Study the Role of Serum Apelin, Obesity, and Duration of the Disease in Type 2 Diabetes Mellitus

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Abstract

Background: Insulin and apelin appears to play a range of roles in β-cell growth and insulin secretion and most importantly interaction with other hormonal mediators and regulators of energy and metabolism.

Objective: The goal of this study was to evaluate the role of serum apelin in obese patients having type 2 diabetes mellitus compared to non-obese diabetic patients and the control group and evaluation of their association with duration of diabetes.

Patients and Methods: This study encompassed 45 diabetic patients (23 obese and 22 non-obese) and they were compared with 22 healthy subjects as control group. All individuals were referred to the Medical city Hospital/ Baghdad during the period from November 2017 through May 2018. All participants experienced anthropometric, biochemical, and clinical examinations.

Results: There was a significant increase (P=0.0001) in serum lipid profiles except high density lipoprotein cholesterol. Also, there was a significant increase in body mass index, fasting serum glucose, serum insulin, homeostasis model assessment for insulin resistance, and serum apelin in diabetic group as compared to the controls. While, there was a significant decrease (P=0.0001) in fasting serum glucose to insulin ratio and quantitative insulin-sensitivity check index in diabetic group as compared to the controls. There was a significant increase in fasting serum glucose to insulin ratio in diabetic patients with duration greater than 2 years as compared to diabetic patients with duration less than 2 years.

Conclusions: The significant alterations in serum apelin levels in diabetic patients as compared to the controls were suggested a possible role of these adipokines with the presence of obesity and insulin resistance.

Keywords: Diabetes mellitus, Obesity, Apelin.

Introduction:

Type 2 diabetes mellitus (T2DM) is a composite condition characterized by the imbalance between insulin resistance (IR) and insulin secretion that induce liver glucose output by inhibiting glycogen formation and stimulating glycogenolysis and gluconeogenesis then extra rates of liver glucose production result in the development of overt DM, especially fasting plasma glucose [1].

It is known that T2DM and obesity are bound common metabolic problems [2]. It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist–hip ratio (WHR) and total cardiovascular diseases (CVD) risk factors [3].

Insulin resistance is recognized to be a major risk factor in the etiology of T2DM, dyslipidemia, hypertension, atherosclerotic vascular disease, and may be a risk influence for coronary heart disease and stroke as well [4]. Numerous risk influences e.g. age, obesity, physical inactivity, body fat distribution, and hyperinsulinemia may be deliberated indicators of IR. Insulin resistance is a interpreter for the development of T2DM even in persons with normal glucose tolerance [5].

The adipokines or adipocytokines are cytokines secreted by adipose tissue, their action is thought to modify several obesity-related diseases [6]. Adipose tissue is an endocrine organ that secretes various protein hormones, encompassing apelin are formed principally in the adipocytes of white adipose tissue [7].

Apelin, an endogenous ligand for the G-protein-coupled APJ receptor, has been newly deliberated in obesity research. It is not only expressed in adipocyte tissue, but also widely expressed in numerous other organs [8].

A significant relationship occurs between adipose tissue, IR, and T2DM. Fat tissue plays a role in the inflammatory status and IR by liberating a variety of hormones and adipokines [9].

Apelin was exposed to prevent insulin secretion [10] and to reduce glycemia in mice [11]. Moreover, during a hyperinsulinemic-euglycemic clamp, apelin increases insulin sensitivity by increasing glucose uptake, primarily in skeletal muscles through an AMP-activated protein kinase dependent pathway. Consequently, apelin-deficient mice progress IR that can be reversed by exogenous apelin treatment [12]. Obesity andT2DM lead to an increase in apelin circulating concentrations, as described in previous study [13]. Interestingly, plasma apelin has been shown to be a novel biomarker for predicting diabetes in humans [14].

Therefore, the aim of this study was to evaluate the role of serum apelin in obese and non-obese type 2 diabetic patients and evaluation of their association with duration of DM.

Patients and Methods:

This study encompassed 45 diabetic patients (23 obese and 22 non-obese) and they were compared with 22 healthy subjects as control group. All individuals were referred to the Medical City Hospital/ Baghdad during the period from November 2017 through May 2018.

