ISSN 2475-5451

Review Article

International Journal of Diabetes & Metabolic Disorders

New Insights to Diabetes: Is Diabetes a Metabolic Disorder or a Neurological Disease?

Ahed J Alkhatib

Department of Legal Medicine, Toxicology of Forensic Medicine, School of Medicine, University of Science and Technology, Jordan

***Corresponding author:**
Dr. Ahed J Alkhatib, Department of Legal Medicine, Toxicology of Forensic Medicine, School of Medicine, University of Science and Technology, Jordan, Mobile: +962795905145 & 00962795905145; E-mail: ajalkhatib@just.edu.jo, drahedalkatib@yahoo.com, ahed.alkhatib64@yahoo.com

Submitted: 27 Jan 2019; **Accepted**: 04 Feb 2019; **Published**: 18 Feb 2019

Abstract

The present study introduces diabetes from neurological point of view. Although existing literature has largely focused on diabetes from metabolic point of view, we think stress biology has impacts on the initiation and progression of diabetes. We have previously demonstrated that diabetes may occur as a functional alteration in white matter in which we examined the phenomenon of overexpression of inducible nitric oxide synthase (iNOS). At the same time, we noticed that the expression of HSP70 in the same area was down-regulated. When we studied different tissues such as kidneys, and liver of diabetic rats, we also found the same trend. According to this context, we developed our new hypothesis that stated that diabetes and diabetic neuropathies are independent events. In other words, we think that the same factors that developed diabetes resulted in diabetic neuropathies. Taken together, we think we have to change some basic concepts and to consider diabetes to be more neurological diseases more than a metabolic disease. Studying biomarkers such as iNOS and HSP70 helps in introducing the concept of epigenetics to play new important roles in initiating and progression of diabetes. The expression of mentioned biomarkers in white matter impacts other tissues and we think it is responsible to initiate diseases such as diabetes.

Keywords: Diabetes, Diabetic Neuropathy, Metabolic Disorder, White Matter, Brain, Liver, Kidney, Epigenetic

Introduction

An overview of diabetes

Diabetes is considered as a metabolic disease characterized by hyperglycemia resulting from insulin insufficiency either in lower levels, insulin function, or both [1-3]. It has been reported that the prevalence of diabetes has dramatically increased from 4.7% to 8.5% of world population between years 1980-2014. Furthermore, it has been estimated that diabetes attributed to 1.5 million deaths in 2012, and increased the risk of cardiovascular diseases which is estimated to attribute in further 2.2 million deaths [4, 5]. Reports by WHO indicated that diabetes is more likely to rank as the 7th cause of death in 2030. Micro-vascular changes associated with diabetes are thought to induce complications of diabetes such as vision impairment, cardiovascular disease, and nerves [3].

The metabolic syndrome (MS) is defined as a group of metabolic abnormalities that increase the risk of both cardiovascular diseases and T2DM. In this syndrome, there are several characteristics including insulin resistance, central obesity, hypertension, and dyslipidemia [6, 7]. According to the study of Tong et al, it has been pointed to the decreased survival rate by 10 years in case of existence of MS in diabetics. Manifestations of MS also include prediabetes in addition to type 2 diabetes [3].

In a recent study, Hannou et al put emphasis on the importance of the trend of increasing sugar consumption as a main factor leading to obesity, diabetes, and cardio metabolic risks [8]. According to Hannou et al, fructose is harmful and has the potential to produce features of MS.

Diabetes and oxidative stress

Free radicals are chemical species characterized by being reactive with short life, and they have one or more unpaired electrons [9]. The free radicals can cause breakdown to cells through the process of giving the unpaired electron leading to oxidizing cell parts and molecules [10].

There are three types of free radical: Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), and Reactive Chlorine Species (RCS) [11].

Free radicals play important roles in activating various signaling pathways within the cell including the Mitogen activated protein kinase (MAPK) and extracellular-signal-regulated kinase (ERK) pathways that modify the expression of genes, in addition to interacting with superoxide dismutase to initiate cell death [12]. RNS are produced by neurons and act as neurotransmitters, while that produced by macrophages act as mediators of immunity. Other biological activities include leukocyte adhesion, thrombosis, angiogenesis and vascular tone. In a similar way, ROS plays a role in gene transcription, single transduction and regulation of other activities in cell [13].

The production of free radicals within cells can occur by exogenous and endogenous substances through the reaction of non-enzymatic reactions with oxygen in addition to products by ionizing radiations [14]. Mitochondrion is likely to be influenced by this process through oxidative phosphorylation [9]. Free radicals can be created through various sources such as radiations, ROS, RNS, Neutrophils and macrophages production, chemicals, different smoking models, and synthetic agents [15].

From a physiological point of view, the body responds to overcome the influence of free radicals through several mechanisms to generate antioxidants either endogenous or exogenous to balance the increased levels of free radicals and to protect the cells from the harmful effects of free radicals and to participate in prevention and development of diseases [14].

