Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 6, 2021, Pages. 1348-1357
Received 25 April 2021; Accepted 08 May 2021.

The Association between Adipolin and Oxidative Stress for Diabetic Female Type II

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ABSTRACT

Obesity is a major public health issue closely linked to obesity-related disorders such as type 2 diabetes, atherosclerosis and hypertension. Adipose tissue secretes a variety of bioactive secretionary substances known as adipocytokines, the majority of which are pro-inflammatory and contribute to obesity-related disorders. Some adipocytokines, by contrast, have anti-inflammatory properties. Adipolin (CTRP12), which is an anti-inflammatory cytokine synthesized and secreted mainly in adipose tissue and reduces obesity and diabetes. Oxidative stress is another important factor in the pathogenesis of metabolism. It is a state of imbalance in cell and tissue systems, leading to the development of excessive free oxidative radicals and reactive oxygen species oxidative stress (ROS).

There were 54 patients with diabetes type 2 and 36 non-diabetic. Individuals of two groups of obese and non-obese compared with apparently healthy control. Before the body mass index (kg/m2) had been calculated, weight (kg) and height (m) were measured as a normal weight (18.49-24.99 kg/m2), or obese (**>** 30kg/m2) according to the WHO classification. Adipolin significantly decreased in obese diabetic patients compared with obese controls and it is low in the obese diabetic patients group compared to the nonobese patients

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group. TAC was significantly increased in the patients compared with controls ($p < 0.05$) and it was low level in obese diabetic patients compared with nonobese patients group, while MAD was high level in obese diabetic patients compared with nonobese patients group.

The study also found weak negative correlated with MDA (r=-0.29, p= 0.13), TAC (r=-0.023, p=0.9), in obese diabetic patients while found weak positive correlated with MDA (r=0.037, p=0.85), TAC (r=0.35, p=0.69) in nonobese diabetic patients. Women patients with diabetes have low serum adipolin levels. MDA levels were high in obese patients compared with obese control while TAC levels were low in obese T2DM patients compared with obese control.

Keywords: Type 2 diabetes mellitus , Obesity, Adipolin (CTRP12) , Oxidative stress.

Introduction

Obesity is the major public health problem that is closely linked with obesity-related disorders such as type 2 diabetes mellitus (T2DM), atherosclerosis and hypertension. According to World Health, it is defined as "abnormal or excessive fat accumulation that may impair health." Since 1980, obesity worldwide has more than doubled. More than 1.9 trillion adults aged 18 and up were overweight in 2014, with 600 million of them obese. In 2014, 30% of adults 18 years of age or older had obesity and 13% were overweight. In 2014, 41 million

children under the age of five were overweight or obese (World Health Organization (WHO). Obesity and overweigh).

Adipose tissue produces a number of secretionary bioactive substances, also referred to as adipokines, which affect adjacent or remote bodies directly. Adipokines are mostly pro-inflammatory, which contribute to obesity related disorders. Some adipokines, by contrast, have anti-inflammatory properties. It is known that adipocyte dysfunction can cause obesity-related complications due to deregulated development or adipocytokine secretion[22].

CTRP12, also known as adipolin (adipose-derived insulin-sensitizing factor), has a low adiponectin similarity (less than 22%) to other members of the family. Adipolin (CTRP12) synthesized and secreted primarily in adipose tissue and reduces obesity and diabetes, is an anti-inflammatory cytokine [1][2]. Adipolin levels are decreased in diabetes patients, while exercise can decrease adipollin-induced diabetic circulation and this effect can rely on a variety of different degrees of exercise. [3].

CTRP12 association with metabolic disorders in humans has been seen in many studies but with different findings. mRNA expression of CTRP12 has been reported to be remarkably up regulated in obese women at both visceral and subcutaneous fat depots[4]. In another study, subjects with T2DM had significantly lower serum CTRP12 concentrations than the control group. [5]. This study discovered that CTRP12 levels decreased significantly in PCOS patients but were not associated with obesity [6]. Similarly, Tan et al. found lower concentrations of CTRP12 in serum and subcutaneous adipose tissue for PCOS participants compared to healthy subjects in two independent research studies [7].

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Oxidative stress is another important factor in the pathogenesis of metabolism. It is a state of imbalance in cell and tissue systems that results in the production of excessive free oxidative radicals and reactive oxygen species[8]. The balance between the pro-oxidant and antioxidant forces is established in the normal cell. However, if reactive oxygen species increase or antioxidant levels decrease, this balance can shift to the pro-oxidants. [9].

Epidemiological studies have shown that both obesity and redox changes are causally related, both in vivo and in vitro. Oxidative stress is assumed to be one of the ties between the accumulation of fat and a cluster of health issues, including the alteration of adipocyte secretion, inflammation and IR. Oxidative stress has emerged as a predisposing condition for a number of morbidities. Elevated markers of oxidative stress have been found in clinical cases[10].

