

Variations of Complement Proteins C3 and C4 Levels in Iraqi Diabetic Type II Patients Infected with Toxoplasmosis

Sarah Ali Saeed ¹ , Israa Kasim Al-Aubaidi ²

Abstract

Background: This study investigates the variation in complement proteins C3 and C4 levels between Iraqi type II diabetic patients infected with *Toxoplasma gondii* and non-diabetic control individuals. *T. gondii* is a widespread intracellular parasite that can infect most warm-blooded animals, including humans. Type II diabetes mellitus is characterized by abnormal metabolism and elevated blood sugar due to insufficient insulin secretion or reduced insulin effectiveness.

Patients and Methods: The study involved 109 blood samples from Iraqi type II diabetic patients and 80 samples from non-diabetic controls. The participants' ages averaged (49.9 ± 1.29). The levels of *Toxoplasma* antibodies (IgG and IgM) were tested using immunochromatography and CMIA, while glucose levels were measured using fasting blood sugar (FBS) and HbA1C tests. Complement protein levels (C3 and C4) were evaluated through ELISA.

Results: The results showed that diabetic patients had higher blood glucose levels, with fasting blood sugar at 174.6 mg/dL and HbA1C at 7.91%. *Toxoplasma* IgG antibodies were detected in 41.29% of diabetic patients and 38.75% of healthy individuals. Moreover, diabetic patients infected with *Toxoplasma* exhibited significantly higher levels of C3 (189.3 ± 5.7 mg/dL) and C4 (38.67 ± 0.89 mg/dL) proteins compared to other groups. All specimens were negative for *Toxoplasma* IgM.

Conclusion: These findings suggest that *Toxoplasma* infection may influence complement protein levels in diabetic patients, highlighting the interaction between these conditions.

Keywords: Toxoplasmosis, Diabetes mellitus (type II), IgM/IgG, C3 and C4

Affiliation of Authors

¹ College of Medicine, Ibn Sina University for Medical and Pharmaceutical Sciences, Iraq, Baghdad, 10001

² College of Education for Pure Sciences, Ibn Al-Haitham, University of Baghdad, Iraq, Baghdad, 10001

¹ sarah.asaeed@ibnsina.edu.iq

² Israa.k.s@ihcoedu.uobaghdad.edu.iq

¹ Corresponding Author

Paper Info.

Published: Oct. 2025

انتساب الباحثين

¹ كلية الطب، جامعة ابن سينا للعلوم الطبية والصيدلانية، العراق، بغداد، 10001.

² كلية التربية للعلوم الصرفة (ابن الهيثم)، جامعة بغداد، العراق، بغداد، 10001.

¹ sarah.asaeed@ibnsina.edu.iq

² Israa.k.s@ihcoedu.uobaghdad.edu.iq

¹ المؤلف المراسل

معلومات البحث

تأريخ النشر: تشرين الاول 2025

اختلافات مستويات بروتينات المتممة C3 و C4 لدى مرضى السكري من النوع الثاني العراقيين المصابين بداء المقوسات

ساره علي سعيد ¹ ، اسراء قاسم العبيدي ²

المستخلص

الخلفية العلمية: تستقصي هذه الدراسة التغيرات في مستويات بروتينات المتمم C3 و C4 بين مرضى السكري من النوع الثاني العراقيين المصابين بالمقوسة الكوندية والأفراد الأصحاء غير المصابين بالسكري. تُعد المقوسة الكوندية طفيليًا داخليًا واسع الانتشار يمكنه إصابة معظم الحيوانات ذوات الدم الحار، بما في ذلك الإنسان. يتميز مرض السكري من النوع الثاني باضطراب في الأيض وارتفاع مستويات السكر في الدم بسبب نقص إفراز الأنسولين أو انخفاض فعالية الأنسولين.

المرضى والطرق: شملت الدراسة 109 عينات دم من مرضى السكري من النوع الثاني العراقيين و80 عينة من الأفراد الأصحاء غير المصابين بالسكري. كان متوسط أعمار المشاركين (49.9 ± 1.29). تم اختبار مستويات الأجسام المضادة لتوكسوبلازما (IgG و IgM) باستخدام تقنية المناعية الكروماتوغرافية والاختبار المناعي باستخدام الجزيئات الصغيرة المضيفة كيميائيًا، بينما تم قياس مستويات الجلوكوز باستخدام اختبار السكر في الدم الصائم واختبار السكر التراكمي. تم تقييم مستويات بروتينات المتمم (C3 و C4) باستخدام تقنية الاختبار المناعي المرتبط بالإنزيم.