All diabetic patients were treated with anti-diabetic drugs. All subjects who have renal or liver or malignant disorders, and pituitary or thyroid gland diseases were not deliberated to be in this study.

Anthropometric Measurements:

Anthropometric parameters involved waist circumferences (WC), WHR, and BMI have been measured. Body mass index was calculated as weight in kilograms divided by height in meters square (kg/m^2). Systolic and diastolic blood pressures (SBP and DBP) also were measured.

Biochemical Assessment:

Blood samples were collected after 12 hours of fast. Fasting serum glucose and lipid profile were estimated by enzymatic colorimetric methods using auto-analyzer

Hormonal Assessment:

Serum insulin concentrations were assessed by the DRG
insulin ELISA kit.

Estimation of IR:

Insulin resistance was estimated based on calculation of the homeostasis model assessment (HOMA) index for each individuals and quantitative insulin-sensitivity check index (QUICKI) according to the following equations:-

$$\text{HOMA-IR} = \frac{I_0 \times G_0}{405}$$

$$\text{QUICKI} = \frac{1}{[\log (I_0) + \log (G_0)]}$$

G_0:Fasting glucose, I_0: fasting insulin

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 way for analysis of variance. Data were expressed as means (±SD); statistical significance was agreed at $P<0.05$.

Results:

Clinical and anthropometric data for DM groups and control are demonstrated in table (1). There was a significant difference in age between the two groups. Also, there was a significant difference in WC, WHR, BMI, and SBP among the groups, ($P < 0.05$).

There was a significant raise (P=0.0001) in FSG, HbA1c, insulin, and HOMA-IR in DM groups as compared to the controls. While, there was a significant decrease (P=0.0001) in glucose/insulin (G/I) ratio and QUICKI in DM groups as compared to the controls, table (2).

There was a significant raise (P=0.0001) in serum TC, TAG, LDL-C, TC/HDL-C ratio, TAG/HDL-C, LDL-C/HDL-C, and serum apelin, while a significant decrease (P=0.0001) in serum HDL-C was noticed in DM groups as compared to the controls as shown in table (3).

Effect of DM duration in some clinical and biochemical factors are characterized in table (4). There was a significant difference in SBP, DBP, and G/I ratio in diabetic patients with DM duration greater than 2 years as compared to diabetic patients with DM duration of less than 2 years.

Table (1): Clinical and anthropometric data for DM groups and control

Parameters	DM		Control	P value
	Obese	Non-obese		
Number (Female/Male)	(12/11)	(12/10)	(12/10)	-
Age (Years)	42.30 ± 0.52a	40.82 ± 0.83a	37.91 ±1.11b	0.0033
WC (cm)	105.61±0.54a	76.41 ± 1.03b	72.4±0.84c	0.0001
WHR	0.96 ± 0.01a	0.92 ± 0.01b	0.73±0.01c	0.0001
BMI (Kg/m2)	33.52 ± 0.62a	24.52 ± 0.16b	22.23±0.37c	0.0001
SBP (mmHg)	133.86±1.33a	132.86 ± 1.38b	120.04 ±0.55c	0.0001
DBP (mmHg)	81.69 ± 0.83a	79.56 ± 0.63b	78.90 ± 0.92b	0.0354

Table (2): Metabolic characteristic of the studied groups

Parameters	DM		Control	P value
	Obese	Non-obese 0.73±0.01c		
FSG (mg/dl)	231.82 ± 10.42a	127.59 ± 6.76b	88.32 ± 1.43c	0.0001
HbA1c (%)	9.92 ± 0.33a	6.99 ± 0.14b	4.44 ± 0.07c	0.0001
Insulin (µU/ml)	40.92 ± 2.02a	32.96 ± 2.01b	13.07 ± 1.29c	0.0001
G/I ratio	3.90 ± 0.07c	5.70 ± 0.08b	8.04 ± 0.66a	0.0001
HOMA-IR	24.50 ± 2.40a	11.04 ± 1.19b	0.33 ± 2.94c	0.0001
QUICKI	0.25 ± 0.001c	0.28 ± 0.004b	0.33± 0.01a	0.0001

