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Interactions of Interferons and SARS-CoV-2 Antibodies With Type 2 Diabetes

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Abstract

Type 2 diabetes mellitus (T2DM), clinically depicted by insulin resistance and long-standing hyperglycemia, predisposes to infections and is further exacerbated in COVID-19 patients, thereby resulting in an increased risk of severe outcomes. The main objectives of this study were to evaluate type 2 diabetes and non-diabetic patients diagnosed with COVID-19 and compare them with control samples for levels of INF-α, INF-β, and SARS-CoV-2 antibodies (IgM/IgG). The study aims to determine the impact of type 2 diabetes on the immune response against SARS-CoV-2 and to understand which immunodeficiency could explain the poor prognosis in diabetic patients. A total number of 430 nasal swabs were collected from patients in Kirkuk between January 1, 2023, and June 7, 2023. The patients' ages ranged from (18 - 83) years, and through their polymerase chain reaction (PCR) tests, there were 72 confirmed cases of SARS-CoV-2, of which (51.4%) were males and (48.6%) were females and the majority were elderly. Type 2 diabetes patients were among the confirmed cases, with 43 patients and 29 non-diabetics. Blood samples were taken from these individuals and distributed into two tubes: one containing EDTA for testing glycated haemoglobin and the other containing gel for immunological studies using an ELISA device that measures the levels of IgG, IgM, INF-α, and INF-β. Immunological analysis showed that type 1 interferons were significantly less abundant in diabetic and non-diabetic patients compared to control samples. However, the antibody response, especially in terms of IgG and IgM levels, was significantly reduced in diabetic patients compared to non-diabetic individuals. This suggests that type 2 diabetes reduces the immune response in patients infected with SARS-CoV-2. This study suggests that type 2 diabetes is associated with reducing the immune cell response to SARS-CoV-2, as supported by lower levels of antibodies and type 1 interferons among the diabetic groups.

Keywords -: IgG & IgM , INF-α & INF-β, SARA-CoV-2, Type 2 Diabetes, Immune Response.

تداخلات الإنترفيرونات والأجسام المضادة لفيروس كورونا المستجد مع مرض السكري من النوع الثاني

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الخلاصة

داء السكري من النوع 2، الذي يتمثل سريريًا بمقاومة الأنسولين وفرط سكر الدم طويل الأمد، يهيئ للإصابة بالعدوى ويتفاقم أكثر لدى مرضى COV−19 مما يؤدي إلى زيادة خطر حدوث نتائج وخيمة. أن الغرض الرئيسي من هذه الدراسة هو إجراء تقييم بين مرضى السكري من النوع 2 وغير المصابين بالسكري الذين تم تشخيص إصابتهم بـ COV−19 ومقارنتهم مع عينات السيطرة في مستويات الانترفيرونات و الأجسام المضادة INF−α و INF−β و (IgM / IgG) SARS−CoV−2 تهدف الدراسة إلى تحديد تأثير مرض السكري من النوع 2 على الاستجابة المناعية ضد SARS−CoV−2 وفهم أي نقص مناعي يمكن أن يفسر سوء التشخيص لدى مرضى السكري.حيث جمعت 430 مسحة أنفية من مرضى في كركوك بين 1 يناير 2023 و 7 يونيو 2023. تراوحت أعمار المرضى (18 – 83) عامًا ومن خلال اختبارات تفاعل البوليميراز المتسلسل (PCR) الخاصة بهم، كان هناك 72 حالة مؤكدة منSARS−CoV−2 ، منها (51.4٪) من الذكور و (48.6٪) من الإناث وكان الغالبية من كبار السن. وكان مرضى السكري من النوع الثاني من بين الحالات المؤكدة حيث بلغ عددهم 43 مريضًا، أما غير المصابين بالسكري فكان عددهم 29 حالة. وتم أخذ عينات دم من هؤلاء الأفراد وتوزيعها في أنبوبين: أحدهما يحتوي على EDTA لاختبار الهيموجلوبين السكري والآخر يحتوي على جل للدراسات المناعية

