DIABETES AND DIABETIC NEUROPATHIES ARE INDEPENDENT EVENTS: A NEW MEDICAL HYPOTHESIS

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ABSTRACT:

In this study, we expressed our views in a very important topic related to diabetes and diabetic neuropathies. In a previous study, I have demonstrated the role of inducible nitric oxide synthase (iNOS) in diabetes and demonstrated that the white matter of diabetic rats expressed iNOS. We think that this event may precede and causes injury of pancreatic injury in a later stage. The possibility of having autoimmune role in diabetes further supports our hypothesis that diabetes and diabetic neuropathies to be viewed as independent events. We think that oxidizing stress causes both diabetes and diabetic neuropathies. In a later stage, diabetes will intensify the onset of diabetic neuropathy. Furthermore, epidemiological studies, including our studies did not show consistent significant association between diabetic neuropathy and diabetes. Taken together, diabetes and diabetic neuropathy have similar contributing factors and they are independent events.

KEYWORDS: diabetes, diabetic neuropathy, iNOS, white matter

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INTRODUCTION

In this study, we tried to build our hypothesis in which diabetes and diabetic neuropathy are independent events. Accordingly, we reviewed the literature regarding diabetes and diabetic neuropathy.

Causes of diabetes

No definite cause of type 1 diabetes has been identified and it is characterized by being a complex disease, stimulated by environmental factors which are more likely to induce their effects in those with genetic susceptibility. The prevalence of T1D has been estimated as 0.4%1.

Environmental factors involved in the etiology of T1D include the exposure to some viruses such as the Epstein-Barr virus, cytomegalovirus, coxsackievirus or the mumps virus. The mechanism involved has been thought to be mediated as triggering the autoimmune system by infectious agents to attack the islet cells, or through infecting the pancreas ending with beta cell destruction2.

Type2 diabetes has been known to have several etiologies. T2D is accumulative disease and develops over years. Contributing factors for the development of T2D are attributed to lifestyle behaviors and environmental factors (Nunley, 2014). Several risk factors have been reported to associate with T2D including age, obesity, race, family history of T2D, abdominal adiposity and physical inactivity. Depression has been recognized as a risk factor for T2D3,4.

Diabetic Neuropathy

Diabetic neuropathy (DN) is microvascular complication influencing the function of nerve. DN includes various types such as focal or diffuse of which distal symmetric polyneuropathy (DSP) and neuropathies involving the autonomic nervous system are the most prevalent5.

Although no exact etiology for DN has been identified, it is thought that the exposure to a variety of factors including hyperglycemia, tissue ischemia, oxidative stress and accumulation of advanced glycationendproducts (AGEs) participates to the development of DN6.

According to the study of Vinik et al. (2013), diabetic neuropathy (DN) is considered the most prevalent complication associated with diabetes mellitus. DN is associated with high morbidity and mortality rates as well as large economic impacts due to providing diabetic care.

Diabetes is a worldwide epidemic, and associated neuropathy is its most costly and disabling complication8.

The study of Hu et al.9 showed the occurrence of both neuroinflammation and neurodegeneration in the brain in type 1 diabetes (T1D). The researchers examined mechanisms related to neurodegeneration, loss of the neuroprotective factors insulin-like growth factor I (IGF-1) and IGF-binding protein-3 (IGFBP-3) and changes in indoleamine 2,3-dioxygenase (IDO) expression in the brain, and compared the response to age-matched controls in the brain of T1D mice. Results indicated to increased expression of IDO and early loss of CD39+ protective cells lead to activation of inflammation in sympathetic centers of the CNS.

The role of oxidative stress in the induction of diabetic neuropathy

Vincent et al.10 conducted a study to highlight the idea that diabetes increases the metabolic activities of glucose which, in turn, generates more free radical production and oxidative stress. Oxidative stress is the result of failure of tissues or cells to detoxify the free radicals that are made through metabolic pathways.

Matough et al.11 conducted a study to review the literature about the role of oxidative stress in diabetes. Several experimental and clinical studies showed that oxidative stress has a crucial role in the etiology of diabetic complications. Hyperglycemia has been reported to induce free radicals which imply the impairment of the endogenous antioxidant defense system in diabetics.

Infectious causes of diabetes

Torres et al.12 conducted a study to report a case of a patient with Cushing’s syndrome who developed central diabetes insipidus as a result of the infection with herpes simplex virus affecting the hypothalamus. According to the authors, it has been reported that viral infections in immunosuppressed patients.

The role of iNOS in diabetes

Keklikoglu and Akinel13 (2013) conducted a study about the role of iNOS in diabetes. They showed that the immunoreactivity of iNOS was demonstrated in islet of Langerhans cells under physiological conditions. Furthermore, it has been shown that the induction of islet iNOS was detected in acute pancreatitis, and type 1 and type 2 diabetes mellitus.
It was interestingly found that when beta cells fight against inflammatory cytokines, lipid stress or hyperglycemia, iNOS is more activated ending with high levels of NO which, in turn, leads to cell dysfunction or death resulting in inhibited secretion of insulin. There is still gap in literature about the exact mechanism explaining the expression of iNOS. However, the development of diabetes cannot be inhibited completely using iNOS inhibitors. It is recommended if possible, both physiological and pathological limits of the expression of iNOS as well as the mechanism of the damage on beta cells by over-expression.

**Experience from our studies**

We have previously showed that the white matter of diabetic rats significantly expressed iNOS compared with control group (p=0.000). We also found less expression of heat shock protein 70 (HSP70) in white matter of diabetic rats compared with control group (p=0.000). It was also found that in control groups, both iNOS and HSP70 were expressed in grey matter and white matter in similar levels, and further, white matter was affected by molecular alterations, while grey matter was not affected.14

In another study, we found that the prevalence of diabetic peripheral neuropathy among participants was about 43%. Diabetic peripheral neuropathy was significantly associated with gender (p=0.018). No significant associations were observed between peripheral neuropathy and metformin use.15

Recently, we found that the prevalence of glaucoma was 50% among diabetic patients, and was not associated significantly with metformin use, gender, age, or metformin dose.16

We also conducted a new study to investigate the prevalence of diabetic foot ulcer among diabetic patients attending out-clinic patients at Jordanian Royal Medical Services and to investigate the impact of metformin treatment in the development of diabetic foot ulcer. Study findings showed that about 66% of patients were prescribed for metformin, the mean of metformin dose was 1617.32±649.49 mg, and the prevalence of DF was 8.1%. No significant relationships were observed between DF and each of gender and metformin use (p>0.05). Both One Way Anova Test and correlation test showed that DF was significantly associated with metformin dose.17

In another study, Al-Refaiet al18 (2017) studied the impact of using aspirin treatment on diabetic neuropathy, the results showed that the prevalence of diabetic neuropathy was 25.8%. The use of aspirin treatment was reported by 50% of the patients. The mean of aspirin dose was 111.37±24.67 mg/day. The data also showed that males were more likely to develop diabetic neuropathy compared with females, but this was not statistically significant (p>0.05). Patients using aspirin treatment were less likely to develop diabetic neuropathy, but this was also not statistically significant (p>0.05).

**CONCLUSION**

In this study, we set up a new medical hypothesis “DIABETES AND DIABETIC NEUROPATHY ARE INDEPENDENT EVENTS”. Although diabetic neuropathy involves the diabetes to be the causative agent of diabetes, we think that diabetes and diabetic neuropathy are both occurred independently, and large probably have common causes.

**REFERENCES:**


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