RESEARCH ARTICLE

Circulating Adipsin as Biomarker and its Implication in Type 2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes (T2D) is a heterogeneous condition caused by insulin resistance and/or decreased insulin secretion. Adipsin is one of the adipokines secreted by adipose tissues, increasing insulin secretion. This study has investigated adipsin concentration in T2D patients and healthy subjects. This case-control study enrolled 30 patients with T2D who attended The Medical City Hospital-Baghdad from September 2020 to April 2021; their ages ranged from 40–55 years. They were compared with 30 healthy subjects as control group.

The results showed significant glycemic and lipid profile increases with their ratios in diabetic patients compared to the controls. Also, there was a significant rise in insulin resistance represented by the homeostasis model assessment in diabetic patients as equated to the control. Moreover, a lower adipsin level was detected in diabetic patients as equated to the control (13.86 ± 3.49 vs. 29.00 ± 4.48, respectively).

This data confirms that high-sensitivity C-reactive protein (CRP) plays a progressive pathogenesis role in T2D Iraqi patients. Also, serum adipsin was interrelated with insulin resistance, particularly in subjects with greater body mass index (BMI) and higher blood glucose levels. These results recommend that Adipsin may be convoluted in the pathogenesis of irregular glucose metabolism, hence additional examination is required.

Keywords: Adipsin High sensitivity C-reactive protein, Insulin resistance, Type 2 diabetes mellitus.

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INTRODUCTION

T2D mellitus (T2DM) is a chronic metabolic disease accompanied by hyperglycemia due to insufficient insulin secretion, insulin action or both. T2DM is predisposed by both host genetics and environmental influences comprising age, family history, diet, and sedentary lifestyle.[1]

The association between T2DM and insulin resistance (IR) has been documented. The IR is essentially not only the most influential predictor of the future progress of T2DM, but it is also a therapeutic target once hyperglycemia is present.[2] It was noted that β-cell mass was already decreased by 50% during the diagnosis of T2DM and continued to decay further during T2DM. Major problems resulting from IR are elevated blood pressure and insulin levels, leading to cardiovascular disease (CVD) and T2DM, respectively. However, mounting evidence shows that these morbidities result from failing metabolism due to IR.[3]

High sensitivity CRP (hs-CRP) is an excellent biomarker of acute phase response and independent predictor of CVD. Concerning the hs-CRP concentration and CVD risk, when it is below 1 mg/ L indicates lower risk, 1–3 mg/L indicates moderate risk and a concentration greater than 3 mg/ L indicates a higher risk. Patients with the highest concentrations of hs-CRP; 5-10, 10-20, or even more than 20 mg/L are most at risk.[4]

Adipose tissue is identified to serve as endocrine organ that secrete pro- and anti-inflammatory mediators comprising adipokines. A human study proposed that diabetic patients with β-cell failure were deficient in Adipsin. Adipsin, also called complementary factor D, is one of the adipokines that were the first adipokines to be described. Adipsin is a member of the trypsin family of peptidases, which was later recognized as a constituent agent D.[5] It is secreted by adipocytes, monocytes, and macrophages, catalyzing the rate-limiting step of the alternative complement pathway. Thus, Adipsin cleaves complement factor B and catalyzes the formation of complementary transformer 3 (C3), leading to a hydrolysis cascade that results in different complement fractions comprising C3a, C3b, C5a, and C5b. It was documented that familial C3 deficit is related to obesity and metabolic diseases, and C3a concentrations are risk factors for DM.[6]

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Some studies proposed that serum adipsin concentrations were negatively correlated with the homeostasis model assessment of IR (HOMA-IR).[7,8] Though, human data concerning the role of Adipsin among people with diabetes is restricted. Moreover, how adipsin modifications disturb the progress of pre-diabetes or early untreated DM remains uncertain.[9] The target of this study was to investigate the serum adipsin level in T2D Iraqi patients.