النتائج: أظهرت النتائج أن مرضى السكري لديهم مستويات أعلى من السكر في الدم، حيث كان مستوى السكر في الدم الصائم 174.6 ملغم/ديسيلتر و التراكمي عند 7.91%. تم اكتشاف الأجسام المضادة للمقوسة IgG في

41.29% من مرضى السكري و38.75% من الأفراد الأصحاء. علاوة على ذلك، أظهر مرضى السكري المصابون بالمقوسة مستويات أعلى بكثير من بروتينات C3 (5.7 ± 189.3 ملغم/ديسيلتر) و C4 (± 38.67) و 0.89 ملغم/ديسيلتر) مقارنة بالمجموعات الأخرى. كانت جميع العينات سلبية للأجسام المضادة للمقوسة الكوندية IgM. **الاستنتاج:** تشير هذه النتائج إلى أن الإصابة بالمقوسات قد تؤثر على مستويات بروتينات المتمم في مرضى السكري، مما يبرز التفاعل بين هذه الحالات.

الكلمات المفتاحية: المقوسة الكوندية، داء السكري (النوع الثاني)، IgM/IgG، C3، C4

Introduction

Toxoplasmosis is considered to be one of the most widespread infections in warm-blooded mammals including humans, this infection is occurred by *Toxoplasma gondii*, an obligate intracellular protozoan [1,2]. This disease leads to a variety of clinical abnormalities; most individuals are asymptomatic; however, some have serious complications [3]. *T. gondii* may infect and multiply in any nucleated host cell, causing the development of various inflammatory markers that aggravate chronic inflammation. Chronic infection behavior could be altered by toxoplasmosis infection [4,5]. Human *T. gondii* infection can be diagnosed utilizing a different of immunological methods [6].

Uncontrollably high blood glucose levels triggered by either a reduction in the physiologic action of insulin or a total loss of insulin production, or both, are indicator of diabetes mellitus, a metabolic disorder [7, 8]. Non-insulin-dependent diabetes mellitus (T2DM) is abnormal high blood glucose levels caused by a proportional insulin deficit [9, 10].

It has been indicated that people infected with toxoplasmosis may be more probable than those who do not to acquire diabetes. Insulin may promote the reproduction of *T. gondii*. Moreover, it has been noticed that individuals with a chronic toxoplasmosis infection have abnormal neurohormonal regulation in some cases of

diabetes [11, 12]. Since that people with type II diabetes have decreased arterial blood flow, weakened immune systems, and neuropathy, which increases their susceptibility to parasitic infections, this could be a reasonable explanation for the relationship between *T. gondii* and the disease [13], but in immunocompromised hosts, the parasite may become a likely fatal infection that leads to severe toxoplasmosis. In healthy individuals, the infection progresses by an acute phase that is related to the prevalence of rapidly dividing tachyzoites that can invade nearly all nucleated cells. A prolonged chronic phase that coincides with the increase in host adaptive immunity occurs after this [14].

The capability of antibodies and phagocytic cells to eliminate pathogens from an organism is aided or improved by the complement system. This immune system component is known as the innate immune system [15].

Primarily, complement was thought to play a principal role in innate immunity where a powerful and rapid response is mounted against invading pathogens. Nevertheless, recently it is becoming increasingly obvious that complement also plays a critical role in adaptive immunity involving T and B cells that aid in elimination of pathogens [16, 17]. After B cells were illustrated to be capable to bind C3, it was found that complement-associated B cell functions were mediated by the complement receptors CR1 and CR2. Both B cells and a

minority of T cells express these receptors [18, 19]. Complement activation by parasites has a role in multiple host-parasite connection pathways, it was discovered to be fatal for the parasites in the majority of in vitro tests [20].

The object of this study is to determine the role of complement system with its proteins C3 and C4 on the diabetic patients infected with toxoplasmosis.