باستخدام جهاز ELISA الذي يقيس مستويات IgG و IgM و INF−α و INF−β. وأظهر التحليل المناعي أن الإنترفيرونات من النوع الأول كانت أقل وفرة بشكل ملحوظ في مرضى السكري وغير المصابين بالسكري مقارنة بعينات السيطرة. ومع ذلك، انخفضت استجابة الأجسام المضادة، وخاصة من حيث مستويات IgG و IgM، بشكل ملحوظ في مرضى السكري مقارنة بالأفراد غير المصابين بالسكري. يشير هذا إلى أن مرض السكري من النوع 2 يقلل من الاستجابة المناعية لدى المرضى المصابين بـ SARS−COV−2. حيث تشير الدراسة الحالية إلى أن مرض السكري من النوع 2 مرتبط بانخفاض استجابة الخلايا المناعية تجاه فيروس SARS−COV−2 معززة بمستويات أقل من الأجسام المضادة والإنترفيرونات من النوع 1 بين مجموعات مرضى السكري.

INTRODUCTION

Since its emergence in late 2019, the virus that causes COVID-19 (SARS-CoV-2) has had a severe impact on global health. Although the virus mainly affects the respiratory system, its effects are systemic and can worsen chronic morbidities, such as type 2 diabetes mellitus (T2DM), clinically depicted by insulin resistance and long-standing hyperglycemia, predisposes to infections and is further exacerbated in COVID-19 patients, thereby resulting an increased risk of severe outcomes [1].

Interferons (IFNs) are critical mediators of the innate immune response, representing the first line of defense against viral infections [2], and they are critical to prevent viral replication and immune cell activation. Because SARS-CoV-2 inhibition of IFN response contributes to poor antiviral defense [3], Meanwhile, antibodies, especially immunoglobulin G (IgG) and immunoglobulin M (IgM), indispensable are for the neutralization of the virus and immune protection [4,5]. It would be useful to view the scenario from the perspective of the interactions occurring between IFNs, antibodies and T2DM and better tailor patient care, which could significantly reduce morbidity/mortality rates in COVID-19-affected individuals.

The interferons are cytokines central to the immune response against viral challenge. Structurally, they belong to three major types: Type I (comprising IFN-α and IFN-β), type II (IFN-γ) and type III (IFN– λ) [6]. Type I and, by extension, type II interferons are present in the innate antiviral response [7]. Where antiviral proteins are expressed and enhanced NK cell activity is observed through macrophage activation. Previous studies have demonstrated

that SARS-CoV-2 has been able to escape the IFN response, which alternately resulted in viral persistence and severe illness [8].

IgG and IgM antibody responses to SARS-CoV-2 play a key role in viral neutralization and long-term immunity [9]. Relation of two cohort studies have reported that the detection of these antibodies is associated with protection against reinfection and milder disease severity. Nonetheless, the strength and duration of antibody responses to the virus differ widely between individuals, being influenced by factors such as age, sex and comorbidities, including T2DM [10].

Thus, the interplay between COVID-19, IFNs, and T2DM is complex and impacts upon disease outcomes. For instance, the IFN response is often impaired in patients with diabetes and results in uncontrolled viral replication in severe COVID-19 [11]. Moreover, the antibody response of diabetic patients is not well in the head, such that the immune system, in response to fighting the virus, will not be effective [12]. This knowledge is essential for the design of individualized therapies to improve COVID-19 management in diabetic patients.

Kirkuk is a province that has a rich ethnic combination, and the availability of healthcare facilities varies from one region to another. It presents its special challenges when it comes to managing the COVID-19 pandemic, especially in cases accompanied by comorbid conditions such as T2DM. These results will help to tease out the regional diversity of immune response among diabetic cohorts, which could further support region-specific public health measures and clinical interventions. Through this scape, the study provides an insight into pathways of interferon-antibody interactions and subsequently aids in understanding such behaviour of disease endemicity across Kirkuk or similarly equivalent precincts.

Materials and methods

The study population

The study included a total of 430 participants in Kirkuk, Iraq, who were clinically suspected of having COVID-19. The study continued with sample collection from February 15 to July 20, 2023.

All participants in this study were among patients who presented to the special PCR unit centers established in different hospitals in Kirkuk after being diagnosed with suspected COVID-19. The sampling criteria were as follows: Obtaining ethical approval number 131 - 13/2/2023.3, adults aged 18 - 83 years with a clinical indication for SARS-CoV-2 testing, individuals who gave informed consent to participate in the study, while individuals with type 1diabetes or gestational diabetes were declined to participate.

