Assessment of Serum Apelin and Some Risk Factors in Type 2 Diabetes Mellitus

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Abstract

Background: Adipose tissue hormones, adipokines, play an important role in diabetes mellitus. Apelin has been added to the family of adipokines. Many risk factors can be complicated in the progress of diabetes.

Objective: The aim of this study was to assess of serum apelin and some risk factors in type 2 diabetic patients and compared them with the control group.

Patients and Methods*:* This study encompassed 45 diabetic patients (23 obese and 22 non-obese). They were compared with 45 healthy subjects as control group. All diabetic patients were attended to the National Diabetic Center/ Al- Mustansiriya University during the period from November 2017 until the end of May 2018. All participants experienced anthropometric, clinical, and biochemical examinations.

Results: There was a significant increase (P= 0.01) in body mass index for obese as compared to non-obese type 2 diabetic patients. Also, there was a significant increase (P < 0.05) in fasting blood glucose, serum insulin, homeostasis model assessment for insulin resistance, and serum apelin in diabetic patients as compared to the controls. While, there was a decrease in quantitative insulin-sensitivity check index in diabetic group as compared to the controls. Also, there was a significant increase (P= 0.01) in serum lipid profiles except high density lipoprotein cholesterol in diabetic patients as compared to the controls.

Conclusions*:* The significant alterations in serum apelin levels in type 2 diabetic patients as compared to the controls were recommended a probable role of these adipokines with the occurrence of obesity and insulin resistance. There was abnormal lipid levels during hyperglycemia induced dyslipidemia are hypercholesterolemia, hypertriglyceridemia, and elevated low density lipoprotein cholesterol.

Keywords: Diabetes mellitus, Apelin, Risk factors for diabetes.

Introduction:

Diabetes mellitus (DM) has been defined as a metabolic disorder characterized by hyperglycemia that progress as a consequence of defects in insulin secretion, insulin action, or both [1].

Several pathogenic processes are complicated in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin insufficiency to abnormalities that result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues which results from inadequate insulin secretion and/or reduced tissue responses to insulin at one or more points in the complex pathways of hormone action [2].

Insulin resistance (IR), earlier thought to be a rare complication of the treatment of diabetes, is now documented as a component of several disorders, comprising obesity, stress, and infection [3].

Obesity is a chronic disease of multi factorial origin. It's now extensively accepted that obesity is connected with many metabolic disorders including type 2 DM (T2DM) [4]. The major relation between obesity and T2DM is IR [5]. Adipose tissue depots are the most vulnerable target to mediate significant immune cells infiltration and inflammation contributing to systemic inflammation and IR in obese humans [6].

A person is obese when body mass index (BMI) ≥ 30 kg/m^2. Increased waist to hip ratio (abdominal obesity) is a greater risk. Obesity is connected with substantially improved cardiovascular (CV) risk. Obesity causes glucose intolerance, IR, hypertension, and dyslipidemia [7].

Adipose tissue secretes a number of bioactive peptides or proteins, collectively named "adipokines". They play a central role in energy and vascular homeostasis, as well as immunity, and are essential to the pathogenesis of the metabolic syndrome [8].

Adipokines family comprises leptin, adiponectin, resistin, and apelin has been added to that family. Adipokines are categorized as pro- and anti-inflammatory adipokines according to their effects on inflammatory responses in adipose tissues [9].

Apelin is an endogenous ligand of the G protein-coupled receptor APJ. Apelin is originally synthesized as a 77-amino acid prepropeptide that is cleaved into shorter forms [10]. Apelin and its receptor APJ are broadly expressed in numerous tissues [11], the main active forms of apelin are apelin-13, -17, and -36 and the pyroglutaminated isoform of apelin-13 (Pyr(1)-apelin-13) categorized by a higher resistance to degradation [12].

Obesity andT2DM lead to a rise in serum apelin levels, as designated in earlier study [13]. Also, plasma apelin has been shown to be an original biomarker for expecting DM [14].

Therefore, the aim of this study was to assessment of serum apelin and some risk factors in type 2 diabetic patients and compared them with the control group.

Patients and Methods:

This study conducted 45 diabetic patients (23 obese and 22 non-obese). They were equated with 45 healthy subjects as control group. All diabetic patients were denoted to the National Diabetic Center/ Al-Mustansiriya University during the period from November 2017 until the end of May 2018. They were treated with anti-diabetic drugs. All subjects who have renal or liver or malignant disorders, and pituitary or thyroid gland diseases were excluded from this study.

