with hyperalgesia[68,69] and allodynia[70]. Over time prolonged hyperglycemia produces axonpathy, demyelination and nerve degeneration in diabetic animals[71,72].

Metabolic alterations are thought to play a central role in the development of neuropathy in diabetes. Elevation in polyol pathway activity, oxidative stress, the formation of advanced glycation end products and a persistent pro-inflammatory response through activation of the NF-κβ and p38 mitogen activated protein kinase signaling have been consistently shown

to contribute to diabetic neuropathy[73-75].

There is considerable evidence that pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 are involved in the pathogenesis of diabetic neuropathy. TNF-α is a potent proinflammatory cytokine that appears to play a role in the pathogenesis of diabetic neuropathy and have a central role in central and peripheral sensitization of neuropathic pain[76]. Pharmacologically inhibiting TNF-α in mice ameliorates the electrophysiological and biochemical effects of the cytokine[77].

IL-1β is an important cytokine that induces the production of a wide variety of cytokines thorough NF-κβ activation. Studies show an increase in the mRNA expression of TNF-α and Il-1β in the spinal cords of STZ-diabetic rats[78]. Activated astrocytes in the spine increase IL-1β expression, which may induce *N*-methyl-*D*-aspartic acid receptor phosphorylation in spinal dorsal horn neurons to enhance pain transmission[79]. Hyperglycemia induces the production of IL-1β through the NOD-leucine-rich repeats-and pyrin domain containing inflammasome[80]. In the spinal dorsal horns of db/db mice, increased IL-1β, TNF-α and IL-6 levels are inhibited by anti-high-mobility group box protein-1, a known RAGE ligand[81].

IL-6 is a member of the neuropoietic cytokine family that participates in neuronal development and has neurotrophic activity. IL-6 is a sensitive marker of diabetic neuropathy and predicts progression and severity of type 1 diabetes[82]. Increased levels of IL-6, IL-1 and TNF-α correlated with the progression of nerve degeneration in diabetic neuropathy[83]. It is believed that these proinflammatory cytokines affect glial cells and neurons to set the pathological process of diabetic neuropathy in motion. However, the role of these cytokines in diabetic peripheral neuropathic pain is unclear[84]. It is clear that inflammation is a complex scenario. To that end other signaling molecules such as interferon-γ, IL-10, C-reactive protein, adhesion molecules, chemokines and adipokines may also play a role in the inflammatory process associated with diabetic neuropathy and neuropathic pain.

NEUROPATHIC PAIN

Pain is the body's perception of actual or potential damage to the nerve or tissue by noxious stimuli. Large A-delta myelinated fibers and small C unmyelinated fibers are sensory afferent nerves that are mainly responsible for carrying nociceptive sensation from the skin, joints, and viscera. Tissue damage results in the release of inflammatory mediators such as prostaglandins, bradykinins, and histamines at the site of injury, which triggers the depolarization of nocioceptors, thereby generating an action potential. The action potential transmits the nociceptive sensation, *via* the dorsal root ganglion (DRG) to the dorsal horn of the spinal cord. The release of glutamate and substance *P* results in the relay of nocioceptive sensations to the spinothalamic tract, thalamus, and subsequently, the cortex where pain is interpreted and perceived.

Nociceptive pain is the normal response to noxious stimuli and nociceptive pain usually subsides upon removal of the stimulus (*e.g.,* healing of injured tissue). Neuropathic pain occurs in the absence of noxious stimuli and represents a pathological change affecting the somatosensory system. Neuropathic pain is characterized by the activation of abnormal pathways of pain at the peripheral nerve and posterior nerve roots. Neuropathic pain is a critical feature in diabetic neuropathy.

The development of painful diabetic neuropathy is complex and not completely understood. However, evidence suggests that glycemic shifts, inflammation and oxidative stress are important contributors. Hyperglycemia affects glial cells leading to demyelination and impaired neurotrophism that culminates in impaired regeneration and decreases nerve conduction velocity; ultimately this results in pain. Hyperglycemia also activated the microvascular endothelium causing endothelial hypertrophy affecting downstream endoneurial circulation to promote hypoxia and ischemia of the nerve. Hyperglycemia and hypoxia affects neurons by promoting axonopathy and neuronal degeneration. Hyperglycemia may also contribute to painful diabetic neuropathy through the polyol pathway[85], advanced glycation end-products[86], hexosamin flux[87], mitogen-activate protein kinases[73], altered activity of the Na^+/K^+-ATPase[88], poly-ADP ribose polymerase (PARP) over activation[89], and cyclooxygenase-2 activation[90]. Nerve cells are prone to hyperglycemic injury as the neuronal glucose uptake is based on glucose concentration.