Blood sample collection and immunological analysis

Blood samples were taken from 72 patients at least 10-15 days after their SARS-CoV-2 infection was confirmed. Blood samples from diabetic patients were collected in two different tubes: EDTA tube for glycated hemoglobin (HbA1c). Venous blood was collected for immunological evaluation using serum separation tubes.

The levels of INF-α, INF-β, IgM, and IgG were detected by ELISA using the corresponding kits (Sunlong Biotech) [13], according to the manufacturer's instructions. ELISA stands for Enzyme-linked Immunosorbent assay; a method used to detect and quantify specific proteins in random biological samples, and is highly sensitive and specific. This protocol involves coating microtiter plates with specific antigens or antibodies and incubating them with serum samples. After incubation and washing, enzyme-linked secondary antibodies were added to induce a colorimetric change and measured in a spectrophotometer.

Statistical analysis

All ELISA assays were measured as per the Sunlong Biotech provided manufacture instructions. These included sample preparation, incubation and detection steps. Optical density units were then used to derive INF-α, INF-β, IgM and IgG concentrations from the ELISA readouts. These values were then compared and analyzed using statistical methods to determine whether or not the immune response differed between diabetics and non-diabetics.

Data were analyzed using statistical software (IBM SPSS Statistics 19). Descriptive statistics were calculated for the demographic and clinical characteristics of participants. The Chi-square test was used to compare categorical variables, including gender, between diabetic and non-diabetic patients. The levels and antibody titers were performed based on the T-test or ANOVA for normally distributed data. A p-value <0.05 was considered statistically significant (meaning that there is a real difference between the groups)[14].

Results and discussion

Result

The study prospectively collected serum from 430 patients who were clinically suspected as infected with SARS-CoV-2. Of the 72 cases, it was confirmed by PCR, and the other cases were not well-defined or poorly characterized. Of these, 43 were known to have had type 2 diabetes (T2DM), and 29 were not. The ages of those involved in the study varied between 3 and 83 years old, though individuals over the age of 60 were most likely to have severe cases. On the other hand, 57% and 43% of nearly confirmed cases were males and females, respectively.

The study also found, upon analyzing blood samples, that levels of two types of interferons known as INF-α and INF-β were low in the diabetic group, as well as the non-diabetic group, compared to control samples where levels were higher. Additionally, those diabetic patients, particularly in HbA1c > 7 %, showed a significantly reduced antibody production , including both IgM and IgG caliber, compared with non-diabetic patients ($P < 0.05$).

Interaction between interferons and antibodies to SARS-CoV-2

Analysis of immune markers revealed that SARS-CoV-2 infection led to lower levels of both INF-α and INF-β in all infected patients relative to healthy controls. This decrease was more significant in the diabetic group. This indicated that reduced interferon levels were associated with weakened antibody responses in T2DM cases. The study also showed that IgM (also known as the antibody produced in the early stages of an infection) and IgG antibodies were more thoroughly formed in non-diabetic patients than diabetics, for late phases of the immune response to SARS-CoV-2. Conversely, diabetic patients, especially if poorly regulated in terms of blood glucose (HbA1c > 7%), showed decreased antibody response.

Immune response in patients with type 2 diabetes

According to the current study, immune response was significantly suppressed among T2DM patients compared with their non-diabetic counterparts. A weak activation of adaptive immunity, in turn, is preceded by decreased induction of INF-α and INF-β among diabetic patients, a phenomenon arguably due to compensatory mechanisms being initiated to hinder early viral control [11]. Low levels of IgM and IgG antibodies also suggest an impaired adaptive immune response in diabetics. This lower immune response probably explains, at least in part, the higher severity of COVID-19 seen in diabetic patients.

Interpretation of the Results

Significant results of the current study have shown reduced immune responses amongst SARS-CoV-2 infected T2DM patients in terms of type 1 interferons (INF-α and INF-β) and antibodies (IgM and IgG). Reduced type I IFN bioactivity in diabetic patients and reduced expression of Interferon-Stimulated Genes would support the notion that SARS-CoV-2 can antagonize host response by enhancing resistance to IFNs, as recently proposed [8]. Furthermore, the findings of lower levels of antibodies in diabetic individuals with uncontrolled glycemia (Table 3) provide additional evidence that T2DM magnifies immune system dysfunction, thereby impeding robust viral clearance.