Anthropometric Measurements: Anthropometric parameters involved waist circumferences (WC), waist to hip ratio (WHR), and BMI. Body mass index was calculated as weight in kilograms divided by height in meters square (kg/m^2) according to the following equation:

$$\mathrm{BMI} = \frac{\mathrm{mass\ (kg)}}{(\mathrm{height(m)})^2}$$

Biochemical Assessment:

Blood samples were collected after 12 hours of fast. Fasting blood glucose (FBG), glycated hemoglobin (HbA1C), and lipid profile including total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were estimated by enzymatic colorimetric methods using auto-analyzer (SIEMENS, Cobas, Roche, Germany).

Hormonal Assessment:

Serum insulin concentrations were assessed by the DRG

insulin ELISA kit.

Estimation of IR:

Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR) index and quantitative insulin-sensitivity check index (QUICKI) according to the following equations:-

HOMA-IR= $G_0 \times I_0/405$

QUICKI= $1/ [\log G_0 + \log I_0]$

G_0:Fasting glucose in (mg/dl) I_0: fasting insulin in (μU/ml)

The cutoff points for defining IR are a fasting insulin levels of 12.94 μU/ml, HOMA-IR ≥ 3.04, and QUICKI= 0.32

Serum apelin level was estimated using ELISA kits (Shanghai Yehua Biological Technology Co., Ltd. China).

Statistical Analysis:

Statistical analysis of data were done using SPSS software version 17, USA. Statistical tests used ANOVA to analysis of variance. Data were expressed as means (±SD); statistical significance was approved at $P < 0.05$.

Results:

Clinical and anthropometric data for T2DM and control group demonstrates in table (1). There was a significant increase ($P < 0.05$) in age and WC in T2DM as compared to the control group. While, there was no significant difference ($P > 0.05$) in WHR and BMI between the two groups.

There was a significant increase (P= 0.01) in BMI for T2DM in obese group who had BMI ≥ 30 kg/m^2 as compared to non-obese group, table (2). Metabolic characteristic of T2DM and control group are illustrate in table (3). There was a significant increase (P= 0.01) in FBG, HbA1c, insulin, and HOMA-IR while, there was a decrease in QUICKI in T2DM group as compared to the controls, but it was not significant.

There was a significant increase (P=0.0001) in serum apelin levels for female group as compared to male group in diabetic patients also, there was a significant difference among DM groups and control group, table (4).

There was a significant raise (P=0.01) in serum TC, TG, LDL-C, and lipoproteins ratios in T2DM as compared to the controls. While, a significant decrease (P=0.01) was found in serum HDL-C for diabetic group as compared to the controls as shown in table (5).

Table (1): Clinical and anthropometric data for T2DM and control group

Parameters	T2DM	Control	P value
Number	45	45	-
Age (years)	41.56 ± 0.56	39.58 ± 0.71	0.01
WC (cm)	91.01 ± 0.69	87.15± 2.25	0.01
WHR	0.94 ± 0.01	0.83 ± 0.01	0.04
BMI (kg/m^2)	29.02 ± 0.39	27.18 ± 0.78	0.07

P < 0.05: Significant

Table (2): Difference between T2DM groups according to BMI

Parameters	T2DM		P value
	Obese	Non-obese	
BMI (kg/m^2)	33.52 ± 0.62	24.52 ± 0.16	0.01

P < 0.05: Significant

Table (3): Metabolic characteristic of T2DM and control group

Parameters	T2DM	Control	P value
FBG (mg/dl)	180.87 ± 10.01	94.08 ± 1.27	0.01
HbA1c (%)	8.49 ± 0.28	4.67 ± 0.06	0.01
Insulin (µU/ml)	37.03 ± 1.53	19.81 ± 1.48	0.01
HOMA-IR	17.92 ± 1.68	4.79 ± 0.41	0.01
QUICKI	0.25 ± 0.01	0.26 ± 0.01	0.24

P < 0.05: Significant

Table (4): Difference in serum apelin levels between gender in T2DM and control group

Parameters	T2DM		Control		P value
	Male (n= 22)	Female (n= 23)	Male (n= 22)	Female (n=23)	
Apelin (ρg/ml)	191.10 ± 7.01	497.45 ± 16.15	136.10 ± 12.22	184.92 ± 9.78	0.0001

