# Diabetes mellitus may induce cardiovascular disease by decreasing neuroplasticity

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**Summary**

**Neuroplasticity has been defined "the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections". The nervous system monitors and coordinates internal organ function. Thus neuroplasticity may be associated with the pathogenesis of other diseases besides neuropsychiatric diseases. Decreased neuroplasticity is associated with cardiovascular disease (CVD) and a disease related to decreased neuroplasticity may confer a greater CVD risk. Diabetes mellitus (DM) is related to CVD and DM induces decreased neuroplasticity, which is manifested as depression, Alzheimer's disease and diabetic neuropathy. Therefore we conclude that DM may induce CVD by decreasing neuroplasticity.**

*KEY WORDS: brain-derived neurotrophic factor (BDNF), cardiovascular disease (CVD), diabetes mellitus (DM), glucocorticoid, neuroplasticity*

## Introduction

The global prevalence of diabetes mellitus (DM) is continuously rising. The number of DM sufferers worldwide was estimated to be almost 285 million in 2010, with the figure expected to rise to 438 million by 2030 (Khuwaja et al., 2010). Cardiovascular disease (CVD) is the leading cause of death among patients with DM. Thus the link between DM and CVD is a matter of concern. The pathophysiology of this link is complex and multifactorial, and neuroplasticity may play a role.

Neuroplasticity is "the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections" (Cramer et al., 2011). Different individuals due to their different experiences might have different degrees of neuroplasticity. Neuroplasticity may play a role in individual differences in the efficacy of treatment of neuropsychiatric diseases (Zheng and Xu, 2012). The nervous system monitors and coordinates internal organ function, and we have therefore proposed that neuroplasticity may also be associated with the pathogenesis of other diseases besides neuropsychiatric diseases. Decreased neuroplasticity is associated with CVD and a disease related to decreased neuroplasticity may confer a greater CVD risk (Zheng et al., 2013b).
In this paper, we discuss the relationship between DM, neuroplasticity and CVD, and, on the basis of the literature evidence, try to explain the causal link between DM and CVD, and the involvement of neuroplasticity.

## Diabetes mellitus (DM) is associated with cardiovascular disease (CVD)

It is well known that DM is a significant risk factor for CVD (Qazi and Malik, 2013). Even the earliest stages of nascent hyperglycemia confer a greater risk of adverse cardiovascular outcomes (Singh et al., 2013). Excess risk for CVD can be found in patients with type 1 DM (T1DM) and type 2 DM (T2DM), and in patients in the pre-diabetic stages (Lteif et al., 2003). A threefold increase in the incidence of CVD in DM patients has been reported and CVD has become the major risk factor for DM-associated morbidity and mortality (Vinik et al., 2013). The overall mortality rate from heart disease is two times higher in men with DM than in those without DM, and four to five times higher in women with DM than in those without DM (Hammoud et al., 2000). As regards its role as a predictor of ischemic stroke and heart failure, DM is frequently found in elderly hospitalized patients with heart failure, and it increases the overall cardiovascular risk in patients with heart failure (Basile et al., 2013; Steg et al., 2004; Vikman et al., 2003).
There are three types heart disease related to DM: i) coronary artery disease (CAD) due to accelerated atherosclerosis; ii) cardiovascular autonomic neuropathy (CAN); and iii) diabetic cardiomyopathy (Pappachan et al., 2013). In addition, increased platelet aggregation is seen in T2DM patients (Singh et al., 2013). DM has been reported to be a risk factor equivalent to CAD

(Lotufo et al., 2001), and CAD is a leading cause of morbidity and mortality in patients with DM (Scholte et al., 2008; Haffner et al., 1998). Cardiac mortality in DM with no known CAD is the same as that in non-DM with a history of acute myocardial infarction (MI) (De Backer et al., 2003). Moreover, DM is a major risk factor for adverse outcomes in patients who suffer from unstable angina or MI, and patients with DM are more likely to die after MI than those without DM (Lteif et al., 2003; Van de Werf et al., 2003; Grundy et al., 2002).