The results of this study are in line with previous study indicating that T2DM poses a significant burden, leading to an impaired immune function exploiting victims to poor risk [15]. As expected, patients with diabetes exhibit a blunted response to interferon, similar to previous study[12,16]. Therefore, this potentially shifts the balance towards unregulated viral replication and severe disease. Further, the decreased antibody response in this study confirms existing reports on the dampening effect of T2DM on both innate and adaptive immunity, leading to increased susceptibility to infections.

Statistical significance

These data were analyzed statistically to compare diabetic with non-diabetic status in (INF-α, INF-β, IgM, and IgG) levels. The differences among these groups were examined via t-tests, with $p < 0.05$ set as the significance level. The data revealed that the levels of INF-α and INF-β were reduced dramatically in diabetic patients *vs*. non-diabetic patients as well as control samples ($p < 0.05$). Conversely, diabetic patients with HbA1c > 7% had lower concentrations of IgM and IgG compared to non-diabetics, showing statistically significant impairment in the immune response of T2DM ($p < 0.05$).

Distributions of patients according to age

The study sample included 72 patients, who were divided by age, as shown in Table 1 and Figure 1. The results in the table detailing the age distribution among the three groups (control, COVID-19 patients without diabetes, and COVID-19 patients with diabetes) showed that the mean age of the control group was (36.32 ± 11.72) years, while it increased to (45.59 ± 18.67) years in the non-diabetic group and reached a maximum of (59.67 ± 14.3) years in the diabetic group. The age ranged across all groups between 18 - 80 years. It is noteworthy that the 18–26 age group represented the highest percentage in the control group (27.3%), while this percentage decreased to (20.7%) in the non-diabetic group and only (2.3%) in the diabetic group. Conversely, the percentages gradually increased with age in the diabetic group, reaching (25.6%) in the 72–80 age group, the highest percentage compared to all groups and categories. In contrast, no cases were recorded in this age group within the control group.

Table 1: Distributions of patients and control according to age.

Characteristic	Control n = 22	Without DMT2 n = 29	With DMT2 n = 43	*P value*
Age (years)				
Mean ± SD	36.32 ± 11.72	45.59 ± 18.67	59.67 ± 14.3	*p <0.0001 S*
Range	18-62	18-80	18-80	
18-26, n (%)	6 (27.3%)	6 (20.7%)	1 (2.3%)	
27-35, n (%)	5 (22.7%)	5 (17.2%)	2 (4.7%)	
36-44, n (%)	5 (22.7%)	4 (13.8%)	4 (9.3%)	
45-53, n (%)	4 (18.2%)	4 (13.8%)	6 (14.0%)	
54-62, n (%)	2 (9.1%)	3 (10.3%)	9 (20.9%)	
63-71, n (%)	0 (0.0%)	3 (10.3%)	10 (23.3%)	
72-80, n (%)	0 (0.0%)	4 (13.8%)	11 (25.6%)	

DMT2:diabetes mellitus type 2 **n**: number of cases; **SD**: standard deviation; **S**: significant at $p < 0.05$; **df** : (2).

