Relation Between Plasma Apelin level and Peripheral Neuropathy In a Sample of TYPE-2 Diabetic Egyptian Patients

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وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
تَعْلَمُ وكَانَ فَضْلُ
اللَّهِ عَلَيْكَ عَظِيماً
صدق الله العظيم
سورة النساءالآية
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List of Abbreviations

Abb.	Full term
A1C	*Average blood glucose*
AGB	*Adjustable gastric banding*
AMPK	*Activated protein kinase*
AP	*Apelin*
APJ	*Apelin receptor*
ARC	*Arcuate nuclei*
BP	*Blood pressure*
CAN	*Cardiac autonomic neuropathy*
CHD	*Coronary heart disease*
CMAP	*Compound muscle action potential*
CN	*Charcot neuroarthropathy*
CRP	*C-reactive protein*
CVD	*Cardiovascular disease*
DCCT	*Diabetes Control and Complications Trials*
DN	*Diabetic neuropathy*
DPP-4	*Dipeptidyl peptidase-4*
DR	*Diabetic retinopathy*
DSPN	*Distal Symmetric Sensorimotor poly neuropathy*
ELISA	*Enzyme-linked immunosorbent one-step process assay*
eNOS	*Endothelium NO synthase*
FDA	*Food and Drug Administration*
GDM	*Gestational diabetes mellitus*
GIP	*glucose-dependent insulinotropic polypeptide*
GLP-1	*Glucagon like peptide*
GLP-1	*Glucagon-like peptide-1*
GPCR	*G-protein-coupled receptor*

List of Abbreviations cont...

Abb.	Full term

GWAS ..... Genome-wide association studies
hs-CRP ..... high sensitive CRP
IENF..... Intraepidermal nerve fibers
IENFD..... Intraepidermal nerve fiber density
IFG..... Impaired fasting glucose
IGT..... Impaired glucose tolerance
MCV..... Motor conduction velocity
MODY..... Maturity-onset diabetes of the young
NeuPSIG .....Pain Special Interest Group on Neuropathic Pain
NPDR..... Nonproliferative diabetic retinopathy
NPH.....Neutral protamine Hagedorn
PDR..... Proliferative diabetic retinopathy
PPAR ..... Peroxisome proliferator-activated receptor
PVN ..... Paraventricular
QSART..... Quantitative sudomotor axon reflex test
ROS..... Reactive oxygen species
RYGB..... Roux-en-Y gastric bypass
SCV..... Sensory conduction velocity
SFN..... Small fiber neuropathy
SGLT2..... Sodium-Glucose co transporter 2
SMBG ..... Self-monitoring of blood glucose
SNAP..... Sensory nerve action potential
SON ..... Supraoptic
SUs..... Sulfonylureas
UKPDS ..... United Kingdom Prospective Diabetes Study
VEGF..... Vascular endothelial growth factor
WHO ..... World Health Organization

INTRODUCTION

Type two Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD) ***(ADA, 2012).***

Prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.The urban population in developing countries is projected to double between 2000 and 2030.The prevalence of diabetes increases with increasing prevalence of obesity ***(ADA, 2004)***

Excess weight is an established risk factor for type 2 diabetes. There are many links between obesity and type 2 diabetes involving pro inflammatory cytokines [TNF & IL-6], insulin resistance, deranged fatty acid metabolism and cellular processes such as mitochondrial dysfunction and endoplasmic reticulum stress ***(Robert et al., 2011).***

Peripheral neuropathy is one of the most common complications of both type one and type two diabetes ***(Abott et al., 2002).***

Long standing peripheral neuropathic pain associated with peripheral neuropathy occurs in one of six diabetic subjects ***(Daousi et al., 2004).***