The incremental risk with increasing hemoglobin A1c (HbA1c) was quantified by a recent meta-analysis. This study reported that for every 1% increase in HbA1c, the risk of any CAD event, a fatal CAD event, or stroke increased by 13%, 16%, and 17%, respectively, although the analysis did not account for the use of DM medications (Selvin et al., 2004). Data from the Nurses' Health Study, which included 117,629 healthy women, demonstrated that women who developed DM during a 20-year follow-up had a relative risk factor of 2.8 for MI or stroke (Hu et al., 2002). An elevated risk was seen 15 years prior to the actual diagnosis of DM. Brunner et al. (2006) examined the relationship between 2-hour postural glucose loading results and CAD mortality over a period of 33 years in 17,869 men; starting from a seemingly normal glucose level of 83 mg/dl, they found a near-linear relationship between increasing serum glucose and CAD mortality. Similar evidence for an increase in CAD and all-cause mortality was demonstrated using data from the European Prospective Investigation into Cancer Study–Norfolk cohort (EPIC-Norfolk) study, in which an elevated risk was noted in patients with HbA1c concentrations ranging from 5% to 5.4% (Khaw et al., 2001).

Patients with DM have more prevalent, extensive and calcified coronary atherosclerosis than those without DM. Patients with DM show an accelerated progression and higher prevalence of multivessel disease (Andreini et al., 2010; Loffroy et al., 2009; Perrone-Filardi et al., 2011). Patients with T2DM also have a higher prevalence (26-36%) of silent atherosclerotic lesions and asymptomatic ischemia (Perrone-Filardi et al., 2011). *In vivo* studies, such as the Northern Manhattan Study (NOMAS), showed that flow-mediated dilation, a measure of endothelial function, was reduced when fasting glucose levels were >100 mg/dl, a finding which suggests that subtle hyperglycemia can have immediate effects on the endothelium (Rodriguez et al., 2005).

## DM decreases neuroplasticity

Diabetes mellitus can lead to complications affecting many functions within the body, including nervous system function. Neurodegeneration is one of the most important complications of DM (Kazkayasi et al., 2013). Excessive glucose and inadequate insulin alter the normal structure and function of the nervous system. It is evident that DM decreases neuroplasticity.

### *Insulin is associated with neuroplasticity*

Evidence shows that insulin plays an essential role in neuroplasticity. Insulin may play important roles in brain metabolism (Karczewska-Kupczewska et al., 2013). Insulin and insulin-like growth factors (IGFs) are involved in development, cell differentiation, plasticity, and survival of the nervous system (Benarroch, 2012). CCAAT/enhancer binding proteins (C/EBPs) are associated with neuroplasticity. Insulin therapy prevents DM-induced alterations in C/EBPα and β immunoreactivities (Kazkayasi et al., 2013).

### *DM increases glucocorticoid level*

Although considered to be a common complication of chronic exposure to excessive glucocorticoid levels (Di Dalmazi et al., 2012), DM also influences the hypothalamic-pituitary-adrenal (HPA) axis and increases glucocorticoid levels (Stranahan et al., 2008). Stranahan et al. (2008), on the basis of the results of a study conducted in two animal models (insulin-deficient rats and insulin-resistant mice), suggested that cognitive impairment in DM may result from glucocorticoid-mediated deficits in neurogenesis and synaptic plasticity. In these models, DM was found to produce adverse effects mediated by the adrenal steroid corticosterone, namely impaired hippocampus-dependent memory, perforant path synaptic plasticity and adult neurogenesis. In this study, the streptozotocin (STZ)-treated rats had reduced levels of insulin and exhibited hyperglycemia, elevated levels of corticosterone, and impairments in hippocampal neurogenesis, synaptic plasticity and learning. Similar deficits were observed in the db/db mice, which are characterized by insulin resistance, increased corticosterone levels and obesity. The authors noted that changes in hippocampal plasticity and function in these models are reversed when normal physiological levels of corticosterone are maintained.