Materials and Methods

Subjects and Samples

One hundred-nine type II diabetes specimens and 80 samples that were taken from non-diabetic outpatient clinics were enrolled with a period between March and June 2022, experts at a private laboratory in Baghdad, Iraq. With age ranged 18 to 85 years old (49.9 ± 1.29). A centrifuge was utilized to extract the serum from 10 milliliters of venous blood of each patient, spinning at 3000 rounds per minute (rpm) for ten minutes. Tests for diabetes, *T. gondii* detection, anti-*Toxoplasma* IgM/IgG antibody titers measurement, and complement proteins C3 and C4 evaluated were carried out using serum that was separated and subsequently used.

Diabetes mellitus diagnosis

As instructed by the manufacturer, the Glucose Architect kit (Abbott GmbH, Germany) is used to assess the level of blood sugar by a fasting test. Following that, the Hemoglobin A1C Architect kit (Abbott GmbH, Germany) is utilized to evaluate the glycated hemoglobin level.

T. gondii serological diagnosis

Initially, *T. gondii* infection was identified using the *Toxoplasma* IgM/IgG antibody rapid test

(immunochromatography) kit (Qingdao Hightop Biotech Company, China) in accordance with the manufacturer's instructions. Then, the mean titers of anti-*Toxoplasma* IgM/IgG antibodies were determined using the chemiluminescent microparticles immunoassay (CMIA) Architect Toxo IgG/IgM kit (Abbott GmbH, Germany) based on the manufacturer's instructions.

Assessment levels of C3 and C4 proteins

Human complement 3 and 4 levels were assessed by Sandwich Enzyme-linked Immunosorbent assay (ELISA) kit (mybiosource Inc., USA) in accordance to the instructions of the manufacturer.

Statistical Analysis

The collected raw results were analyzed using SPSS program (V.20, IBM), by using one way ANOVA and obtaining Least Significant Difference (LSD). The results were presented as mean $\pm$ S.E, and significant difference was considered at $p \leq 0.05$. [21].

Results and Discussion

Due to diabetics are more susceptible to infection than healthy individuals, with opportunistic diseases like toxoplasmosis are more popular in this demographic. The risk of contracting numerous infectious diseases is raised in diabetic patients, rising their sensitivity to infection [22]. The outcomes of this study revealed that in comparison to the non-diabetic group, the diabetic group had the highest mean titers of glycated hemoglobin and blood sugar in HbA1C and FBS tests as shown in Figure (1).

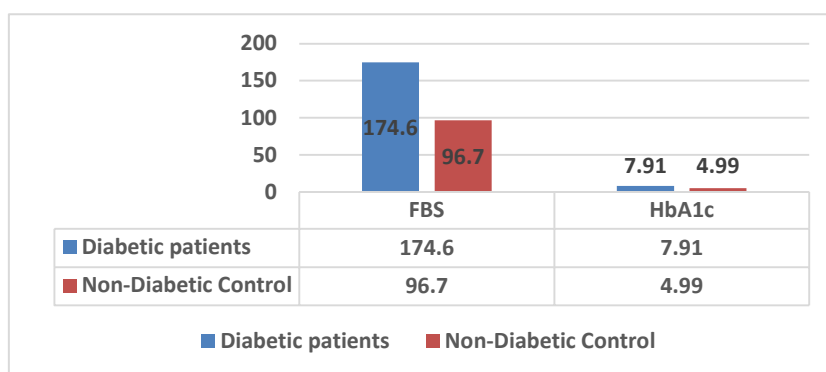


Figure (1): State the sugar concentrations of FBS and HbA1c tests in the studied groups

The above results were resembled to the results of Waheed *et al.* [23] which demonstrated that the group of diabetic type II patients (30/50) had the highest levels of sugar (130.8 ± 16.575 mg/dl and 7.993 ± 0.646) in FBS and HbA1C respectively, while the Iraqi non-diabetic group (20/50) had results of (83.8 ± 9.689 and 4.68 ± 0.484) in the same tests. Besides, the blood sugar test results obtained from fasting are similar with those of Al-Aubaidi *et al.* [24], who revealed that there are noticeable differences in the fasting test sugar levels between the diabetic patient groups (155.2 ± 7.1 UI/mL) and the case control group (111.4 ± 2.1 UI/mL). Furthermore, the present results were comparable to the results of Elkholy *et al.* [25] which demonstrated that 15% of the group of patients with toxoplasmosis had glycated hemoglobin in HbA1C test. The recommended test is HbA1C since it is more beneficial over an extended period of time and more time-variable. The HbA1C test has become one of the best tests for emphasize that diabetes is under control in recent times.