An oxidative and an inflammatory imbalance develops components such as obesity, IR, T2D, and CVD. While all inflammatory and metabolic processes begin initially within AT, chronic systemic inflammation ultimately has an effect on different skin, liver and brain, among other things, physiology and metabolism. This can lead to control of many of the related inflammatory and oxidative stress pathologies in MetS and obesity. More details on AT's immune function will help to identify suitable solutions to MetS-related disorder or avoid it[11].

The research aimed at assessing the levels of Adipolin in women with T2DM and the relation between oxidative stress with Adipolin levels as an indicator for diagnosis of the relationship between obesity and T2DM.

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Methods

This research involved two groups of females. The first group consists of 54 patients with diabetics and the second group consists of 36 as a healthy control. According to BMI, the first group was split into two groups. Group 2 was likewise split into two groups, namely obese women and non-obese women in another group. The BMI (i.e. a normal weight (18.49-24.9 kg/m^2) or obese (by the WHO definition) ≥ 30 kg/m^2.

This was a case-control study at Hilla District, Babylon, Iraq, Marjan Teaching Hospital, Diabetes and Endocrinology Centre. Patients and healthy people are included in the following criteria: Between September and December 2020, the age of type 2 diabetes patients (35 to 60) who visited a diabetes center on Sundays, Saturdays, and Tuesdays.

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Sampling of Blood

Blood samples were obtained for the patient and control (5ml). Coagulation and then centrifugation was enabled for 10 minutes at 4500 rpm in samples of blood. Until analysis, Sera was isolated and stored in a deep freeze. There are samples that were measured directly, especially in oxidative stress.

Laboratory studies

Serum Adipolin (AD)level was measured by ELISA sandwich (Bioassay Technology Laboratory (BT LAB; China Cat.No.E3692Hu).During the reaction between Thiobarbiturus acid (TBA) and MDA, the MDA was based on spectrophotometric color measurements. The CUPRAC assay measures a sample's antioxidants' ability to reduce Cu^{2+} to Cu^{1+} in the presence of a chelating agent. The chelators form stable coloured complexes with Cu^{1+} which have an absorption limit of 450 nm.[12].

Statistical analyses

For statistical analysis, statistics from the SPSS version (V.26.0) and Microsoft Excel 2010 were used. The findings were shown to be mean ± SD, one way ANOVA to test the significance of difference in meanings between more than two groups. Pearson correlation coefficients were used. The P values recorded were two-tailed, and the P values were deemed significant at 0.05.

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Results

Ninety participants were involved in the study, divided into two groups: 54 diabetic women (27 obese, 27 non-obese) and 36 female monitors (18 obese and 18 non obese). In Table 1, Adipolin and TAC were was significantly decreased in patient group compared with control group, while MDA was significantly increased in patients compared with controls.

Table 1-Laboratory properties for DM2 patients and Controls

parameter	Patients 54 mean± SD	Controls 36 mean± SD	P value
Adipolin (ng/mL)	1.32±0.48	1.56±0.61	0.05
TAC (µmol/L)	0.75±0.26	0.89±0.28	0.02
MDA(µmol/L)	4.87±2.16	2.34±1.05	<0.001

Table 2-The Comparison of Patient and Control Groups for AD (ng/mL)

Parameter	Patients 54		Controls 36		Compared groups		P value
	GP1 No.27 mean± SD	GP2 No.27 mean± SD	GC1 No.18 mean± SD	GC2 No.18 mean± SD			
Adipolin(AD) (ng/ml)	1.30±0.34	1.34±0.59	1.48±0.49	1.64±0.73	GP1	GP2	0.7
						GC1	0.26
						GC2	0.04
					GP2	GC1	0.37
						GC2	0.07

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GP1								

patients obese , GP2 patients non obese, GC1 controls obese, GC2 controls non obese

The mean difference is significant at P≤ 0.05

In Table 2, AD was nonsignificantly decreased in patients obese compared to obese controls, (p **>** 0.05). and non-obese patients (p**>**0.05) respectively .While AD levels were non significantly increased in GP2 compared to GC2 (P=0.07). It is higher in healthy control compared to diabetic patients.

Tan et al. demonstrated that the circulatory content of CTRP12 in healthy lean persons, inducing hyperinsulinemia, was significantly increased and the insulin sensitizing agent rosiglitazone significantly increased the expression and secretion of AD in foreign subcutaneous adipose[7].These studies indicate that serum levels of AD are closely associated with inflammation, diabetes and resistance to insulin, and may be a therapeutic goal for type 2 diabetes. In patients with polycystic ovary syndrome (PCOS) and type2 diabetes, serum AD values in humans have been found to be lower.[6][5].

Jinqiu Du et al. found that T2DM for serum levels of CTRP12 were lower than diabetic renal dysfunction were associated with the degree of renal dysfunction[13].