Oxidative stress is the alteration of the balance between the oxidants and non-oxidants in which oxidants overcome this imbalance, and this may due to various agents including ageing, drug actions and toxicity, inflammation and/or addiction [16]. This imbalance implies the existence of accumulation of free radicals as a result of increased production of free radicals, or the inability to remove them in an appropriate rate [17].

The role of oxidative stress in diabetes

Oxidative stress has significant role in the progression of vascular complications in diabetes [14]. Increased levels of ROS among diabetics are thought to due to defects in oxidant / non-oxidant system including catalase, superoxide dismutase (SOD) and glutathione peroxidase (GSH–Px) antioxidants, ending with diabetic complications [18]. Oxidative stress has crucial roles in the occurrence of both type 1 and type 2 diabetes. The excess formation of free radicals in diabetes induces breakdown of enzymes, cellular machinery and increased insulin resistance because of resultant oxidative stress [19]. In diabetes mellitus, oxidative stress is mainly resulting from mitochondria in which oxidative metabolism in mitochondria leads to reduce oxygen to water, and the remaining oxygen becomes oxygen free radical [20]. There are two ways to modulate insulin signaling by free radicals: the first way involves the production of ROS/RNS as a response to insulin, and the other way implies the existence of negative regulation regulating insulin signaling leading to the progression of insulin resistance [21].

Literature showed a relationship between oxidative stress and diabetes mellitus as indicated through measuring the levels of different biomarkers such as DNA damage biomarkers and lipid peroxidation products. It is believed that hyperglycemia has a role in oxidative stress development leading to the progression of endothelial dysfunction in blood vessels of diabetics [22].

Our experience from our studies: diabetes as a neurological disorder

From our experience, we think that diabetes is more likely to be a neurological disease more than metabolic disease, although metabolic aspects still exist. Our first group of experiments showed the existence of functional alterations in white matter of diabetic rats. We demonstrated up-regulation of inducible nitric oxide synthase (iNOS) in white matter of diabetic rats. In comparison with control group, there was a significant difference in the expression rate of iNOS ($p<0.001$). We also examined the expression of heat shock protein (HSP70) in both groups and found that the expression of HSP70 was down-regulated in white matter of diabetic rats compared with that in control group. This was also statistically significant ($p<0.001$) [23].

We further developed our hypothesis "Functional alterations of white matter participate in inducing functional alterations in other tissues including heart, liver, pancreas, and kidneys". To examine if this hypothesis is likely to work or not, we examined each of liver, heart, and kidneys for the expression of iNOS and HSP70. Our findings showed that the expression of iNOS was up-regulated in liver, heart, and kidneys of diabetic rats compared with control groups ($p<0.001$). At the same time, we found that the expression of HSP70 was down-regulated in the same tissues [24-27].

Taken together, we think that these findings can frame our hypothesis that diabetes can be neurological disorder, and neurological signals can be part of initiation of both diabetes, and diabetic neuropathies. We further developed another hypothesis in which diabetes and diabetic neuropathies are independent events [28-32].

Conclusion

Although studies in literature about diabetes reviewed the disease from metabolic points of view and have made focus on the disease as part of metabolic syndrome, our previous experiments denoted that the possibility of being a neurological disease at the first degree framed our hypothesis.

References

1. American Diabetes Association (2010) Diagnosis and classification of diabetes mellitus. Diabetes Care 33: S62-S69.
2. Vikas Jain, Sachin Singh Yadav, Jyoti Jain (2018) Metabolic syndrome in type 2 diabetes, an anthropometric and biochemical evaluation - A cross-sectional study from Central India. International Journal of Medical Science and Public Health 7: 784-789.
3. Zubin Punthakee, Ronald Goldenberg, Pamela Katz (2018) Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. Can J Diabetes 42: S10-S15.
4. World Health Day (2016) WHO Calls for Global Action to Halt Rise in and Improve Care for People with Diabetes. First Who Global Report on Diabetes.
5. World Health Organization (2011) Global Status Report on No communicable Diseases 2010. Geneva: World Health Organization 2011: 176.
6. Zafar KS, Pious T, Singh PS, Gautam RK, Yadav SK, et al. (2017) Prevalence of metabolic syndrome in a rural population-a cross sectional study from Western Uttar Pradesh, India. Int J Res Med Sci 5: 2223-2228.
7. Tong PC, Kong AP, So WY, Yang X, Ho CS, et al. (2007) The usefulness of the international diabetes federation and the national cholesterol education program's adult treatment panel III definitions of the metabolic syndrome in predicting coronary heart disease in subjects with type 2 diabetes. Diabetes Care 30: 1206-1211.
8. Sarah A Hannou, Danielle E Haslam, Nicola M McKeown, Mark A Herman (2018) Fructose metabolism and metabolic disease. Clin Invest 128: 545-555.