Study of Circulating Apelin in Type 1 Diabetic Patients and its Association with Glycemic Control in a Group of Egyptian Population

Thesis

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Doaa Abd Ellatif Ahmed Taha

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List of Abbreviations

Abb.	Full term
ACE2	*Angiotensin-converting enzyme 2*
ACTH	*Adrenocorticotropic hormone*
AGEs	*Activating glycation end products*
AGTRL1	*Angiotensin II receptor type 1*
Akt	*Protein Kinase B*
AMPK	*AMP-activated protein kinase*
AMPK/eNOS pathway	*AMP-activated protein kinase/ Endothelial nitric oxide synthase pathway*
AMPK-PGC1α	*Adenosine monophosphate-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor- γ coactivator 1 α (PGC-1 α)*
AngII	*Angiotensin II*
APE	*Apelin*
APJ /AR	*Apelin receptor*
AQP2	*Aquaporin type 2*
AT1	*Angiotensin II receptor type 1*
AVP	*Arginine vasopressin*
BMI	*Body mass index*
cAMP	*Cyclic adenosine monophosphate*
CSII	*Continuous subcutaneous insulin infusion*
CTGF	*Connective tissue growth factor*
CVD	*Cardiovascular disease*
DKA	*Diabetic ketoacidosis*
ECM	*Extracellular matrix*
eGDR	*Estimated glucose disposal rate*
eGFR	*Glomerular filtration rate*
eNOS	*Endothelial NO synthase*
EPA	*Eicosapentaenoic acid*
ER stress	*Endoplasmic reticulum stress*
ERK	*Extracellular-regulated kinases*

List of Abbreviations **cont...**

Abb.	Full term
ET-1	*Endothelin-1*
FFA	*Free fat acid*
FPs	*Fasting plasma suger*
FSH	*Follicle-stimulating hormone*
GAD	*Glutamic acid decarboxylase*
GFAP	*Glial fibrillary acidic protein*
GLP-1	*Glucagon-like peptide-1*
Glut2	*Glucose transporter 2*
Glut4	*Glucose transporter type 4*
GPCR	*G-protein-coupled receptor*
HDAC1	*Histone deacetylase 1*
HDL	*High-density lipoprotein*
HIF-1a	*Hypoxia-inducible factor 1a*
HLA	*Human Leukocyte Antigen*
HSL	*Hormone-sensitive lipase*
I/R	*Ischemia/reperfusion*
I/R	*Ischemia/reperfusion*
I:C ratio	*Insulin-to-carbohydrate ratio*
IA-2	*Islet-associated autoantibody -2*
IAAs	*Insulin autoantibodies*
ICAs	*Islet cell autoantibodies*
IL-6	*Interleukin-6*
IP3	*Inositide triphosphate*
ISF	*Insulin sensitivity factor*
LADA	*Latent Autoimmune Disease of Adults*
LDL	*Low-density lipoprotein*
LH	*Luteinizing hormone*
LPL	*Lipoprotein lipase*

List of Abbreviations **cont...**

Abb.	Full term
MAPK pathway	*Mitogen-activated protein kinase pathway*
MCP1	*Monocyte chemo attractant protein-1*
MDI	*Multiple daily injections*
miR-361-5p	*micro RNA*
NF-κB	*Nuclear factor-kappa B*
NO	*Nitric-oxide*
NOS/NO pathway	*Nitric oxide synthase /Nitric oxide pathway*
PAI-1	*Plasminogen activator inhibitor type-1*
PARP	*Poly(ADP-ribose) polymerase.*
PCSK3	*Proprotein convertase subtilisin/kexin 3*
PDE3B	*Phosphodiesterase 3B*
PGC1-α	*Peroxisome proliferator-activated receptor γ co-activator 1α*
PI3K	*Phosphatidylinositol 3-kinase*
PI3K/AKT/mTOR pathway	*Phosphoinositide 3-kinases/ Protein kinase B/ mammalian target of rapamycin pathway*
PI3K-Akt Pathway	*Phosphatidylinositol 3-kinase / Protein Kinase B pathway*
PKC	*Protein kinase C*
PKCα	*Protein kinase Cα*
PPARc	*Peroxisome proliferator-activated receptor gamma*
PPs	*Postprandial suger*
PRL	*Prolactin*
PUFA	*Polyunsaturated fatty acid*

List of Abbreviations **cont...**

Abb.	Full term
RAS	*Renin-angiotensin system*
ROS	*Reactive oxygen species*
SGLT1	*Sodium-glucose co-transporter 1*
Sirt3	*Sirtuin 3*
T1D	*Type 1 diabetes*
T2D	*Type 2 diabetes*
TG	*Triglycerides*
TGF-β	*Transforming growth factor-β*
TGF-β	*Transforming growth factor-β*
TNFa	*Tumor necrosis factor-alpha*
TNFβ	*Tumor necrosis factor-beta*
VEGF	*Vascular endothelial growth factor*
ZnT8	*Zinc transporter protein*

ABSTRACT

Background: Type 1 diabetes mellitus (T1DM) is one of the most common chronic and metabolic diseases worldwide. The incidence of T1DM is reported to be increasing by 3-5% per year, and the number of people with diabetes is estimated to reach 380 million by 2025. Several studies have shown that TIDM is associated with metabolic abnormalities and alteration of adipose tissue hormones (adipokines)**.** Apelin, one of the most abundantly expressed adipocytokine, is a bioactive peptide and produces its effects through a cell surface G protein-coupled receptor called APJ.The apelinergic system, is involved in a wide range of functions including regulation of body fluid homeostasis**,** cardiovascular system **,** angiogenesis and energy metabolism **.** Additionally, apelin participates in pathological processes, including obesity and diabetes. Apelin plays a beneficial role in energy metabolism.