The expression of voltage-gated sodium and calcium channels and voltage-independent potassium channels in the DRG has a significant role in the generation of nociceptive sensation and peripheral sensitization. Indeed voltage gated sodium channels are active following nerve injury and demonstrate continued generation of ectopic impulses; similar findings have been observed from some voltage-gated calcium channels suggesting that voltage-gated calcium channels play a role in neuropathic pain. Calcium entry through voltage-gated calcium channels causes the release of substance P and glutamate, which results in the modulation of pain at the dorsal horn. The transient receptor potential vanilloid 1 (TRPV1) channel has been found to be associated with neuropathic pain as well. Methylglyoxal, a reactive intracellular by-productive of glycolysis and hyperglycemia, depolarizes the sensory neuron by activating the TRPV1 channel[91] in the DRG and also induces posttranslational modification of the voltage-gated sodium channel Nav1.8[92]. In addition, these changes increase electrical excitability and facilitate firing of nociceptive neurons.

Neuroplasticity is the brain's response to changes within the body or the external environment. In response to chronic neuropathic pain, neuroplasticity

is associated with somatosensory cortex remodeling, reorganization, and hyperexcitibility in the absence of external stimuli. Provoked pain and spontaneous stimuli may reverse the remodeling and reorganization at the somatosensory cortex[93]. In a study of patients with chronic neuropathic pain and nonneuropathic pain Gustin *et al*[93] found using functional and anatomical resonance imaging cortical reorganization and changes in somatosensory activity in patients with neuropathic pain.

IMPAIRED COGNITION AND DEPRESSION

Diabetes can lead to a number of secondary complications, and the most common brain complications include cognitive decline and depression. The incidence of cognitive decline, measured by behavioral testing may be as high as 40% in people with diabetes[94]. Subjective feelings of cognitive decline have also been reported from persons with diabetes[95], which illustrates the impact of diabetes on the individuals perception of how well their brain functions. Indeed multiple studies have reported that diabetic patients have a 2-5 fold increased risk for Alzheimer's Disease compared to non-diabetic subjects[96,97]. Furthermore, alterations in cognitive functioning in type 1 diabetic children (less than 5 years old) has been reported[98,99], as well as evidence of changes in white matter structure[100].

The mechanisms responsible for the development of high rates of cognitive decline in diabetics are not well understood, although evidence suggests that neuroplasticity may play an important role. The dentate gyrus of the hippocampus and the subventricular zone are two important areas in neurogenesis[101], the process of proliferation of progenitor cells or their differentiation into astrocytes, oligodendrocytes or neurons and survival and incorporation of the newborn cells into target regions. Hippocampal neurogenesis is diminished by exposure to environmental stress, HPA axis hyperactivity and increased inflammation[102,103]. Changes in neurogenesis alter a number of key functions of the hippocampus, such as learning and memory, affective expression and regulation of the HPA axis[104,105].

Wide variations in glucose levels and oxidative stress may also play an important role in the development of cognitive decline in diabetics. In animal models, studies show that repeated bouts of hypoglycemia inhibits hippocampal neurogenesis, presumably through oxidative injury to hippocampal CA1 dendrites[106]. Hyperglycemia also promotes oxidative stress and neurodegeneration[107]. Prolonged hyperglycemia promotes the development of AGEs which bind to their receptor, RAGE, to promote and sustain an inflammatory response through NF-κβ, AP-1 and CREB signaling pathways. RAGE ligation also promotes increases expression through an autocrine feedback mechanism[108]. RAGE is also responsible for the transport of amyloid-β (Aβ) across the blood-brain barrier. Aβ contributes to the development of Alzheimer's Disease[109,110] by participating in the formation and accumulation of amyloid plaques and fibrils that facilitate neurodegeneration and impair cognition[107]. Also, Aβ and hyperglycemia have been shown to activate microglia to induce oxidative injury[111].

The relationship between diabetes and depression is reciprocal as either is known to be a risk factor for the other[112]. The importance of depression is diabetes is highlight by studies consistently report a higher prevalence rate for depression among type 1 and type 2 diabetics compared to the general population[113]. Comorbid depression and diabetes is associated with poor self-care, lack of exercise, and nonadherence to dietary or medication routines, leading to inadequate glycemic control.

The mechanisms responsible for the development of depression in diabetics is unclear, although there is likely overlap between physiological and non-physiological factors to account for the pathogenesis of their comorbidity. Non-physiological factors such as sedentary life style, lack of self-care, and diet, as well as the emotion burden of managing diabetes, contribute to the development and progression of diabetes. Insulin resistance is gaining attention as a potential link between diabetes and depression and cognitive decline[114,115]. Neuroendocrine signaling, through hyperactivity of the HPA axis, is thought to cause or exacerbate depression in diabetics[116]. Indeed antidepressant treatment has been shown to abrogate abnormal HPA responses while facilitating recovery from depression[117].

