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# Estimation of Resistin and Immunoglobulins (IgA and IgM) Levels in the Serum of Iraqi Patients with Type 1 and Type 2 DiabetesMellitus

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**Abstract**

Resistin (RE) is a cysteine rich polypeptide. It has been established that in humans adipocytes, pancreatic cells, muscle, and mononuclear cells all express this 108 amino acid polypeptide. It is important to note that resistin is primarily produced by peripheral blood mononuclear cells (PBMCs) in humans. Its part in the inflammatory processes has been proven. Immunoglobulins IgA and IgM are crucial elements of humoralimmunity. They increase inflammatory responses and the removal of immunological complexes by activating the complement system, sensitizing natural killer cells, phagocytes, and mast cells, and regulating cytotoxic cellular activity. The aim of this study was to determine resistin and immunoglobulin IgA and IgM levels in the serum of type 1 diabetic (T1DM) and type 2 diabetic (T2DM) patients and the healthy control. This respective study was carried out at the National Center for Diabetes Treatment and Research and the consulting clinics in Al-Muqdadiya District and Baquba District in Iraq during the period from January 2022 to April 2022. It included 153 participants; divided into 3 groups (51 patients with T1DM and 52 patients with T2DM, and 50 healthy control). The result of serum resistin showed that there was a highly significant difference when comparing the mean of serum resistin of T1DM with that of T2DM patients group and the control group. While no significant difference was detected when the mean of serum resistin ofthe T2DM patients group with that of the control group was compared. The mean of immunoglobulins IgA and IgM were compared in T1DM , T2DM patients and the healthy controls with significant differences between the three groups. It can, therefore, be concluded that increased serum resistin levels were recorded in T1DM patients than T2DM patients and healthy control. Increased serum immunoglobulins IgA and IgM levels were also noticed in T1DM and T2DM patients compared with control.

**Keywords:** Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), Resistin, IgA, IgM.

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# تحديد مستويات الResistin والكلوبيولينات المناعيةIgAوIgMفي مصل المرضى العراقيين المصابين بداء السكري النوع 1 والنوع 2

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**الخلاصة**

Resistinهو ببتيد متعدد غني بالحامض الأميني السيستين. يتم التعبير عنه في الخلايا الدهنية وخلايا البنكرياس والعضلات وخلايا أحادية النواة، ويتكون من سلسلة من الأحماض الأمينية والبالغ عددها 108 حامض أميني. ينتج resistin بصورة رئيسية من الخلايا أحادية النواة في الدم المحيطي للأنسان. وقد ثبت دوره المهم في العمليات الألتهابية. تعد الكلوبيولينات المناعيةIgA و IgM من العناصر الأساسية للمناعة الخلطية، أذ أنها تزيد من الأستجابات الألتهابية وتزيل المعقدات المناعية عن طريق تنشيط نظام المتمم، وتزيد من تحفيز الخلايا القاتلة الطبيعية والخلايا البلعمية والخلايا البدينة، وتنظم نشاط الخلايا السمية. كان الهدف من هذه الدراسة هو تحديد مستويات الresistin والكلوبيولينات المناعيةIgA و IgM في مصل المرضى الذين يعانون من داء السكري النوع 1 والنوع 2 والأشخاص الأصحاء. أجريت دراستنا في المركز الوطني للسكري والعيادات الأستشارية في قضاء المقدادية وقضاء بعقوبة في العراق، خلال الفترة من كانون الثاني 2022 إلى نيسان 2022. وشملت 153 مشاركاً. مقسمين إلى ثلاث مجموعات (51 مريضاً يعانون منT1DMو 52 مريضاً يعانون منT2DM و 50 من الأشخاص الأصحاء). نلاحظ من النتائج وجود فروق معنوية ذات دلالة إحصائية في مستوى تركيز الresistin في مصل الدم لدى مجموعة مرضىT1DMبالمقارنة مع مجموعةمرضى T2DMومجموعة السيطرة. بينما لم يكن هنالك فروق معنوية في مستوى تركيز الـ resistin في مصل الدم لدى مجموعة مرضىT2DMبالمقارنة مع مجموعة السيطرة. كما كان هنالك فروق معنوية في مستوى تركيز الكلوبيولينات المناعيةIgA و IgM في مجموعتي مرضىT1DM و T2DMبالمقارنة مع مجموعة السيطرة. تم أستنتاج أن هنالك زيادة في مستويات تركيز الresistin في مصل مجموعة مرضىT1DMمقارنة مع مجموعة مرضىT2DMومجموعة السيطرة، وزيادة في مستويات الكلوبيولينات المناعيةIgA و IgM في مصل مجموعتي مرضىT1DMوT2DMمقارنة مع مجموعة السيطرة.