Adipolin has a lower sequence identity with adiponctin. This adipokine decreases fatty tissue inflammatory responses and promotes liver and adipose tissue (AT) is through insulin signals, which blocks gluconeogenesis and increases glucose uptake[14] .

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Adioline decreases macrophage penetration and decreases proinflammatory cytokine expression (TNFα, IL-1b and MCP-1)[11]. In the adipoline stage, obesity with increased tail and hyperglycemia in white tissue fat and serum adipolines was reduced. In clinical trials, the negative relationship between obesity, adipoline and T2D was tested[11].

Recent studies show that expression of adipoline under obese conditions is blocked by Krüppel protein factor (KLF3) up and (KLF15) down. KLF3 and KLF15 are binds adipoline transcription of DNA repressive (KLF3) or activating (KLF15). Furthermore, a rodent study discovered that obesity increases the cleavage of complete adipoline in the bloodstream of less active cleaved adipolin by introducing furinal end peptidase in the AT[11].

Table 3-The TAC Levels (µmol/L) and MDA (µmol/L) for Patient Groups Compared to Control Groups

Parameter	Patients 54		Controls 36		Compared groups		P value
	GP1 No.27 mean± SD	**GP2 No.27 mean± SD**	**GC1 No.18 mean± SD**	**GC2 No.18 mean± SD**			
Total Antioxidant Capacity (TAC) (µmol/L)	**0.68±0.27**	**0.82±0.23**	**0.95±0.24**	**0.83±0.32**	**GP1**	**GP2**	**0.05**
						GC1	**0.002**
						GC2	**0.08**
					GP2	**GC1**	**0.13**
						GC2	**0.9**
Malondialdehyde (MDA) (µmol/L)	**5.27±2.53**	**4.53±1.68**	**2.63±1.14**	**2.03±0.87**	**GP1**	**GP2**	**0.13**
						GC1	**<0.001**
						GC2	**<0.001**

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					GP2	GC1	0.001
						GC2	<0.001

The mean difference is significant at p≤0.05.

TAC levels and MDA were comparison between different groups for patients and controls as illustrated in Table 3. Obese patients have low TAC (0.68±0.27) with high MDA(5.27±2.53) compared to nonobese patients TAC (0.82±0.23) with MDA (4.53±1.68), respectively compared to obese control TAC (0.95±0.24) with MDA (2.63±1.14) compared another nonobese control TAC (0.83±0.32) with MDA(2.03±0.87).

In our study, the levels of MDA were significantly elevated in obese diabetic patients groups compared with obese control obese groups ($p < 0.001$). Das P, et al. found that MDA levels in diabetic patients were significantly higher than in nondiabetic controls .Obesity can lead to oxidative stress which can further contribute to the insulin resistance pathogenesis of type 2 diabetes mellitus. [15].

Md. Tarek Adnan, et al observed that Bangladeshi obese individuals had elevated serum MDA concentrations. Therefore, increased serum MDA in Bangladeshi obese people can affect to development of obesity. Higher MDA levels and lower antioxidant vitamins are indicative of any tissue damage in obese people owing to oxidative stress[16].

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Oxidative stress is linked to the free radical increase and can interfere with important cellular components such as membrane lipids, DNA and proteins that have a bearing on the normal roles and affect cells of these components [17]. Therefore, the MDA increases with a decreased amount of antioxidants could be a possible cause of obesity pathogenesis [16].

However, the results of our study indicate that the antioxidant defense system is compromised in general and abdominal adiposity, as evidenced by increased MDA levels and decreased levels of TAC in serum. This finding was in line with previous reports, which found decreased plasma TAC levels in general, and central adiposity[18][19]. In addition, Suzuki et al. discovered lower serum levels of antioxidant components in serum in women with abdominal adiposity. [20].

Decreased serum TAC levels in obesity and fat accumulation may indirectly indicate whole free radical activity. Interestingly, serum TAC levels decreased in the obese diabetic patients group, perhaps because the free radical activity was more marked in this group. These states of oxidative stress and TAC levels in general and abdominal adiposity might be closely linked to the occurrence of cardiovascular events[21].

Farshad Amirkhizia, et al found that obesity and, especially, abdominal adiposity leads to oxidative stress, which in turn, may contribute to obesity related diseases such as atherosclerosis, diabetes mellitus and arterial

hypertension[21]. The study shows that in healthy women, plasma oxidative stress and TAC levels are associated with abdominal adiposity are independent of BMI.

conclusion of our study suggested that the anti-inflammatory factor (AD) for women patients with diabetes have low levels, which causes the development of obese complication and affect link between adipose tissue and development of complication .This enhances the result compared MAD and TAC in T2DM patients .

Competing interests

The authors declare that they have no competing interests.

Ethical committee

Ethics Committee (University of Babylon/ College of Science), Reference number of approval: 7 /18/5114 in 1/10/2020

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