P < 0.05: Significant

Table (5): Lipid characteristic of T2DM and control group

Parameters	T2DM	Control	P value
TC (mg/dl)	272.65 ± 18.78	163.00 ± 5.26	0.01
TG (mg/dl)	272.51 ± 14.84	116.17 ± 6.60	0.01
HDL-C (mg/dl)	40.49 ± 0.66	63.27 ± 1.13	0.01
LDL-C (mg/dl)	178.19 ± 15.47	76.33 ± 5.22	0.01
TC/HDL-C ratio	7.16 ± 0.61	2.67 ± 0.14	0.01
TG/HDL-C ratio	7.11 ± 0.79	1.93 ± 0.14	0.01
LDL-C/HDL-C ratio	4.68 ± 0.47	1.28 ± 0.11	0.01

P < 0.05: Significant

Discussion:

Obesity occurrence has been collective extremely over the last 30 years. Metabolic diseases such as IR, T2DM, hypertension, non-alcoholic fatty liver disease, polycystic ovarian diseases, and numerous types of cancer are initiated by severe adiposity [15].

In this study, there was an elevation in WC, WHR, and BMI in diabetic patients as compared to the controls.

This study exposed a significant elevation in FBG and HbA1c in diabetic patients comparing with control group. These results are probable due to the fact that the main distinguishing feature of DM is hyperglycemia.

Concerning metabolic parameters, significant improved values of fasting serum insulin among T2DM were detected. There was evidence of deteriorating of IR indicators with significantly improved fasting insulin and HOMA-IR; and diminished QUICKI in T2DM group, compared to the control group [16]. This is may be due to increase glucotoxicity and lipotoxicity lead to the progressive loss of β-cells [17].

This is in accordance with the study by Zuliani et al, [18] which recommended that IR and

visceral adiposity, as measured by WC, donated rise to low grade inflammation. Waist circumference is strongly connected to visceral fat and abdominal adiposity [19].

Visceral adipose tissue has number of metabolic, endocrine, and immunological functions that are complexly related to the pathogenesis of the metabolic syndrome [20]. This is accomplished through secretion of a diversity of cytokines or adipokines. Altered secretion of these led to inflammation along with variations in glucose and lipid homeostasis [21]. This has in turn been related to nutrient excess, which causes adipocyte hypertrophy and hyperplasia inciting hypoxic injury that activates the inflammatory response. How this inflammation causes metabolic dysfunction is not absolutely unstated; however, a number of molecular signaling pathways are reflected to be complicated in directing a metabolic challenge into an inflammatory response, such as inhibition of the insulin receptor [22].

The results of this study demonstrate that patients with T2DM have significantly increased in serum apelin levels compared to non-diabetic individuals, also it was a significantly increase in female as associated to male. The relationship between T2DM and apelin is dependent on the presence of alterations in glucose homeostasis. This study also show that determinant of serum apelin levels is the basal disposition index, a surrogate measure of the two major defects in T2DM, defective insulin secretion and decreased insulin-sensitivity. Further support on this relationship is assumed by the low levels of apelin detected in type 1 diabetic subjects, where insulin secretion is absent and IR is usually not current. Also it has been observed improved apelin concentrations in insulin-resistant type 2 diabetic patients, and this increase associated positively with insulin levels. The compensatory role of apelin in glucose homeostasis was also established by the phenotype of apelin null mice that are hyperinsulinemic and IR. It was shown that apelin treatment in these insulin-resistant obese-mice improves insulin sensitivity [23]. All together, these facts may designate that the increased apelin levels in T2DM could represent a compensatory mechanism to diminish both IR and reduced insulin-secretion. Alternatively, the apelin increase may be due to a so called apelin-resistance, driven by yet unknown mechanism determining this effect.

In this study, dyslipidemia performed among diabetic patients whom show a significant increase in serum levels of TC, TG, LDL-C, and lower level of HDL-C as compared to non-diabetic patients which is parallel to earlier studies [24, 25]. The dyslipidemia observed in diabetic patients group are common in and has varied clarifications [26].

Dyslipidemia is one of the main risk factors for cardiovascular diseases (CVD) in hyperglycemic patients. High TG, low HDL-C, and increased LDL-C are the distinctive feature of diabetic dyslipidemia [27].

Conclusions:

The significant alterations in serum apelin levels in T2DM as compared to the controls were recommended a probable role of these adipokines with the occurrence of obesity and IR. This study showed common abnormal lipid levels during hyperglycemia induced dyslipidemia are hypercholesterolemia, hypertriglyceridemia, and elevated LDL-C. Results recommend dyslipidemia is more predominant in patients consuming poor glycemic control which might play a main role in the progress of CVD among diabetic patients. Combined lipid abnormalities are more as associated to isolated or single irregularity in lipid profile. Optimal care, regularly monitoring of blood glucose level and lipid profile should be cooperative to cure this irregularity.

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