PATIENTS AND METHODS

The study enrolled 30 patients with T2DM who attended The Medical City Hospital-Baghdad from September 2020 to April 2021. All diabetic patients with a known history of T2DM and their ages ranged from 40–55 years. Diabetic patients were treated with oral anti-diabetic agents. None of them were taken lipid-lowering drugs or antihypertensive drugs. An endocrinologist examined them in the Medical City Hospital. They were compared with 30 healthy subjects as control group. All the clinical and biochemical examinations were done.

Ethical Considerations

This study was agreed by the Ethics Committee of University of Baghdad, College of Education for Pure Science (Ibn Al-Haitham)/ Department of Chemistry (approval number: 5145 at 25/10/2020).

Informed Consent

Written informed approval was acquired for all patients prior to participation in the current study.

Anthropometric Measurements

Systolic- and diastolic- blood pressure (SBP and DBP) were measured with a mercury manometer in the sitting position. The waist circumference (WC) was measured from the narrowest point and to the nearest 0.1 cm. Also, waist to hip ratio (WHR) was measured. BMI was calculated as weight (kg)/ height (m^2) according to WHO classification.[10] Additionally, body fat percent (BF%) was measured according to the following formula:

$$Body\,fat\% = (1.2 * BMI) + (0.23 * age) - 5.4 - (10.8 * gender)$$

Gender = 0 if female and 1 if male.

Laboratory Measurements

Fasting venous blood samples were drawn from all individuals. Biochemical assessments comprised fasting serum glucose (FSG) and glycated hemoglobin (HbA1c) using a biochemical auto-analyzer (Roche, Hitachi). Fasting venous blood samples were collected from all the subjects after 10–12 hours of fasting. Laboratory assessments were down, which encompassed fasting serum glucose (FSG), glycated hemoglobin (HbA1c), lipid profile comprising: total cholesterol (TC), triacylglycerol (TAG), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C). They were measured using a chemical analyzer- Hitachi.

The IR was estimated by the homeostasis model assessment (HOMA) index and quantitative insulin-sensitivity check index (QUICKI)[11] as in the following formula:-

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

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

G_0:Fasting glucose (mg/dL)

I_0: fasting insulin (μU/ml)

Fasting serum insulin was measured by enzyme-linked immunoassay (ELISA) kit, and IR was calculated from homeostasis model assessment-2 (HOMA2-IR) using Microsoft downloaded freely.[12] Serum hs-CRP was also determined turbidimetrically using (Cobas, Roche).

Exclusion Criteria

Patients with chronic diseases such as liver disease, renal failure, and CVD, which can directly or indirectly affect the result, preceding or current treatment with medications recognized to influence glucose and lipid metabolism were excepted from the study.

Statistical Analysis

Data were studied using the statistical package for social sciences (SPSS) program, version 20. Descriptive statistics were used; presented as numbers and proportions (%), or mean ± standard deviation (SD) according to the data type. The t-test was used to equate between the two groups, and the significance level was deliberated at p-value ≤ 0.05.

RESULTS

Table 1 shows the anthropometric and clinical features of DM and control groups. There was no significant difference in age between patients and control group. While, there were significant increases (p = 0.0001) in WC, WHR, BMI, BF%, SBP, and DBP in diabetic patients as equated to the control.

Glycemic profile of the studied groups is illustrated in Table 2. There were remarkable increases ($p \leq 0.05$) in FSG, HbA1c, insulin, HOMA1-IR, and HOMA2-IR. Whereas remarkable decreases (p = 0.0001) were found in glucose to insulin (G/I) ratio, HOMA2-B%, HOMA2-S%, 1/HOMA, and QUICKI in diabetic patients as equated to the control.