### *DM decreases BDNF level*

Brain-derived neurotrophic factor (BDNF) is a critical cytokine in neuroplasticity (Numakawa et al., 2010a). BDNF may also influence energy homeostasis via its role in neurogenesis, in the neuroplasticity of the HPA axis (Noble et al., 2011; Taliaz et al., 2011), and in the maintenance of cardiometabolic homeostasis (Chaldakov, 2011). BDNF expression is regulated by stress-responsive corticosteroids, and increased glucocorticoid exposure induces a reduction in BDNF levels (Numakawa et al., 2010b). Hyperglycemia decreases BDNF expression (Wang et al., 2011). Plasma and serum BDNF levels were decreased in patients with T2DM (Fujinami et al., 2008; Krabbe et al., 2007). Secretion of BDNF is suppressed in STZ-induced DM (Navaratna et al., 2011), implying that DM decreases BDNF. Low BDNF is associated with cognitive deficits in patients with T2DM. Studies suggest that BDNF

plays an important role in regulating memory-related neuroplasticity in the hippocampus. T2DM is associated with impairment in many domains of cognitive function, which may result from reduced BDNF. Decreased BDNF may have a role in the pathophysiology of cognitive deficits, especially delayed memory in T2DM (Zhen et al., 2013). In the DM brain, both protein and mRNA levels of BDNF have been found to be severely reduced (Nitta et al., 2002). On the basis of these results it was suggested that synapse dysfunction in DM is, at least in part, due to a failure of BDNF synthesis in the brain (Nitta et al., 2002).

### *DM is associated with some diseases related to decreased neuroplasticity*

Depression is common both in T1DM and in T2DM, affecting approximately 20% of patients (Ali et al., 2006; Barnard et al., 2006). A meta-analysis and two systematic reviews (Anderson et al., 2001; Nouwen et al., 2010, 2011) reported that patients with DM had 2.9-fold significantly increased odds of having depression compared with individuals without DM. Depressive disorders are associated with increased medical morbidity and mortality in patients with DM (Zhang et al., 2005). A higher prevalence of DM complications, including retinopathy, nephropathy, neuropathy, macrovascular complications and sexual dysfunction, has been demonstrated among DM patients with depression compared with DM patients not affected by depression (de Groot et al., 2001). Depression has been associated with poor glycemic control, including hyperglycemia and high HbA1c levels (Roy et al., 2007; Van Tilburg et al., 2001; Lustman et al., 1997). Recently, a biological mechanism has been suggested, the theory being that both depression and DM are associated with deregulated and overactive HPA axis activity. Depression is associated with subclinical hypercortisolism secondary to HPA axis activation (Champaneri et al., 2010). In addition, serum BDNF level is a biomarker for depression and is significantly decreased in major depression (Yoshimura et al., 2011; Bocchio-Chiavetto et al., 2010). As noted above, DM increases glucocorticoid and decreases BDNF levels. Therefore, it is suggested that a pattern of increased glucocorticoid and decreased BDNF in DM can be a risk factor for the development and presence of depression. BDNF is critical in neuroplasticity and depression is a disorder of decreased neuroplasticity (Zheng et al., 2013b). This implies that DM induces depression through decreased neuroplasticity.
DM is a major risk factor for Alzheimer's disease (AD) (Serbedzija and Ishii, 2012). Pathological changes occurring in DM lead to both AD-type neurodegeneration (i.e., hippocampal atrophy) and vascular damage (i.e., infarcts). It is the mix of these changes that forms the anatomical basis for clinical and subclinical cognitive impairment in DM (Launer, 2009; Korf et al., 2006). Axonal and dendritic changes, which are associated with diabetic encephalopathy, are major risk factors for AD (Zhou et al., 2013). Insulin and IGFs, whose levels are reduced in DM, maintain adult brain mass by preserving brain protein content. The concomitant loss of insulin and IGFs is the leading cause of age-dependent, progressive brain atrophy with degeneration and cognitive decline. Replacement of both these ligands has been shown to be capable of preventing total brain protein loss, widespread cell degeneration, and demyelination. IGFs support synapses and are needed for learning and memory. It has been shown in DM rats that replacement doses can cross the blood-brain barrier and prevent hippocampus-dependent memory impairment (Serbedzija and Ishii, 2012). Insulin deficiency in T1DM may lead to cognitive impairment, cerebral atrophy and white matter abnormalities (Francis et al., 2008). AD is related to HPA axis dysfunction and to elevated cortisol and reduced BDNF levels (Brureau et al., 2013; Allen et al., 2011). Synaptic plasticity is generally believed to provide a cellular mechanism for learning and memory (Alberini, 2009); changes in synaptic plasticity were observed in hippocampal slices from STZ-induced DM rats (Kamal et al., 1999). Thus, it is suggested that DM induces AD by decreasing neuroplasticity.
Diabetic neuropathy (DN), which is a common complication of DM, occurs as a result of nervous system damage caused by persistent hyperglycemia (Sharma et al., 2012). The pathogenesis of DN possibly involves a complex of metabolic factors inducing nerve ischemia (Bansal et al., 2006). The two main types of DN are diabetic peripheral neuropathy (DPN) and diabetic autonomic neuropathy (DAN). Autonomic dysfunction is related to CAD. For example, elevated sympathetic nerve activity results in increased systemic catecholamine levels, and then leads to aggregation of platelets, which play an important role in CAD (Haft and Fani, 1973; Amadi et al., 1995). Cardiovascular autonomic neuropathy (CAN), which is clinically important in DAN, is a significant cause of morbidity and mortality associated with a high risk of cardiac arrhythmias and sudden death (Vinik and Ziegler, 2007). DN has been shown to be a manifestation of decreased neuroplasticity; DN is associated with HPA axis hyperfunction and decreased BDNF in the hippocampus (Chiodini et al., 2006; Al-Amin et al., 2011). The BDNF gene is responsible for DPN (Guttula et al., 2010), and DPN is characterized by loss and/or degeneration of neurons, Schwann cells, and neuronal fibers, and by slowing of nerve conduction velocities (Brownlee et al., 1986; Greene et al., 1992). The features of CAN include damage to the autonomic nerve fibers that innervate the heart and blood vessels, which results in abnormalities in heart rate control and vascular dynamics (Vinik and Ziegler, 2007). The antidepressant duloxetine is the most important new drug among agents for symptomatic relief of DN (Várkonyi et al., 2013). Duloxetine increases cortical and hippocampal mRNA expression of BDNF (Engel et al., 2013), and thus increases neuroplasticity.
In addition to the above evidence there exists other evidence demonstrating that DM decreases neuroplasticity. Individuals with DM, compared with non-DM