Table (3): Lipid characteristic and serum apelin for the studied groups

Parameters	DM		Control	P value
	Obese	Non-obese		
TC (mg/dl)	359.52 ± 10.11a	187.98 ± 7.03b	140.63 ± 1.66c	0.0001
TAG (mg/dl)	356.56 ± 14.43a	184.63 ± 6.75b	104.66 ± 4.21c	0.0001
HDL-C (mg/dl)	38.69 ± 0.75c	42.36 ± 0.98b	67.83 ± 1.35a	0.0001
LDL-C (mg/dl)	245.80 ± 11.73a	107.52 ± 6.61b	51.82± 2.12c	0.0001
TC/HDL-C ratio	9.65 ± 0.90a	4.55 ± 0.25b	2.09 ± 0.06c	0.0001
TAG/HDL-C ratio	9.62 ± 1.34a	4.47 ± 0.26b	1.57 ± 0.08c	0.0001
LDL/HDL-C ratio	6.64 ± 0.71a	2.63 ± 0.20b	0.78 ± 0.05c	0.0001
Apelin (ρg/ml)	420.19 ± 12.07a	299.73 ±10.55b	115.04 ± 6.99c	0.0001

Table (4): Effect of DM duration in some clinical and biochemical factors

Parameters	Duration of DM (Mean ± SD)	
	< 2 years	> 2 years
BMI (kg/m2)	30.33 ± 0.33	29.03 ± 0.80 NS
SBP (mmHg)	122.00 ± 1.15	134.19 ± 0.89**
DBP (mmHg)	75.00 ± 0.00	79.54 ± 0.56*
FSG (mg/dl)	180.74 ± 10.72	182.67 ± 3.48 NS
Insulin (μU/ml)	31.61 ± 0.31	37.42 ± 1.62 NS
G/I ratio	5.78 ± 0.11	4.75 ± 0.15*
HOMA-IR	14.26 ± 0.33	18.18 ± 1.79 NS
QUICKI	0.27 ± 0.01	0.26 ± 0.003 NS
Apelin (ρg/ml)	154.96 ± 2.22	376.04 ± 14.45 NS

** (P<0.05), ** (P<0.01), NS: Not-Significant.*

Discussion:

This study revealed a significant elevation in FSG in diabetic patients comparing with control group and in obese diabetic as compared to non-obese. These results are expected due to the fact that the main characteristic feature of DM is hyperglycemia. Blood glucose is tightly controlled by two key processes: insulin secretion by pancreatic ß-cells in response to a nutrient and insulin action on major target organs, i.e., skeletal muscle, liver and adipose tissue. Type 2 diabetes mellitus is often associated with obesity and results from insufficient insulin production/secretion and IR [15].

Insulin resistance is a precursor and mechanism of T2DM and is accompanied with progress of hypercoagulability and atherosclerosis. It is a essential pathophysiologic contributor to the increased risk of CVD [16].

In the present study, there was a significant increase in serum insulin in diabetic patients as compared to the controls and there was an elevation in G/I ratio in non-obese diabetic as compared to obese. This is may be due to increase glucotoxicity, lipotoxicity, endoplasmic reticulum-induced stress, and apoptosis lead to the progressive loss of β-cells [17]. A combination of peripheral IR and dysfunctional insulin secretion by pancreatic β-cells is associated with the pathogenesis of T2DM [18]. However, DM is associated with a wide variety of complications such as cardiomyopathy, neuropathy, and nephropathy; therefore, innovative mechanistic approaches deciphering IR are needed. Many pathophysiological parameters are implicated in IR [19]. Although the exact natures of these parameters are not absolutely understood, it is widely established that inflammation, genetic, habitual, environmental, and other epigenetic factors play a significant role [20]. To further elucidate on dysfunctional insulin signaling, it has been considered the impact of IR on lipid metabolism at preclinical level and found that IR and DM are powerful predictors of quantitative and qualitative features of lipoprotein dysfunction and are directly related with increased atherogenic risk. Obesity, dyslipidemia, and visceral adiposity are common risk features for IR, T2DM, and CVD [21].