Objectives: The aim of this study is to evaluate serum Apelin levels in patients with type 1 diabetes and to correlate the serum Apelin level and glycemic control.

Patients and Methods: This study was a cross sectional study. Participants were classified into two groups. The first group included 60 patient with T1DM recruited from Ain Shams University Endocrinology and Diabetes outpatient clinics in Cairo during the period from June 2019 to January20٢٠ and the second group included 40 healthy controls. Serum apelin (APLN), FBS, 2hrPP, HbA1c, lipid profile and eGDR were measured for each case.

Results: Comparison between T1DM patients and controls revealed that serum apelin levels, were significantly increased in cases compared to controls. Negative correlations were found between Apelin and HbA1c% in the diabetic group as a marker for glycemic control so apelin may have a promising role as biomarkers in T1DM.

Conclusion: Our study showed that apelin concentrations were increased in type 1 diabetic patients compared to healthy controls. The potential association of apelin with insulin secretion and action may reveal new pathways in the pathogenesis of type 1 diabetes. Apelin in T1DM patients may be considered as promising adipokines for predicting glycemic control.

Keywords: Adipokines, Circulating Apelin, Type 1 Diabetic Patients, Glycemic Control.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a common, chronic and metabolic disease characterized by hyperglycemia as a cardinal metabolic feature, results in the destruction of the insulin-producing beta cells of the pancreas ***(International Diabetes Federation, 2018).*** Global epidemiological studies have demonstrated that the incidence of T1D has been increasing to 2–5% annually ***(Shojaeian et al., 2018).*** Several studies have shown that TIDM is associated with metabolic abnormalities, and alteration of adipose tissue hormones (adipocytokines or adipokines) ***(Bulcão et al., 2006).***

Apelin, a recently described adipocytokine, is abundantly expressed in adipose tissue and produced in many body parts by the endothelial cells ***(Kleinz et al., 2005).*** Apelin is a bioactive peptide, produced by white adipose tissue. It is synthesized as a prepropeptide then modified into smaller peptides with higher potency. It produces its effects through a cell surface G protein-coupled receptor called APJ ***(Shin et al., 2017)***. Preproapelin is cleaved from its C-terminus to produce a mature apelin peptides.

Its extensive tissue distribution suggests, that the apelin/APJ system, also known as an apelinergic system, is involved in a wide range of functions including regulation of body fluid homeostasis**,**blood pressure (***Wu et al., 2014),*** cardiac contractility ***(Perjes et al.,2014)***, angiogenesis (***Zhang***

et al., 2014), and energy metabolism ***(Bertrand et al., 2015)***. Additionally, apelin participates in pathological processes, including heart failure (***Azizi et al., 2015)***, obesity (***Boucher et al., 2005***), diabetes ***(Alipour et al., 2017)***, and cancer (***Cabia et al.,2016).***

Apelin, as a member of the adipose tissue-derived peptides, might contribute to metabolic disorders. Some data have indicated that there is a correlation between plasma insulin level and apelin expression in adipocytes. Apelin plays a beneficial role in energy metabolism by increasing glucose uptake and insulin sensitivity (***Bertrand et al., 2015***). One of the first apelin effects observed on glucose metabolism, apart from that on insulin secretion (***Sorhede et al., 2005)*** is Apelin stimulated glucose transport and its glucose-lowering effect was additive to that of insulin ***(Dray et al., 2008).*** Apelin inhibits lipolysis in adipocytes and is involved in angiogenesis in adipose tissue.

Literature data documented also that glucose arrival in the intestine causes its own absorption by inducing the paracrine secretion of apelin. A transient increase in blood glucose levels in the portal vein could induce rapid secretion of insulin ***(Fukaya et al., 2007***), and an improved insulin sensitivity ***(Delaere et al., 2010)***. Thus, apelin could also regulate glucose metabolism, by promoting glucose absorption by the enterocytes and then by increasing portal blood glucose and insulin secretion. This could be in agreement with the fact

that apelin was shown to increase GLP-1 secretion (***Wattez et al., 2013).***

Levels of apelin and APJ mRNA increase in white adipose tissue and plasma with obesity. Hyperinsulinemia may be the main cause for the rise in the expression of apelin ***(Boucher et al., 2005)***. Data showed a positive correlation between the level of apelin in plasma and the body mass index ***(Heinonen et al., 2005).*** Patients with obesity have impaired insulin-stimulated vasodilation and increased ET-1 (endothelin 1) vasoconstriction, which may contribute to insulin resistance and vascular damage. Apelin enhances insulin sensitivity and glucose disposal but also acts as a nitric oxide (NO)–dependent vasodilator and a counter-regulator of AT_1 (angiotensin II type 1) receptor–induced vasoconstriction so, apelin might beneficially impact obesity-related vascular dysfunction ***(Schinzari et al., 2017).***

In diabetes-related diseases, such as retinopathy, nephropathy or cardiomyopathy apelin has a protective effect against oxidative stress and apoptosis ***(Day et al., 2013).***

Additionally, apelin play a role in retinal neovascularization under diabetic retinopathy (***Liu et al., 2017)***. In diabetic cardiomyopathy Overexpression of apelin resulted in augmented myocardial angiogenesis, attenuated diabetic cardiac hypertrophy, and improved cardiac function ***(Hou et al., 2015)***. Literature data documented also that apelin has anti-