Table 3 clarified the lipid profile for both groups. There have been noticeable increases (p = 0.0001) in serum TC,

Table 1: Anthropometric and clinical characteristics of the studied groups

	Means ± SD		
Parameters	*DM (n = 30)*	*Control (n = 30)*	*p-value*
Age (years)	45.30 ± 5.67	42.36 ± 2.26	0.062
Gender (Number, %)	Male: 15 (50%) Female: 15 (50%)	Male: 15 (50%) Female: 15 (50%)	0.307
WC (cm)	105.10 ± 2.95	71.53 ± 3.29	0.0001
WHR	0.950 ± 0.03	0.720 ± 0.03	0.0001
BMI (kg/m^2)	30.35 ± 3.40	22.31 ± 1.67	0.0001
BF%	36.04 ± 6.72	25.72 ± 7.12	0.0001
SBP (mmHg)	135.76 ± 8.25	119.60 ± 2.44	0.0001
DBP (mmHg)	80.83 ± 2.29	78.67 ± 2.34	0.0001
Duration of DM (Years)	8.23 ± 4.85	-	0.932

$p \leq 0.05$: Significant.

Table 2: Glycemic profile of the studied groups

	Means ± SD		
Parameters	*DM (n = 30)*	*Control (n = 30)*	*p-value*
FSG (mg/dL)	201.87 ± 12.84	85.63 ± 6.62	0.0001
HbA1c (%)	7.94 ± 1.37	3.93 ± 0.76	0.0001
Insulin (μU/mL)	31.77 ±7.02	4.39 ± 1.55	0.0001
G/I ratio	6.24 ± 1.47	20.95 ± 4.59	0.0001
HOMA1-IR	16.94 ± 11.02	0.949 ± 0.41	0.0001
HOMA2-IR	21.51 ±7.83	0.568 ± 0.21	0.050
HOMA2-B%	4.00 ± 1.53	70.88 ± 8.03	0.0001
HOMA2-S%	75.52 ± 16.06	194.55 ± 17.66	0.0001
1/HOMA1	0.078 ± 0.03	1.210 ± 0.42	0.0001
QUICKI	0.321 ± 0.06	0.656 ± 0.02	0.0001

$p \leq 0.05$: Significant.

Table 3: Lipid profile of the studied groups

	Means ± SD		
Parameters	*DM (n = 30)*	*Control (n = 30)*	*p value*
TC (mg/dL)	219.03 ± 13.52	134.46 ± 6.50	0.0001
TAG (mg/dL)	177.90 ± 14.67	96.38 ± 17.16	0.0001
VLDL (mg/dL)	35.58 ± 8.13	20.47 ± 6.66	0.0001
HDL-C (mg/dL)	49.60 ± 7.77	68.71 ± 5.54	0.0001
LDL-C (mg/dL)	133.85 ± 14.02	45.27 ± 10.36	0.0001
Non HDL-C (mg/dL)	169.43 ± 17.38	65.75 ± 9.11	0.0001
TC/HDL-C ratio	4.60 ± 1.65	1.971 ± 0.21	0.0001
TAG/HDL-C ratio	3.74 ± 1.45	1.418 ± 0.32	0.0001
LDL-C/HDL-C ratio	2.86 ± 1.38	0.671 ± 0.20	0.0001

$p \leq 0.05$: Significant.

Table 4: Serum hs-CRP levels of the studied groups

	Means ± SD		
Parameters	*DM (n = 30)*	*Control (n = 30)*	*p value*
hs-CRP (mg/L)	5.77 ± 0.82	0.703 ± 0.22	0.0010

$p \leq 0.05$: Significant.

Table 5: Serum adipsin levels of the studied groups

	Means ± SD		
Parameters	*DM (n = 30)*	*Control (n = 30)*	*p value*
Adipsin (ng/mL)	13.86 ± 3.49	29.00 ± 4.48	0.0001

$p \leq 0.05$: Significant.

Table 6: Sensitivity and Specificity for the studied groups

Groups	*Sensitivity*	*Specificity*
DM	53.29	44.66
Control	41.37	64.72

TAG, LDL-C, VLDL, non HDL-C, and the ratios (TC/HDL-C, TAG/HDL-C, LDL-C/HDL-C) in diabetic patients as equated to the control. Moreover, hs-CRP level was considerably elevated ($p = 0.0010$) in diabetic patients as equated to the control, Table 4.

Serum adipsin level was considerably decreased ($p = 0.0001$) in diabetic patients as equated to the control, Table 5. Sensitivity and specificity for DM and control group were explained in Table 6.