individuals, have been suggested to show brain structural changes that reflect neuronal degeneration; DM probably induces microstructural changes that are not visible on standard magnetic resonance imaging (MRI). Many factors modulate the strength of the association between DM and brain structure/function (Launer, 2009). As an endogenous stressor, STZ-induced DM accelerates the effects of exogenous stress to alter hippocampal morphology; at the same time it changes hippocampal structure. These changes overlap only partially with those produced by stress and corticosterone in the non-DM state (Magariños and McEwen, 2000). Cross-sectional studies using either visual rating scales or automated volumetric techniques on MRI showed that T2DM is associated with a moderate degree of cerebral atrophy (van Harten et al., 2006). Patients with T2DM also show changes on brain MRI, such as cortical and hippocampal atrophy (Schmidt et al., 2004; den Heijer et al., 2003).

The risk of decreased neuroplasticity may be further modulated by comorbidities of DM. For instance, patients with DM and hypertension have been reported to have a higher risk of global atrophy and to perform poorly on a test of visual memory, which depends on hippocampal plasticity (Schmidt et al., 2004; Elias et al., 1997; Wiescholleck and Manahan-Vaughan, 2012).

## Decreased neuroplasticity induces CVD

The cardiovascular system is controlled by the nervous system, mainly the autonomic nervous system. Stress influences the HPA axis, leading to increased glucocorticoid levels, which lead to decreased BDNF concentrations. Neuroplasticity is reduced in the presence of increased glucocorticoid and deceased BDNF levels. Decreased neuroplasticity influences the autonomic nervous system, both directly and through the HPA axis and the hippocampus. And the autonomic dysfunction may then lead to CVD (Zheng et al., 2013b). DM acts as an endogenous stressor (Magariños and McEwen, 2000). Autonomic dysfunction predicts cardiovascular risk and sudden death in patients with T2DM (Vinik et al., 2013). Microstructural changes of brain areas involved in visceral sensory processing are associated with autonomic dysfunction in patients with DM (Frøkjaer et al., 2013).