Referring to the results of Taher *et al.* [26] and Hammad *et al.* [27], they recommended that

HbA1c (glycosylated hemoglobin) is most accurate test to give an actual reading over the past 2-3 months, and to assessing the risk of glycemic damage to the tissues but it can't be utilized to monitor day-to-day blood glucose concentration due to it's not influenced by fluctuation in blood concentration.

Figure (2) illustrates the results of immunochromatography test, which it is a rapid test, was used to identify IgM and IgG antibodies of *T. gondii* infection, which it shown that 2/109 (1.84%) of diabetic patients had positive results for Toxo IgM antibody, 45/109 (41.29%) of the same group had positive results for Toxo IgG antibody, and 10/109 (9.17%) of the same group were sero-positive for both antibodies. On the other hand, the non-diabetic control group had sero-positive results for 1 (1.25%) Toxo IgM, 31 (31.75%) Toxo IgG, and 2 (2.5%) Toxo IgM and IgG. Additionally, 52 (47.7%) of diabetic patients and 46 (57.5%) of non-diabetic control cases had sero-negative detection, respectively. as shown in Figure (2).

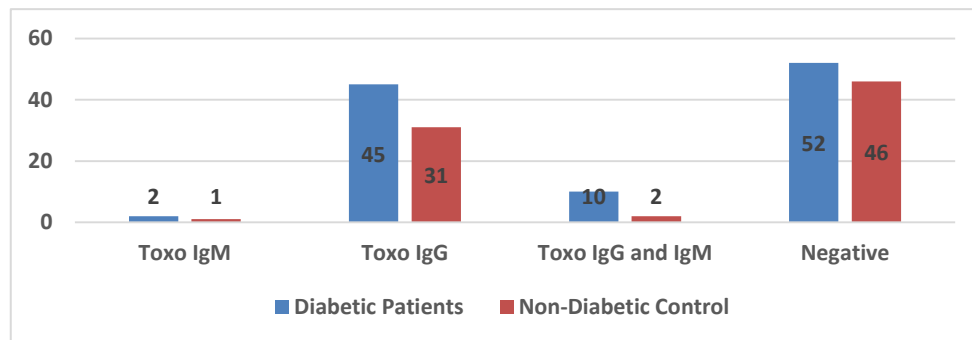


Figure (2): State the detection of *T. gondii* infection in the studied cases by immunochromatography rapid test

Even so, the current immunochromatography test results are comparable to those published by Al-Khafajii *et al.* [28], who demonstrated that 22/45 (48.88%) of the diabetic patients and 28/55 (50.9%) of the non-diabetic control group were sero-positive for anti-*Toxoplasma* IgG antibody. The outcomes of this study similarly resemble to the findings of Al-Aubaidi *et al.* (24), which shown that there were very significant variations between the 47 diabetes patients who had sero-positive for the *Toxoplasma* IgG antibody and the healthy control group that had sero-negative for the same antibody, the immunochromatography test has been examined as a

feasible screening technique replacement for toxoplasmosis detection because it is less expensive than other tests, easier to use (results can be received in 15 minutes), and takes no additional equipment or training [29].

Using the chemiluminescent microparticle immunoassay (CMIA), **figure (3)** demonstrated that 51/109 (46.79%) of the diabetic patients and 30/80 (37.5%) of the non-diabetic control were sero-positive for *Toxoplasma* IgG antibodies. However, using the same technique, every instance tested seronegative for *Toxoplasma* IgM antibodies. as shown in Figure (3).