DISCUSSION

The global occurrence of DM is predictable at 415 million (8.8%), which is expected to rise to 642 million in next 25 years. Also, worldwide around 193 million diabetics persist undiagnosed, influencing them to the progress of numerous long-term complications of chronic hyperglycemia.[13]

Numerous prospective studies have studied the connection between grade of obesity, BF% and weight gain with consequent incidence of T2DM. Elevated BMI is now a well-established independent risk factor for the progress of T2DM.[14] In the current study, the BMI of diabetic patients was greater than control subjects. Nevertheless, the BMI of non-diabetic subjects was about 22 kg/m^2 which is in normal range as per WHO approvals. While, in diabetic subjects BMI was found to be about 30 kg/m^2, which denotes borderline obesity.[15] The BMI was designated as the strongest predictor of T2DM. It is clear from the current study that BMI elevates with age and obesity, in central obesity is closely related with IR. Among obese subjects, suppression of lipolysis and release of free fatty acids restricts peripheral insulin uptake of glucose in a dose-dependent manner while inhibiting insulin secretion simultaneously.[16]

Fasting blood glucose and HbA1c levels are generally used as glycemic control markers, revealing the disease's progress and complications.[17]

The IR is key to the evolution of T2DM, which is considered a risk for CVD and death rate. Consequently, a detailed of understood mechanisms in IR is required for the occurrence of T2DM and its related diseases.[18]

Both HOMA1-IR and HOMA2-IR in this data indicated a remarkable increase along with WHR. Mishra *et al*.,[19] also found a strong association of HOMA1-IR with WHR. A parallel data was found in a large study from Europe.[20] Also, the WHR for the estimate of IR and T2DM was considerably greater than that of BMI. All these studies have revealed that WHR is a good sign of IR and can hence be used to recognize at risk persons. Though BMI may be a simple measure of obesity and extreme fat stores, it is less dependable in paralleling body composition. One of the causes for reduced dependability of BMI is that there may be identical distributions of BMI in 2 persons, but they might reveal large alterations regarding the accumulation of intra-abdominal fat responsible for IR progression.[21]

The outcomes of this study suggested that WHR is a more consistent marker of IR. This study also revealed that the more reduced insulin sensitivity (HOMA2-S%) is paralleled to a decrease in β-cell function (HOMA2-B%) in diabetic patients. This can be illustrated by the fact that South Asians have preferential fat deposition in the abdominal region, which is

related to decreased insulin-mediated glucose disposal. Thus South Asian population being more disposed to abdominal obesity and also low muscle mass, has been assumed to progress IR and subsequently T2DM earlier than the population of European origin.[22]

It has been found that HOMA-β in T2D patients with a history of DM of less than 1 year was around 52% that of healthy subjects, and HOMA-β with a history of more than 30 years of DM was around 32% of the pancreatic islet function left in healthy subjects. So, HOMA-IR in T2D patients with a history of DM of less than 1 year was 1.5-fold that of healthy subjects, while HOMA-IR in patients with a history of DM of between 20-30 years was lesser than that in other diabetic patients.[23] The duration of DM in this study was 8.23 ± 4.85 years with lower HOMA2-B% and HOMA2-S%, which agrees with this data.

According to the current results of this work, there is a direct correlation between HbA1c and IR, as it was revealed that HbA1c is more closely related to insulin sensitivity in diabetics and control subjects. Hence, HbA1c is a reliable biomarker and an excellent infrared marker for testing diabetes and pre-diabetes in individuals with a higher BMI.