The mechanisms responsible for increased DM-related CVD mortality and morbidity are multifactorial, and the ones involving autonomic dysfunction are worthy of consideration. Cardiovascular autonomic dysfunction, e.g. decreases in both heart rate variability and arterial baroreflex sensitivity, is a common complication of T2DM, and generally associated with a high mortality of patients with DM (Chen et al., 2001; Miller et al., 1999; Sanya et al., 2003; Takahashi et al., 2004). For example, increased mortality in DM patients with left ventricular dysfunction and heart failure can be partly attributed to autonomic dysfunction. Autonomic dysfunction lowers the threshold for life-threatening arrhythmias and increases the risk of hemodynamic instability (Grundy et al., 2002).

## Concluding remarks

On the basis of the above discussion, we can conclude that DM, acting as an endogenous stressor, influences the HPA axis and, as a result, increases glucocorticoid levels. Increased glucocorticoid levels decrease BDNF levels. This pattern of increased glucocorticoid and deceased BDNF induces decreased neuroplasticity, which is manifested as depression, AD and DN. Decreased neuroplasticity may influence the autonomic nervous system both directly and through the HPA axis and the hippocampus, and lead to CVD. Depression, AD and DN are, in fact, closely related to CVD (Zheng et al., 2013b; Vinik and Ziegler, 2007). Figure 1 presents an integrative pathophysiological model showing the possible association between DM and CVD together with the involvement,

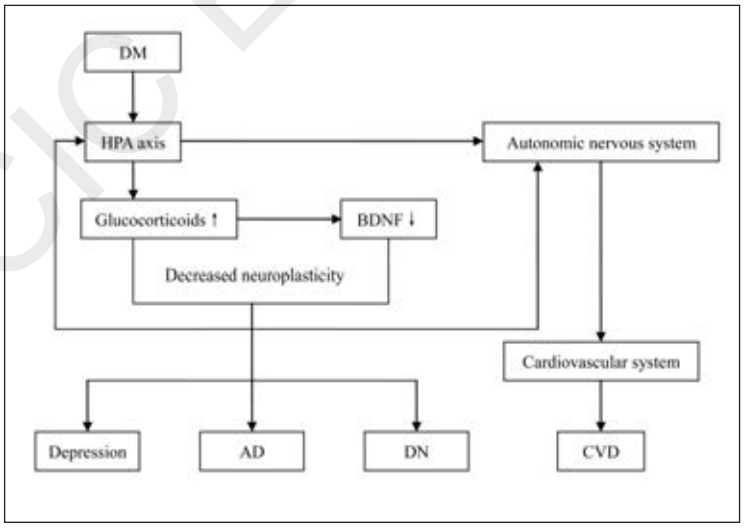


Figure 1 - An integrative pathophysiological model associating DM with neuroplasticity and CVD. Decreased neuroplasticity plays a role in the pathogenesis of the coexistence between DM and CVD.
Abbreviations: DM=diabetes mellitus; HPA=hypothalamus-pituitary-adrenal; BDNF=brain-derived neurotrophic factor; AD=Alzheimer's disease; DN=diabetic neuropathy; CVD=cardiovascular disease.

in this association, of neuroplasticity. This model is not intended to be complete or all-encompassing, but rather to highlight and connect certain interesting evidence pointing to this association. Furthermore, DM may induce CVD by other mechanisms, which are not discussed in this paper.

Increased neuroplasticity cannot lead to β-cell regeneration after apoptosis. However, increased neuroplasticity may protect against DM-induced CVD. For example, exercise, which can increase neuroplasticity, may be beneficial for patients with DM and CVD (Patel and Zheng, 2012; Davidson, 2012).

There are some common factors, such as microRNA-132, which may play roles in both neuroplasticity and cardiovascular function (Zheng et al., 2013a). The factors and mechanisms involved in DM, neuroplasticity and CVD could be a promising field for further study.

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