## 1. Introduction

Diabetes mellitus (DM) is a syndrome characterized by abnormal glucose tolerance and inappropriate hyperglycemia, either as a result of inadequate insulin secretion or as a result of both insulin resistance (IR) and insufficient insulin secretion to make up for it. Pancreatic islets ß-cells are mostly destroyed by an autoimmune mechanism in T1DM. The most common kind of T2DM is caused by insulin resistance with a failure in compensatory insulin secretion [1, 2]. Diabetes mellitus is a growing global health concern. Around the world, diabetes was expected to have afflicted 171 million people in 2000, 366 million by 2011, and 552 million by 2030 [3]. Furthermore, an estimated 5 million deaths worldwide from all causes were attributable to diabetes in 2017 which accounted for 9.9% of the total mortality rate for those aged 20 to 99. According to estimates, managing diabetes will cost the world's healthcare system 850 billion, making it one of the biggest financial strains [4]. Diabetes has been linked to an increased risk of skin and soft tissue infections, urinary tract infections, and lower respiratory tract infections such as pulmonary tuberculosis and pneumonia [5]. The world health organization (WHO) claims that DM causes harm to the heart, blood vessels, eyes, kidneys and nerves over time [6]. Obesity and physical inactivity are frequently linked

to T2DM which is a leading cause of stroke, heart attacks, renal failure, poor vision and lower limb amputation [7]. Overnutrition starts the inflammatory cascade and triggers the release of many adipokines and cytokines from adipose tissue. To mediate inflammatory reactions and IR, visceral and subcutaneous adipose tissues each produce a distinct composition of adipokines and cytokines. Leptin, resistin, IL-1, IL-2, IL-6, IL-8, IL-18, TNFα, monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1) are among the proinflammatory adipokines and cytokines produced by adipose tissue [8, 9]. Resistin, a cysteine-rich polypeptide, is also known as FIZZ3 or adipose tissue-specific secretory factor (ADSF). The hormone is thought to be a key player in the emergence of insulin resistance; it was initially identified in a screen for targets of thiazolidinediones (TZDs) in white adipose mice. It has been established that in humans adipocytes, pancreatic cells, muscle and mononuclear cells all express this 108 amino acid polypeptide. It is important to note that resistin is primarily produced by PBMCs in humans and. its part in the inflammatory processes has been proven in numerous investigations [10]. Resistin affects multiple human cell targets and plays a part in insulin sensitivity and glucose metabolism. It may also cause pro-inflammatory effects in adipose tissue and the vascular endothelium. Resistin encourages the growth of vascular smooth muscle cells and promotes angiogenesis. Insulin resistance, obesity, T2DM, cardiovascular disease, atherosclerosis, endothelial dysfunction, hypertension, thrombosis, angiogenesis, inflammation, energy metabolism, feeding behavior, smooth muscle cell dysfunction, tumorigenesis and rheumatic diseases are just a few physiological processes in which resistin is involved [11].

It is known that B cells play a crucial role in the development of T1DM in humans; abnormally high levels of islet-infiltrating B cells are linked to the rapid progression of T1DM in young children; and a variety of serum antibodies to beta antigens significantly raise the risk factor for the occurrence of children who are genetically predisposed to the disease [12]. The primary roles of immunoglobulin IgM, which was the first antibody expressed and generated, are complement activation and agglutination [13]. Immunoglobulin IgA, whose major function is agglutination, is the most prevalent in the mucosal tract. IgA and IgM are crucial elements of humoral immunity, serving as purifiers and pathogen neutralizers during primary and/or secondary antibody responses [14]. They also increase inflammatory responses and the removal of immunological complexes by activating the complement system, sensitizing natural killer cells, phagocytes, and mast cells, and regulating cytotoxic cellular activity [15]. Isotopic IgM, which is present in the auto Abs implicated in T1DM and has been demonstrated in studies to have diverse functions in the disease [16], may also be a key player in the immuno-pathogenesis of obesity and T2DM [17]. Diabetic individuals exhibit elevated circulating IgA concentrations [18]. The aim of the current study was to ascertain resistin and immunoglobulin IgA and IgM levels in Iraqi patients with T1DM and T2DM.