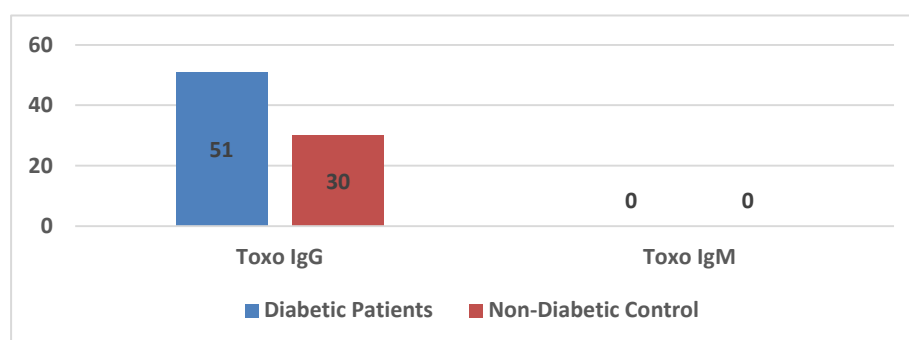


Figure (3): State *Toxoplasma* IgG and IgM antibody detection in the studied samples via CMIA

According to the above results, the studied cases were divided into four groups: diabetic patients infected with toxoplasmosis, diabetic patients, toxoplasmosis asymptomatic individuals

considered as a positive control and healthy individuals considered as a negative control. **Table (1)** results show that there are substantial variations in the sero-positive response for

Toxoplasma IgG antibody between 51/109 (46.79%) titer of diabetic patients and 30/80 (37.5%) titer of non-diabetic control group. The

CMIA found no significant differences in the sero-negative responses for the IgM *Toxoplasma* antibody.

Table (1): State means titers of *Toxoplasma* IgG and IgM antibodies in the studied groups via CMIA

Groups	Samples count	Mean $\pm$ SE of Toxo IgG IU/mL	Mean $\pm$ SE of Toxo IgM IU/mL
Diabetic patients with toxoplasmosis	51 (26.98%)	34.951 $\pm$ 7.52 ac	0.08 $\pm$ 0.005 a
Diabetic patients	58 (30.69%)	0.024 $\pm$ 0.06 b	0.07 $\pm$ 0.0031
Toxoplasmosis asymptomatic individuals (positive control)	30 (15.87%)	32.71 $\pm$ 8.5 a	0.11 $\pm$ 0.042 a
Healthy individuals (negative control)	50 (26.46%)	0.4 $\pm$ 0.06	0.04 $\pm$ 0.005
LSD value		14.78 **	0.0388 **
P-value		P < 0.001	0.034
^a vs. negative control, ^b vs. positive control, ^c vs. diabetic patients			
** High significant, * Significant			
Reference range of Toxo IgM: Primary (acute) infection $\geq$ 0.6.			
Reference range of Toxo IgG: Secondary (chronic) infection $\geq$ 0.3			

The above outcomes are agreed with those of Al-Aubaidi *et al.* [24] who found that diabetic patients with toxoplasmosis 45/100 had the highest level of IgG (106.2 $\pm$ 13.1) in comparison to other groups, with highly significant differences. They also showed no evidence of *Toxoplasma* IgM antibody in the study. Moreover, another study supports the present study, Salman *et al.* [30] revealed that 36/69 (52.1%) of the groups of diabetic patients infected with toxoplasmosis had sero-positive results for the *Toxoplasma* IgG antibody (159.04 $\pm$ 12.32) in ELISA, but no detection for the *Toxoplasma* IgM antibody in the same assay.

The explanation for the raised IgG antibody levels, according to Tenter *et al.* [31] is that it is an essential component of the humoral immune

response that aids in limiting and controlling the parasite's dissemination. It is observed, however, that IgG antibodies are often found 1-2 weeks after infection, peak in concentration in the next 6-8 weeks, and then gradually drop over a year or two, with potentially lifelong low levels. Also, it has been demonstrated that in immunological individuals, the levels of antibody IgM decrease more quickly than the levels of antibody IgG after a protracted damage that could last for years.

Additionally, because the IgG antibody may alternate large molecules in the absence of antibody makers, the half-life of IgG antibody is longer than that of the IgM antibody. Referring to the above information, diabetic individuals were more possibility than healthy controls to contract

toxoplasmosis. Patients with toxoplasmosis may therefore be more probably to gain diabetes than those who are not affected [32].

Thirty samples of each group were analyzed via ELISA to measuring the concentration of

complement proteins C3 and C4, which appeared in the table (2). C3 protein raised in the group of diabetic patients infected with toxoplasmosis with highly significant difference when compared with other groups.