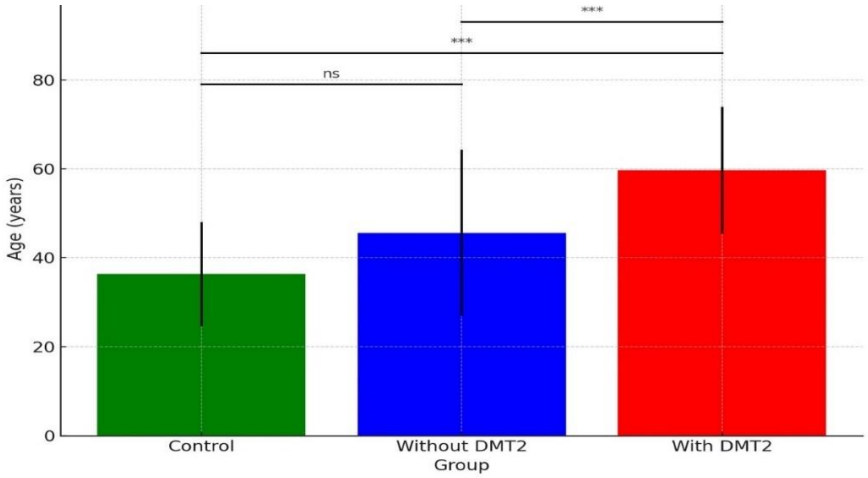


Figure 1: Average age by group with standard deviation and significance. The bar graph in the figure shows that there is a statistically significant difference between the mean ages of the three groups. The significant signs (***) indicate that the difference between the control group and the diabetic group is statistically highly significant, reinforcing the hypothesis that advanced age is an independent and complementary risk factor with diabetes in increasing the severity of COVID-19 infection. The difference between the control group and the non-diabetic group was not significant (ns), indicating that diabetes adds an additional risk factor beyond the effect of age alone.

The results of our current study are consistent with those of Zhang *et al .,* [17], which showed that the majority of hospitalized COVID-19 patients were aged 60–75 years, and diabetes was the most common comorbidity among this group. Globally, these results are consistent with extensive studies, such as a study in China [18], which confirmed that the average age of COVID-19 patients increases with the severity of the condition and that diabetic patients have among the highest rates of admission to intensive care units. A study in England analyzed data from 17 million patients and showed that type 2 diabetes patients were among the most at risk of death from COVID-19, especially with advancing age [12]. On the other hand, another study indicated that good control of blood sugar levels may mitigate the effect of diabetes on the risk of infection and death, indicating that the relationship may be more complex and requires a deeper analysis of lifestyle factors and treatment [19].

Distributions of patients according to sex

A similar relationship exists with sex, as male patients are frequently more severely affected by COVID-19 than female patients. However, this speculation may be due to some biological reasons e.g. differences in host immunity and angiotensin-converting enzyme 2 (ACE2) receptor, which serve as key binding sites for SARS-CoV-1 [17]. The claim of "no significant difference" between diabetic and non-diabetic outcomes is, therefore, seemingly implying that the male susceptibility to more severe COVID-19 cases apply equally across all diabetics when compared to their non-diabetic counterparts, as illustrated in Table 2.

A systematic review was conducted, and diabetes was demonstrated to be an independent risk factor for severe outcomes in COVID-19 patients, but it did not reach statistical significance among age and sex variants. The findings highlighted the need for glycemic and cardiovascular risk factor management while concluding that the impact by age and sex was parallel to that seen in the non-diabetic reference group.

This study also observed that while among those with severe status, mean age was higher in patients with diabetes than non-diabetic (77.05 years versus 64.04 years), older age independently predicted severe COVID-19, in accordance with data from China; the presence of diabetes was found to interact additionally with increasing age and male gender when estimating mortality rates by sex across all ages.

Looking at sex differences in COVID-19, while males have worse outcomes overall with or without comorbidities, the difference between males and females is not as stark when combined with diabetes as those with hypertension or cardiovascular disease [18].

Table 2: Distributions of patients according to sex.

Variables	Without DMT2 (n = 29)	With DMT2 (n = 43)	Overall (n = 72)	P. Value
Female	17 (58.6 %)	18 (41.9 %)	35 (48.6 %)	*P > 0.05*
Male	12 (41.4%)	25 (58.1 %)	37 (51.4 %)	

DM2: diabetes mellitus type 2. There is no significant difference between the sex of DMT2 patients and those without DMT2.

Comparison of HbA1c levels between DMT2 and without-DMT2 SARS-CoV-2 patients

Hba1c is a measure for long-term control of blood sugar over the last 2–3 months. In patients with SARS-CoV-2 and diabetes, an elevated HbA1c is an indicator of worse glycemic control and thus results in more severe COVID-19 outcomes, including mortality. This is probably due to the fact that these are two more factors generally also present in subjects of uncontrolled diabetes, namely chronic inflammation and immune incompetence. Contrastingly, non-diabetes patients generally display lower HbA1c levels with better glucose control and partly account for less vulnerability to inflammatory complications that come from SARS-CoV-2, as illustrated in Table 3 and Figure 2.

A difference in HbA1c levels between diabetics and non-diabetics ($p = 0.05$) was noted, which provides supporting evidence that pre-existing hyperglycaemia has a very important impact on the clinical course of COVID-19. Elevated HbA1c levels in diabetic patients are also associated with a pro-inflammatory state that may be permissive for the “cytokine storm” seen in severe COVID-19 [22].