Hyperglycemia and lipotoxicity have roles in the potential mechanisms underlying impaired β-cell function. The severity of dyslipidemia elevates in patients with upper HbA1c values, following the existent results when diabetic and obese subjects had higher HbA1c and lipid disorders. Type 2 diabetes is related to lipid and lipoprotein abnormalities, comprising decreased HDL-C and elevated TAG.[24]

About lipid parameters, LDL-C was found to be considerably related with HOMA-IR and HOMA-B% values. Diabetes is well defined for distinctive dyslipidemia, comprising higher TAG, decreased HDL-C, and a preponderance of small dense LDL particles. Any association between LDL particles and IR might be employed through insulin's influence on lipoprotein metabolism. Accumulated fatty acids and their metabolic returns may negatively influence converting proinsulin into insulin and reducing nitric oxide production, which reduces glucose oxidation and induces β-cell apoptosis β. Also, it has been proposed that LDL-C above 6 mmol/L to prompt apoptosis of β-cells.[25]

This study indicated TC/HDL-C, TAG/HDL-C, and LDL-C/HDL-C ratios to be used as surrogate markers for IR, which agrees with previous data.[26] However, an association between TAG and TAG/HDL-C with insulin may vary by ethnicity and using it to assess IR may not be suitable.[27]

The trend of T2DM is altered from metabolic disorder to inflammation as effects of the pro and anti-inflammatory cytokines like CRP are proposed in insulin signaling pathways, cross-linking and ultimately developing IR in β-cells of pancreas, which endorse risks to T2DM. Stability among these pro- and anti-inflammatory cytokines is essential to make β-cells immune to any infection leading to T2DM.[28] Some studies had documented elevated levels of CRP in T2DM as an independent biomarker for T2DM.[29,30]

In T2DM, many acute-phase proteins like CRP's levels are elevated, which relates to the progress of characteristics linked with the state (deficiency of IR revealed by HOMA1 and HOMA2).[31]

Obesity's influence on T2DM has been associated with dysregulation of adipokines, i.e., improper production of adipokines by adipose tissue and glucose uptake. Adipokines play a vital role in maintaining lipidogenesis, chemical attraction of immune cells in adipose tissue, adipocyte function via autocrine/ paracrine signaling, appetite regulation, energy expenditure, and insulin sensitivity in the brain and peripheral target tissues.[32]

Adipsin stimulates glucose transport which promotes TAG accumulation in fat cells and also prevents lipolysis. The adipsin-acyl-stimulating protein system is complex in regulating TAG metabolism in adipocytes. This system raises the rate of TAG synthesis in adipocytes by transporting glucose transporters from intracellular vesicles to the plasma membrane, which increases the specific membrane glucose transporter.[33]

It has been suggested that Adipsin improved β-cell function in diabetic mice, and a lesser adipsin level was detected in T2D patients and β-cell function failure. The mechanism by which Adipsin was negatively related to HOMA-IR might be associated with inflammation. Type 2DM is a chronic inflammatory disease with a negative correlation between Adipsin and HOMA-IR. This might be due to the expression of inflammatory cytokines like interleukin-17 in T2DM. Circulating adipsin levels were decreased in T2D patients with impaired glucose tolerance; which is related with the first-phase insulin secretion of pancreatic β-cells and glucose metabolism.[34]

The current data proposed a noticeable decline in serum adipsin level in diabetic patients with a sensitivity of 53.29 and specificity of 44.66.

In obesity convoluted with T2DM, there is an imbalance between adipsin and leptin levels. Elevating adipsin production among obese individuals can be considered a compensatory response for stabilizing carbohydrate and lipid metabolism limitations. Hence, adipcin could stimulate insulin secretion and stabilize blood glucose levels. Moreover, the diabetic mice treated with Adipsin revealed a substantial decrease in FSG and improved glucose clearance.[35]

CONCLUSIONS

The present results found more reduced insulin sensitivity related to decline in β-cell function among diabetic patients. This data confirms that hs-CRP shows a positive role in the pathogenesis of T2DM in Iraqi patients. Additional studies are needed on the diverse range of these inflammatory mediators in conjunction with other biochemical agents, hematological and immunoassay agents to determine the role of inflammatory markers as biomarkers of the initial predictor that can inhibit T2DM in this group. Also, serum adipsin was related with IR, particularly in patients with greater BMI and higher blood glucose. These outcomes recommend that adipsin

may be complicated in the pathogenesis of abnormal glucose metabolism, and therefore more investigation is necessary.

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ETHICAL CLEARANCE

The research was conducted under the guidance of Ethical Committee at Scientific Research with the approval of both MOH and MOHSER in Iraq

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