In this study, dyslipidemia appeared among diabetic patients whom show a significant increase in serum levels of TC, TAG, LDL-C, and lower level of HDL-C as compared to non-diabetic patients which is similar to previous studies [22, 23]. The dyslipidemia noticed in diabetic patients group are common in and has diverse clarifications [24].

The present results also showed a significant increase in serum apelin levels in diabetic patients in comparing with the controls which is in agreement with some studies [25, 26]. Also, it is in agreement with other studies [27] which found that apelin levels showed higher significant values in obese diabetic group as compared to non-obese and control groups. It may be postulated that a longer duration of DM might worsen IR and insulin secretion, further influencing apelin levels. The obese diabetic patients were in the early stage of their natural history, when the metabolic defects were not fully expressed, as shown by the possible reversal of T2DM with lifestyle measures [28]. Therefore the differences in DM duration may underlie discrepancies between studies. In contrast to non-obese diabetic, this study found that serum apelin concentration was significantly increased in obese diabetic as compared to controls which was dis agreement with the findings of Li and co-workers [29] who observed a significant elevation of apelin level of non-obese diabetic as compared to obese. The possible explanation of high apelin level may also inhibit the release of insulin, aggravating the disorders of glucose metabolism which was also proved by Beltowski and this may provide evidence that apelin might have a causal role in T2DM story or it may be a compensatory response to further worsening of IR in chronic diabetic patients [30] as well as the anti-diabetic treatment may be related to this elevation of apelin level specially with chronic use of these drugs as observed by Fan et al., who found that treatment with metformin elevates apelin levels in type 2 diabetic patients [31].

Conclusions:

The significant alterations in serum apelin levels of diabetic patients as compared to controls were suggested a possible role of these adipokines with the presence of obesity, IR, and, T2DM. So, the assay and assessment of serum apelin levels could be beneficial in early detection of T2DM and prevention of its unfavorable consequences especially the CV complications and atherosclerosis. It was still unclear whether altered adipokines and inflammatory cytokines were a cause or compensatory mechanism to IR and T2DM.

References:

1- Holt RIG and Hanley NA. Essential endocrinology and diabetes, Wiley-Blackwell. 2012, 6th ed., Part 3, P. 285.

2- Jung UJ and Choi MS. Obesity and its metabolic complications: The role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and non-alcoholic fatty liver diseases. Int J Mol Sci. 2014; 15(4): 6184–6223.

3- Sweeting HN. Measurement and definitions of obesity in childhood and adolescence: A field guide for the uninitiated. Nutr J., 2007; 6(1):32

4- Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab 2004; 89(6):2583‑9

5- Boden G. Pathogenesis of type 2 diabetes. Insulin resistance. Endocrinol Metab Clin North Am 2001; 30(4):801-15.

6- Lehr S, Hartwig S, and Sell H. Adipokines: a treasure trove for the discovery of biomarkers for metabolic disorders. Proteomics clinical applications., 2012; 6(1-2): 91–101

7- Sharabiani MT, Vermeulen R, Scoccianti C, Hosnijeh FS, Minelli L, Sacerdote C, Palli D, Krogh V, Tumino R, Chiodini P, Panico S, and Vineis P. Immunologic profile of excessive body weight. Biomarkers, 2011; 16(3): 243–51.

8- Lee DK, George SR and O'Dowd BF. Unravelling the roles of the apelin system: prospective therapeutic applications in heart failure and obesity. Trends Pharmacol. Sci 2006; 27(4):190-4.

9- Cha JJ, Min HS, Kim K, et al. Long-term study of the association of adipokines and glucose variability with diabetic complications. Korean J Intern Med 2016; 4(2):367-382.

10- Sorhede-Winzell M, Magnusson C, Ahren B. The apj receptor is expressed in pancreatic islets and its ligand, apelin, inhibits insulin secretion in mice. Regul Pept. 2005; 131(1-3):12–7.

11- Dray C, Knauf C, Daviaud D, et al. Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. Cell Metab. 2008; 8(5):437–45.