## 1.2 Materials and Methods

### 1.2.1 Subjects

This study was conducted at the National Center for Diabetes Treatment and Research, Al-Mustansiriya University, Baghdad Governorate, and the consulting clinics in Al-Muqdadiya District and Baquba District, Diyala Governorate in Iraq during the period from January to April 2022. The study involved 153 blood samples from patients with T1DM and T2DM, and healthy people, where 51 blood samples were collected from patients with T1DM, 28 from males, and 23 from females, with ages ranging from 15-58 years, and 52 blood samples were collected from patients with T2DM, where 18 samples were from males and 34 from females, with ages ranging from 41-83 years. Fifty blood samples were collected from healthy people (Control), whose ages were close to the patients' ages.

### 1.2.2 Sample Collection

Around 6 mL of blood was placed in a gel tube to separate the serum by leaving the tubes for 10-30 minutes at room temperature for agglutination, and then centrifuging for 5 minutes at 3000 rpm to separate the serum.

### 1.2.3 Sample Measurements

The level of resistin was quantitatively determined in the serum of T1DM and T2DM patients and the group of healthy people using the sandwich Enzyme-Linked Immunosorbent Assay (ELISA) and according to the instructions contained in the examination kit manufactured by Al-Shukairate Company, and immunoglobulin IgA and IgM levels were measured in the sera of the T1DM and T2DM patients' group and the healthy subjects using the single radial immune diffusion technique (RID) according to the instructions of the test kit manufactured by LTA S.r.l. Company.

### 1.3 Statistical Analysis

Data was conducted by using SPSS program. Duncan test was used to compare the significant differences of the resistin and immunoglobulin IgA and IgM levels among the T1DM and T2DM patients, and control group.

### 1.4 Results

The study included 153 samples collected from diabetes patients and healthy people distributed into three groups: the first group included 51 samples with T1DM (28 males and 23 females) with 27.94±10.04 years mean age, and the second group included 52 samples with T2DM (18 males and 34 females) with 60.27±10.08 years mean age, and the third group included 50 samples of an apparently healthy control group with 41.98±16.30 years mean age. The percentage of males in the T1DM group was 54.9% and that of females was 45.1%. As for the T2DM group, the percentage of males was 34.6% and that for the females it was 65.4%. Moreover, in the control group, the percentage of males was 48.0% and that of the females was 52.0% (Table 1).

**Table 1:** Distribution of T1DM, T2DM patients and control groups according to gender and age

| Studied Parameters | | T1DM | T2DM | Control | Probability |
|---|---|---|---|---|---|
| Age mean ± SD (Years) | | 27.94±10.04 | 60.27±10.08 | 41.98±16.30 | |
| Gender No. (%) | Males | 28 (54.9) | 18 (34.6) | 24 (48.0) | 0.110 |
| | Females | 23 (45.1) | 34 (65.4) | 26 (52.0) | |
| | Total | 51 (100.0) | 52 (100.0) | 50 (100.0) | |

**No significant differences at ($p$<0.05).**

The results of serum resistin levels summarized in Table 2 show an increase in the concentration of resistin in the serum of patients with T1DM compared to patients with T2DM and control group, as the concentration in the blood serum of patients with T1DM was 2.40±0.34 pg/ml. A decrease in its concentration was observed in the serum of people with T2DM, compared to those with T1DM, and an increase in its concentration compared to control group as the concentration in the serum of people with T2DM was 1.46±0.62 pg/ml. While its concentration in control group was 1.28±0.65 pg/ml, with statistically significant differences between the T1DM and T2DM groups, and control group, and there were no significant differences between the T2DM group and control group, below the level of significance ($p$<0.05).