DMT2 vs. without-DMT2 SARS-CoV-2 patients IgM and IgG antibodies

Since IgG has a lag time for it to be produced in response to an infection, the presence of only isolated (i.e., not combined with a positive IgM result) IgG diagnoses indicate past infection. For example, among patients who have diabetes, immune dysfunction was common, including anti-T-cell responses, ability to antibody output, and incapacity to

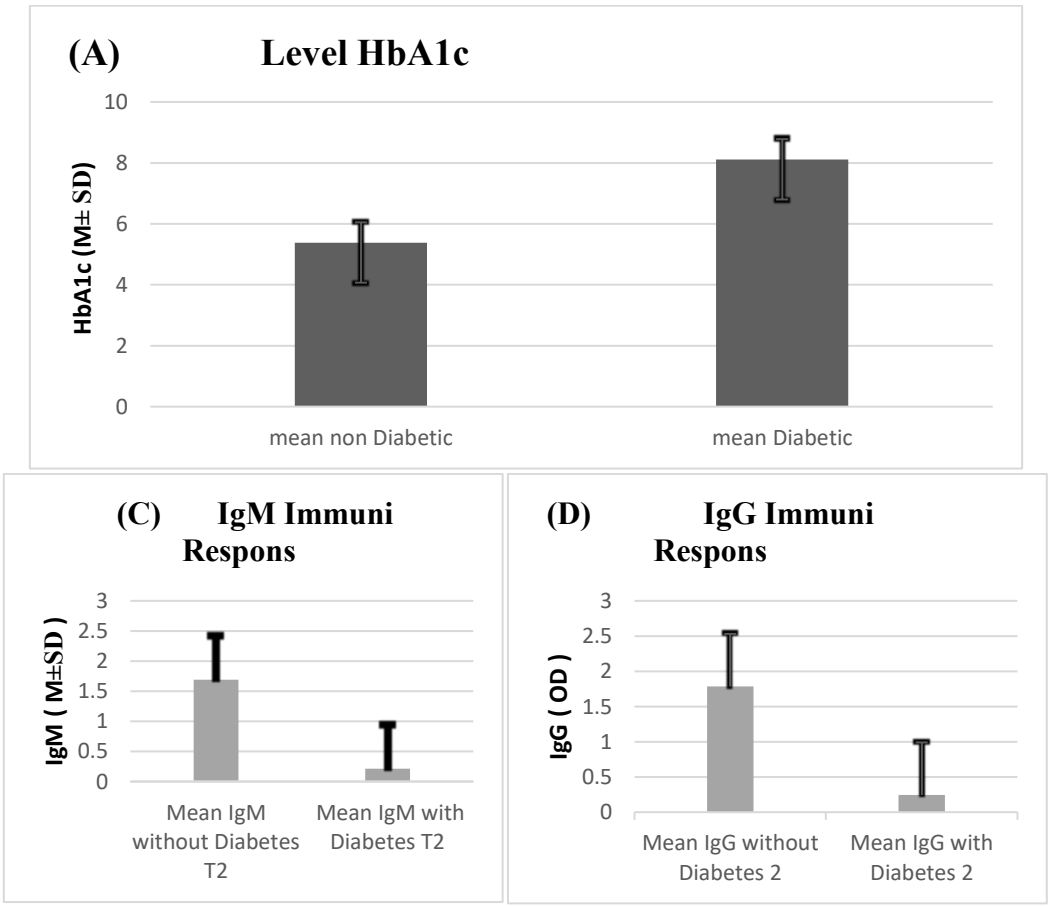
produce both IgM and IgG reactions for SARS-CoV-2. This could mean that diabetics produce fewer, or potentially slower, levels of antibodies compared to non-diabetic counterparts.

IgM and IgG responses tend to be more pronounced in non-diabetic individuals, facilitating better viral clearance. The fact that a major difference in IgM and low levels of IgG ($p = 0.05$) between diabetic and non-diabetic patients, together with the significantly lower levels of both immunoglobulins found within the first week of hospitalization could lead to the notion that diabetes is compromising not only immediate but also subsequent immune responses against SARS-CoV-2 infection, which may then explain one part of the less favourable outcomes seen among diabetic group, as illustrated in Table 3 and Figure 2.

Table 3: Anti-SARS-CoV-2 serological findings among DM 2 and non DM 2.