Stress has been shown to decrease brain derived neurotrophic factor (BDNF) in the hippocampus. Stress also appears to decrease the expression of other types of neurotrophic and growth factors such as nerve growth factor and neurotrophin-3[118], which could lead to the alteration in the structure and function of hippocampal neurons. Stress also decreases the expression of vascular endothelial cell growth factor, a growth factor that influences vascular permeability and the proliferation of endothelial cells, in the hippocampus[119]. The significance is that antidepressant treatment increases expression of BDNF and other growth factors in individuals recovering from depression[120-122].

There is also considerable evidence that inflammation plays an important role in the pathogenesis of depression and diabetes[123]. Many studies describe an increase in peripheral cytokine of individuals with depression that is often comorbid with other chronic diseases such as coronary artery disease and chronic obstructive pulmonary disease[124]. Interestingly, cytokines have been shown to be associated with suicidality and depression[125]. Diabetes and inflammation have been associated with alterations of dopamine, serotonin, brain derived neurotrophic factor and insulin growth factor-1 which have been implicated

in depression[126].

CARDIOVASCULAR DISEASE, NEPHROPATHY AND ASSOCIATED SYMPTOMS

Given the worldwide increase in the incidence of diabetes, the dual complications associated with cardiovascular disease and nephropathy heighten the importance of preventive therapies through early identification of biomarkers of inflammation and causative etiologies for stress responses regardless of age or type of diabetes[127]. In 2010, high blood pressure was the leading risk factor for deaths due to cardiovascular diseases, chronic kidney disease, and diabetes in every region of the world, causing more than 40% of worldwide deaths from these diseases[128]. The National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014[129], indicated that from 2003-2006 after adjusting for population age differences, cardiovascular disease (CVD) death rates were approximately 1.7 times higher among adults (≥ 18 years) with diabetes than among adults without diabetes. Regardless of the type of diabetes, the risk of CVD is evident and likely begins at an earlier age for those diagnosed with type 1 diabetes. Endothelial dysfunction is an integral part of the pathogenesis underlying the increased cardiovascular complications seen in individuals with T1D but it is unclear how early it appears[130].

Results from the Epidemiology of Diabetes Interventions and Complications study, a long term follow up study of the Diabetes Control and Complications Trial (DCCT), showed that adults with T1D had increased carotid intima medial thickness (CIMT) compared to a healthy non-diabetic population 6 years into the study. Individuals receiving intensive insulin treatment during the DCCT had much less progression in their CIMT compared to those who had received conventional treatment. However there was not a significant difference in their percent HbA_{1c} at that time, suggesting the effect of "metabolic memory"[131]. These data suggest that glycemic control may have long lasting effects on cardiovascular morphology and function[130]. Hence, there exists a caveat to minimize exposure to toxic stressors in early life and at the onset of T1D that may aggravate optimal glycemic targets.

Cardiovascular morbidity related to diabetes is associated with vascular changes due to inflammation, resulting in both macrovascular (*i.e.,* atherosclerosis)[132] and microvascular (*i.e.,* cardiovascular autonomic neuropathy)[133] alterations. In type 1 diabetes, several causative factors are implicated in these inflammatory vascular changes[134]. The oxidative modification of LDL and associated immune responses[135] may be one of these key factors, resulting in damage to the endothelium[136], activation of macrophages, adherence of monocytes[137] and impairment of nitric oxide action with resulting vascular cell cytotoxicity[138]. Although markers of inflammation have not been extensively studied in the development of CAD in T1D, the Eurodiab study group, using a standard score based on combined levels of C-reactive protein, IL-6, and TNF-α, reported a significant difference between those with and without CAD ($P < 0.001$) after adjusting for age, gender, HbA_{1c}, diabetes duration, and systolic blood pressure[139]. Research has also indicated that in subjects with known coronary atherosclerosis, low-degree inflammatory activity (*i.e.,* C-reactive protein, fibrinogen, erythrocyte sedimentation rate and white blood cell count) is not only increased in patients with T1D and T2D diabetes, but also increased with increasing HbA_{1c} in non-diabetic individuals. This later finding indicates an early association between degree of glycaemia, inflammation and atherosclerosis prior to the development of diabetes[140].

Cardiovascular autonomic neuropathy is a common form of autonomic neuropathy and one of the most overlooked of all serious complications of diabetes, resulting from microvascular damage to parasympathetic and sympathetic fibers and increased risks for cardiovascular arrhythmias, sudden death, and myocardial infarction in adults with diabetes[141]. There are multiple etiologies of diabetic neuropathy, including hyperglycemic activation of the polyol pathway leading to accumulation of sorbitol causing direct neuronal damage and/or decreased nerve blood flow[142], oxidative stress with increased free radical production leading to vascular endothelium damage and reduced nitric oxide bioavailability[143,144], and the formation of advanced glycosylated end products with reduced blood flow, activation of inflammatory cytokines (*e.g.,* IL-6, TNF-α), nerve hypoxia and altered nerve function[141].