**Table 2:** Comparison in serum resistin levels among study groups.

| Resistin means levels ± SD (pg/ml) | | |
|---|---|---|
| **T1DM** | **T2DM** | **Control** |
| $2.40 \pm 0.34^{A}$ | $1.46 \pm 0.62^{B}$ | $1.28 \pm 0.65^{B}$ |

**$^{A, B}$: Referred to significant differencesat ($p$<0.05) among the compared groups.**

The results in Table 3 show the means of immunoglobulins IgA and IgM in T1DM, T2DM patients, and control group. The table shows that there was an increase in immunoglobulin IgA concentration in the serum of patients with T1DM, compared to patients with T2DM and control group, as the concentration in the serum of patients with T1DM was 678.31±8.34mg/dl. A decrease was observed in its concentration in the serum of people with T2DM compared to those with T1DM, and an increase in its concentration compared to control group, as the concentration in the serum of people with T2DM was 524.68±63.62mg/dl. While its concentration in the control group was 84.96±17.35mg/dl, with statistically significant differences between the group of T1DM, group of T2DM, and control group, and the presence of significant differences between the group of T2DM and control group, below the level of significance ($p$<0.05). Furthermore, there was an increase in immunoglobulin IgM concentration in the serum of patients with T1DM compared to patients with T2DM and control group, as the concentration in the serum of patients with T1DM was 508.47±73.93mg/dl. A decrease in its concentration was observed in the serum of people with T2DM, compared to those with T1DM, and an increase in its concentration compared to control group, as the concentration in the serum of people with T2DM was 469.43±92.39mg/dl. While its concentration in control group was 125.69±23.86mg/dl, with statistically significant differences between the T1DM group, T2DM group, and control group, and the presence of significant differences between the T2DM group and control group, below a significant level ($p$<0.05).

**Table 3:** Comparison between studied groups to immunoglobulins IgA and IgM.

| Immunoglobulinstests | Means levels ± SD (mg/dl) | | |
|---|---|---|---|
| | **T1DM** | **T2DM** | **Control** |
| **IgA** | $678.31 \pm 8.34^{A}$ | $524.68 \pm 63.62^{B}$ | $84.96 \pm 17.35^{C}$ |
| **IgM** | $508.47 \pm 73.93^{A}$ | $469.43 \pm 92.39^{B}$ | $125.69 \pm 23.86^{C}$ |

**$^{A, B, C}$: Referred to significant differences at $p$<0.05 among the compared groups.**

### 1.5 Discussion

Resistin is a peptide released by white adipose cells that have been linked to DM in humans. It is a new cytokine that plays a role in inflammation, insulin resistance, and obesity [19]. Consequently, the autoimmune and inflammatory background of the disease can be used to explain the elevated level of resistin in T1DM. Resistin was first introduced to humans as an inflammatory cytokine. For instance, Tofighi *et al*. reported that processes other than obesity cause resistinto play a proinflammatory role [20]. The results of this study are consistent with Kollari *et al*. in Greece [21], and Geyikli *et al*. in Turkey [22] as it found that resistin level was higher in T1DM patients compared to healthy subjects. According to research by Saboktakin *et al*., T1DM causes macrophages and apoptotic cells to produce cytokines which act as mediators of inflammatory processes [23]. Additionally, in several pathological circumstances, resistin may initiate the development of TNF-α, interleukin-6, and other related inflammatory markers. Finally, the metabolic cascade signal and inflammatory pathways activated by resistin may exacerbate T1DM complications [24].