12- Yue P, Jin H, Aillaud-Manzanera M, et al. Apelin is necessary for the maintenance of insulin sensitivity. Am J Physiol Endocrinol Metab. 2010; 298(1): E59–E67.

13- Castan-Laurell I, Dray C, Attane C, Duparc T, Knauf C, Valet P. Apelin, diabetes, and obesity. Endocrine. 2011; 40(1):1–9.

14- Ma WY, TY Y, Wei JN, et al. Plasma apelin: a novel biomarker for predicting
diabetes. Clin Chim Acta. 2014; 435:18–23.

15- Paz, Vital, Elena, Larrieta and Marcia, Hiriart. Sexual dimorphism in insulin sensitivity and susceptibility to develop diabetes in rats. J. End., 2006; 190(2):425-32.

16- Laakso M, Kussisto J. Insulin resistance and hyperglycemia in cardiovascular diseases development. Nature review Endocrinology 2014; 10(5):293-302.

17- Petersen MC, Vatner DF, and Shulman GI. Regulation of hepatic glucose metabolism in health and disease, Nature Reviews

Endocrinology, 2017; 13(10): 572–87.

18- Mishra M and Ndisang JF. A critical and comprehensive insight on heme oxygenase and related products including carbon monoxide, bilirubin, biliverdin and ferritin in type-1 and type-2 diabetes, Current Pharmaceutical Design, 2014; 20(9):1370–91.

19- Vladu M, Clenciu D, Efrem IC, et al., Insulin resistance and chronic kidney disease in patients with type 1 diabetes mellitus, Journal of Nutrition and Metabolism, 2017; 2017:1-5.

20- Ndisang JF and Jadhav A. Heme arginate therapy enhanced adiponectin and atrial natriuretic peptide, but abated endothelin-1 with attenuation of kidney histopathological lesions in mineralocorticoid-induced hypertension, The Journal of Pharmacology and Experimental Therapeutics, 2010; 334(1):87–98.

21- Couture P, Tremblay AJ, Kelly I, Lemelin V, Droit A, and Lamarche B. Key intestinal genes involved in lipoprotein metabolism are downregulated in dyslipidemic men with insulin resistance. J Lipid Res. 2014; 55(1): 128–37. 22- Sawant AM, Shetty D, Mankeshwar R and Ashavaid TF. Prevalence of dyslipidemia in young adult Indian population. JAPI .2008; 56: 99-102.

23- Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease, European Journal of Clinical Investigation, 2017; 47(8): 600–11

International Journal of Scientific & Engineering Research, 2014; 5(11):264-70.

25- Pietilainen KH, Sysi-Aho M and Rissanen A. Acquired obesity is associated with changes in the serum lipid profile independent of genetic effects a monozygotic twin study, 2007; 2(2):e218.

26- Castan-Laurell I, Dray C, Attane C, Duparc T, Knauf C, Valet P. Apelin, diabetes, and obesity. Endocrine, 2011; 40(1):1-9.

27- Abd-Elbaky AE, Abo-ElMatty DM. Omentin and apelin concentrations in relation to obesity in diabetes mellitus type 2 and cardiovascular diseases in Egyptiant population. Endocrinol Metab Int J, 2015; 2(2):18

28- Cavallo MG, Sentinelli F, Barchetta I, Costantino C, Incani M. Altered glucose homeostasis is associated with increased serum apelin levels in type 2 diabetes mellitus. PLOS One, 2012;7(12): e51236.

29- Li L, Yang G, Li Q, Tang Y. Changes and relations of circulating visfatin, apelin, and resistin levels in normal, impaired glucose tolerance, and type 2 diabetic subjects. Exp Clin Endocrinol Diabetes 2006; 114(10):544–8.

30- Beltowski J Apelin and visfatin: unique beneficial adipokines up-regulated in obesity. Med Sci Monit, 2006; 12(6):112–9.

31- Fan Y, Zhang Y, Li X, Zheng H. Treatment with metformin and a dipeptidyl peptidase-4 inhibitor elevates apelin levels in patients with type 2 diabetes mellitus 2015; 14(9):4679-83.