Table (2): Estimation of serum complement protein C3 levels in the studied groups

Groups		Number of samples	Mean ± SE mg/dL
Patients	Diabetic with toxoplasmosis	30	189.3 ± 5.7 abc
	Diabetic	30	160.67 ± 10.2 ab
Control	Toxoplasmosis asymptomatic (positive)	30	145 ± 0.82 a
	Healthy individuals (negative)	30	113 ± 0.12
LSD value		8.49 **	
P-value		P < 0.001	
^a vs. negative control, ^b vs. positive control, ^c vs. diabetic patients			
** High significant			
Reference range of protein C3: 4 mg/dL – 500 mg/dL			

Moreover, table (3) clarified that the group of diabetic patients with toxoplasmosis has the

highest level of protein C4 with highly significant difference in comparison with the other group.

Table (3): Concentrations of protein C4 in the studied cases by ELISA

Groups		Number of samples	Mean ± SE mg/dL
Patients	Diabetic with toxoplasmosis	30	38.67 ± 0.89 abc
	Diabetic	30	32.3 ± 1.06 ab
Control	Toxoplasmosis asymptomatic (positive)	30	28.5 ± 1.5 a
	Healthy individuals (negative)	30	21.3 ± 0.75
LSD value		3.12**	
P-value		P < 0.001	
^a vs. negative control, ^b vs. positive control, ^c vs. diabetic patients			
** High significant			
Reference range of protein C4: 10 mg/dL – 40 mg/dL			

Referring to the above results, it has revealed that there are no previous studies similar or compatible

to current study. However, some studies confirm that these proteins play a role in the aborted

women such as the study Al Kalaby *et al.* [33] which demonstrated that 11/35 (31.4%) and 4 (11.4%) of aborted women infected with toxoplasmosis has highest concentration of C3 and C4 respectively, when compared with the control group 0/10 (0%) and 0/10 (0%) in C3 and C4 respectively.

Moreover, Al Jubouri *et al.* [34] showed that C3 and C4 levels in the group of pregnant women infected with toxoplasmosis reached to (0.3708 ± 0.0107) and (0.3851 ± 0.0306) respectively. Whereas, in the control group, C3 and C4 levels reached to (0.2528 ± 0.0463) and (0.2142 ± 0.0608) respectively.

Furthermore, Mustafa *et al.* (35) revealed that evaluation of C3 and C4 in 60 blood samples from Iraqi type II diabetic patients and 30 healthy donors, their results demonstrated that the kidney disease patients had a significantly higher quantity of C3 (199.0 mg/dL) than the healthy donors (135.4 mg/dL). Conversely, there were no appreciable variations in the C4 concentration, which was found to be (30.04 mg/dL) in healthy donors compared to (27.25 mg/dL) in a group of diabetes patients. Also, the findings of Ahmed and Saleh (36) showed that the increased median level of C3 in 60 blood samples of diabetic type II patients (150 mg/dL), compared to the 30 blood samples of healthy control (120 mg/dL). In contrast, the decreased median level of C4 in the

group of diabetic type II patients was 23.00 mg/dL with significant differences when compared with the group of healthy control group (40 mg/dL). One of the main components of the complement system is complement protein C3, which its activation is necessary for all of the system's significant operations. The complement activation process implies the activation of C3b by C4b2b,

that it is a significant step since each C4b2b complex can activate up to 200 C3 molecules. C3 is the most concentrated protein in serum and is consistently activated by both classical and alternative pathways (37). C3 controls the adaptive immune response to select the appropriate antigens for a humoral response, facilitates phagocytosis, and supports local inflammatory responses against pathogens nevertheless its disorderly activation causes harm to host cells (38).

Through the inflammation, the levels of the acute phase proteins C3 and C4 might elevate by 50%. Additionally, raised complement protein levels in diabetes individuals may activate increased membrane attack complex (MAC) deposition on cells, which lead to the beginning of an inflammatory phase (39). The complement system may play a role in both innate immunity and the metabolic syndrome. The protein C3 has a strong correlation with diabetes (40).

Conclusion

The complement proteins C3 and C4 play a role in the diabetic type II patients infected with toxoplasmosis.

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