In diabetes a complex array of metabolic, vascular and perhaps hormonal factors shift the balance between nerve fiber damage and nerve fiber repair in favor of the former ***(Callaghan et al., 2012).*** This occurs in a fiber selective pattern that preferentially affects distal sensory and autonomic fibers, leading to the progressive loss of sensation that underlies the clinical manifestations of diabetic neuropathy ***(Edwards's et al., 2008).***

Among the ischemic factors, endothelial dysfunction may be especially important, particularly in patients with type 2 diabetes mellitus in pathogenesis of neuropathy ***(Kilos et al., 2000).***

Apelin is a peptide that was identified in 1998 by Professor M. Fujino's team. Apelin is a peptide secreted from adipocytes up regulated in obese state that displays beneficial effects. It lowers blood pressure, modulates pituitary hormone release, food and water intake and regulate insulin ***(Lee et al., 2006).***

Apelin level seems to be beneficial in early detection of diabetic neuropathy. It is noted that it increases in diabetic patients compared with healthy control subjects. When the apelin level was evaluated with regard to the presence of neuropathy; diabetic patient with neuropathy had significantly higher apelin level than the healthy control subjects ***(Hakan et al., 2009).***

AIM OF THE WORK

The aim of this work is to study the relation between plasma apelin level and peripheral neuropathy in a sample of type 2 diabetic Egyptian patients.

Chapter One

DIABETES MELLITUS

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications. Significant evidence exists that supports a range of interventions to improve diabetes outcomes ***(ADA, 2017).***

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood glucose), or when the body cannot effectively use the insulin it produces. Raised plasma glucose, a common effect of uncontrolled diabetes, may, over time, lead to serious damage to the heart, blood vessels, eyes, kidneys and nerves. More than 400 million people live with diabetes ***(WHO, 2016).***

In 2016, 422 million people have diabetes worldwide, up from an estimated 382 million people in 2013 and from 108 million in 1980. Accounting for the shifting age structure of the global population, the prevalence of diabetes is 8.5% among adults, nearly double the rate of 4.7% in 1980 ***(Shi and Hu, 2014).***

The World Health Organization (WHO) estimates that diabetes mellitus resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death. However another 2.2 million

deaths worldwide were attributable to high plasma glucose and the increased risks of cardiovascular disease and other associated complications (e.g. kidney failure), which often lead to premature death and are often listed as the underlying cause on death certificates rather than diabetes ***(WHO, 2016).***

Types of diabetes mellitus

Diabetes can be classified into the following general categories ***(ADA, 2017).***

1. Type 1 diabetes (due to autoimmune B-cell destruction, usually leading to absolute insulin deficiency)
2. Type 2 diabetes (due to a progressive loss of B-cell insulin secretion frequently on the background of insulin resistance)
3. Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
4. Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young [MODY]), diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).
5. Prediabetes mellitus; impaired fasting glucose and impaired glucose tolerance.

Impaired fasting glucose (IFG) refers to a condition in which the fasting plasma glucose or the 3-month average plasma glucose (A1C) is elevated above what is considered normal levels but is not high enough to be classified as diabetes mellitus. It is considered a pre-diabetic state, associated with insulin resistance and increased risk of cardiovascular pathology, although of lesser risk than impaired glucose tolerance (IGT). IFG sometimes progresses to type 2 diabetes mellitus. There is a 50% risk over 10 years of progressing to overt diabetes. Many newly identified IFG patients progress to diabetes in less than three years. IFG is also a risk factor for mortality ***(Nichols et al., 2007).***

Impaired glucose tolerance (IGT) is a pre-diabetic state of dysglycemia, that is associated with insulin resistance and increased risk of cardiovascular pathology. IGT may precede type 2 diabetes mellitus by many years. IGT is also a risk factor for mortality ***(Barr et al., 2007).***

Etiology of diabetes

Causes of type 1 diabetes mellitus**:** Many theories are identified ***(NIH, 2014).***

- Genetic Susceptibility: many risk genes or gene regions have been identified to be related to type 1 diabetes. The most important are HLA-DR3 and HLA-DR4 genes.