Without an agreement with the study Majewska *et al*. [25], the hyperglycaemic impact of resistin, which is considered "redundant," may be subject to suppression by reducing its secretion at high glucose blood concentrations. In a study by Wijetunge *et al*. visceral and subcutaneous white adipose tissue were evaluated in female patients with obesity, IR, and dysglycemia to determine the relationship between these variables. Their findings showed that systemic and adipose tissue resistin levels rely on dysglycemia and can be taken for granted as a key biomarker in the T1DM population [26]. In the present study, no significant difference in resistin levels between T2DM patients and control was recorded. This study is in agreement with Husain *et al*. in Iraq [27] and Mir *et al*. in Saudi Arabia [28]. In isolated adipocytes, resistin in humans lowers hyperglycemia induced by insulin. While studies aim to reduce resistin-activated protein kinasel (AMPK) activity, mainly in the liver, as a result of cytokine stimulation-3 suppressor activation, the fundamental processes underlying these effects are yet unknown [29]. Resistin may be a strong link between obesity, IR, and diabetes by disrupting the insulin signaling pathway, according to Hussain *et al*. [27] and this study disagrees with Peng *et al*. who found a close relationship between resistin and diabetic nephropathy [30]. Contrarily, a research indicated that there was no significant difference in resistin concentrations between non-obese, obese, and T2DM participants, and that serum resistin levels were not connected with body mass index or blood glucose [31].
Studies provide evidence that T1DM is characterized by the presence of T cells and humoral antibodies to islet proteins (antigens) [32]. The present study found a significant difference in IgA levels between T1DM patients and control. This study is in agreement with Huang *et al*. in China [33], and Alnek*et al*. in Estonia [34]. Higher IgA levels and T1DM are related, possibly as a result of patient immune-inflammatory disorders. The human intestine produces about 40 mg/kg of IgA per day which is used to maintain gut homeostasis. IgA immune responses can be triggered by microbes and/or ER stress in intestinal epithelial cells. IgA-induced is typically polyreactive and can bind to a variety of microorganisms [33]. However, this study disagrees with Elsayed *et al*. who found no relationship between serum IgA concentration and glycemic control [35]. Another study found that IgA levels rose with aging and linked this to the maturity of the immune system in T1DM patients [36]. The results of this study showed a significant difference in IgA levels between T2DM patients and control. This study concurs with Kostov and Blazhev in Bulgaria [37] and Martirosyan*et al*. in the United States [38]. In this study, IgA concentration was high which might be a result of the development of inflammatory diseases linked to T2DM. IgA is also said to be a general marker for the emergence of T2DM problems. A co-factor in the synthesis of immunoglobulins and a measure of inflammation, IL-6, is also correlated with IgA levels in the serum. Monitoring IgA may therefore give early notice of such issues [39]. Studies have demonstrated that people with T2DM had altered serum IgA responses. However, little is known about IgA in the gut in T2DM or hyperglycemia [40].

Numerous research conducted in the last few decades revealed that respiratory viruses, particularly enteroviruses (EV), are involved in the etiology of T1DM [41]. In addition, viruses can kill β-cells directly or indirectly [42]. The results of this study showed there was a significant difference in IgM levels between T1DM patients and control. This study is in agreement with Karaoglan and Eksi in Turkey, [43] and Rolim *et al*. in Portugal [44]. According to research by Karaoglan and Eksi, there is a substantial correlation between the existence of IgM against IVB, ECHO7, PIV4, CAV7, and H3N2. It shows that enteroviruses and respiratory viruses may all contribute to the etiopathogenesis and clinical start of T1DM [43]. On the other hand, this study does not agreem with Greco and Maggio that the level of IgM did not rise in patients with T1DM compared to the control group [45]. Thus, it has been demonstrated that influenza viruses can impact islet cells in both experimental and epidemiologic research [43]. In addition, the present study found a significant difference in

IgM levels between T2DM patients and control. This study is in agreement with Hasso *et al*. in Iraq [46], and Kostov and Blazhev in Bulgaria [47]. Research revealed that the human intestine has a significant number of IgM+B cells that secrete IgM that is reactive to various microbiota [48]. IgM can bind more bacterial antigens and possibly different microorganisms since it has a pentameric structure and more antigen-binding sites than IgG and IgA. Increases in bacterial products, particularly lipopolysaccharide, in blood and adipose tissue are one way that changes in gut microbiota cause an inflammatory environment. This can also lead to insulin resistance [17]. In addition, this study did not agree with Cheţa *et al*. who suggested that low IgM levels may help explain some of the poorly understood rise in infection susceptibility in T2DM [49]. On the other hand, a study has shown that gut bacteria stimulate B cells and are immunogenic. It is crucial for both local and systemic immunological tolerance or intolerance that B cells produce antibodies to the gut microorganisms [50].

### 1.6 Conclusion

Increasing the level of resistin stimulates the secretion of inflammatory cytokines that induce an immune response that damages beta cells in the islet of the pancreas in patients with T1DM. An increase in immunoglobulin IgA and IgM levels in the serum of patients with T1DM and T2DM have an effect on the intestinal microenvironment which is associated with an increase in blood sugar.

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