Cardiovascular autonomic neuropathy has been linked to postural hypotension, exercise intolerance, enhanced intraoperative cardiovascular lability, increased incidence of asymptomatic (*i.e.,* painless) ischemia, myocardial infarction, and decreased likelihood of survival after myocardial infarction[145]. The presence of palpitations and tachycardia at rest due to loss of parasympathetic modulation can be present early in the development of this complication prior the onset of other associated symptoms. Cardiovascular autonomic neuropathy occurs in approximately 17% of patients with T1D and 22% of those with T2D. An additional 9% of T1D and 12% of T2D have borderline dysfunction[133]. Since the 1970s, the seminal work by Ewing *et al*[146] unveiled the predictive relationship between cardiovascular autonomic neuropathy and mortality in adults with T1D. The Hoorn Study also found increased mortality in adults with T2D who had decreased cardiovascular autonomic function[147]. Within the pediatric literature, heart rate variability (a measure of cardiovascular autonomic function) was lower in adolescents with T1D compared with healthy control

subjects[148,149] and lower in youth with T2D *vs* T1D[150].

New pathways in the development of diabetic nephropathy also implicate inflammatory processes due to hyperglycemia, renin-angiotensin system and oxidative stress, involving infiltration of the kidneys with monocytes and lymphocytes that increase pro-inflammatory cytokine production, reactive oxygen species and tissue damage[151,152]. This leukocyte activity amplifies the inflammatory response and promotes cell injury and organ tissue fibrosis. Improved future understanding of the inflammatory response in diabetic kidneys is expected to identify novel anti-inflammatory strategies for the potential treatment of diabetic nephropathy. Familial predisposition to disease, including risks for toxic stress, race and other environmental factors interact with hemodynamic changes producing advanced glycation end products, glucose reduction and sorbitol accumulation into the cell, and overproduction of reactive oxygen species[151]. For individuals exposed to toxic stress that may further exacerbate dysglycemia, glycemic control is of upmost importance for preventing the onset and progression of nephropathy by influencing both hyperglycemia itself and hyperglycemia induced metabolic abnormalities. Evidence for this premise is supported by randomized controlled clinical trials in both type 1 and type 2 diabetes[153,154].

CLINICAL IMPLICATIONS FOR SYMPTOM RECOGNITION

The complications of diabetes related to neuropathy, nephropathy and cardiovascular disease are the major contributors to morbidity and mortality in this population. Given the projected increase in the worldwide numbers of individuals to develop diabetes in the coming years, the potential additional burden of toxic stress on the development of disease related complications is of tremendous concern. Key symptoms that warrant clinician recognition during routine assessment in persons with diabetes include signs of cognitive decline, depression, fatigue (including disturbed sleep patterns), exercise intolerance and pain associated with peripheral neuropathy. Although the emphasis in diabetes management is achievement of glycemic targets, weight, lipid and blood pressure control, the environmental and physiological effects of daily stress may be "ticking away" at the emergence of subtle inflammatory changes leading to devastating complications. Therefore, diabetes care management should emphasize symptom palliation as well as cardiometabolic control[155].

Chronic low-grade inflammation in metabolic disorders such as diabetes contributes to behavioral symptoms, including depression, cognitive impairment, fatigue, sleep disturbance and pain[156]. The quality and quantity of sleep may play a key role in the inflammatory processes associated with diabetes and related cardiovascular disease[157]. Additionally, several biomarkers of inflammation, specifically IL-6 and CRP, have been found to be associated with fatigue, poor concentration and sleep quality in a healthy adult cohort[158], which has implication for the stress-induced inflammatory effect on individuals prior to the development of diabetes. There is increasing evidence that hypercytokinemia and activated innate immunity affect the pathogenesis of T2D and related symptoms of fatigue, sleep disturbance and depression[159].

CONCLUSION

Toxic stress exposes individuals at all ages to chronic, low-grade inflammation that is a risk for the development of diabetes and may increase the physiological alterations leading to neuropathy, nephropathy and cardiovascular disease that are so prevalent in diabetes. Evidence supports the importance of minimizing toxic stress to promote glycemic control and lessening immune and inflammatory responses in an attempt to prevent the emergence or worsening of diabetes complications. At a time when the evaluation of immune and inflammatory biomarkers is not standard clinical practice, routine examination strategies are essential for the assessment of stressful life experiences and the effects of these experiences that contribute to the symptoms related to neuropathy, nephropathy and cardiovascular disease and overall quality of life.

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