Unit	Mean ± SD		*P* .Value
	Non-Diabetic	Diabetic	
HbA1c (%)	5.38 ± 0.67	8.11 ± 1.31	0.0001
IgM (OD)	1.69 ± 0.72	0.21 ± 0.31	0.0001
IgG (OD)	1.88 ± 0.70	0.25 ± 0.35	0.0001

HbA1c, and levels of IgM and IgG antibodies, and the probability value was 0.05.



Figures 2: The results of (A) Level HbA1c, (C) IgM immune response, and (D) IgG immune response between DMT2 and non DMT2.

IFN-α Levels.

As illustrated in Table 4 and Figure 3. The marked IFN-α decrease in COVID-19 patients with T2DM suggested a defect in the antiviral response. Significance of IFN-α among the interferons, type I IFNs (such as IFN-α) are required to initiate an immune response against viral infections at a very early stage [3]. Nevertheless, in subjects with T2DM, the reduced interferon response described may contribute to enhancing viral replication and facilitate constructive infection [23].

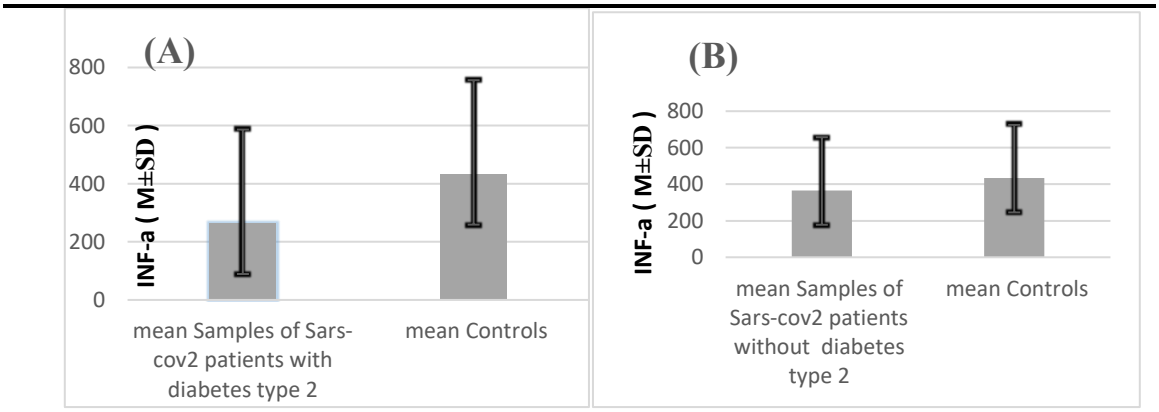
This general low-grade inflammation in T2DM seems to affect also the ability of immune cells, e. g., interferon-producing cells from proper function Hyperglycaemia and insulin resistance, such as in diabetes, have pro-inflammatory effects, also impairing growth factor availability to optimize immune response [20]. This might account for the less pronounced increase in IFN-α transcripts observed in the COVID-19 group compared with controls. Similar reports exist in other studies for lower IFN-α levels among diabetic individuals during viral infections, including influenza and hepatitis [24].

As illustrated in Table 3 and Figure 2, the data suggest that SARS-CoV-2 and/or the innate immune responses to this virus in patients without Type 2 diabetes suppress or dysregulate interferon responses, enabling increased replication of the virus while avoiding appropriate recognition by neighboring cells [23, 29].

Table 4: Levels of INF-α in DMT2, non-DM2, and control groups.

	Mean ± SD		***P.* Value**
	Control	**INF-α (pg/mL)**	
SARS-Cov-2 with DM2	433.27 ± 326.89	263.25 ± 176.18	0.0035
SARS-Cov-2without DM2	433.27 ± 326.89	365.64 ± 190.88	0.319

For interferon alpha levels, a significant difference was observed between control samples and those infected with SARS-CoV-2 for type 2 diabetes patients, while there was no significant difference between control samples and those infected with SARS-CoV-2 who did not have type 2 diabetes.



Figures 3 : The results of levels of INF-α between (A) sars-cov2 patients with DMT2 and control (B) sars-cov2 patients without DMT2 and control.

Reduced serum IFN-β in SARS-CoV-2 patients with and without DMT2

Chronic systemic low-grade inflammation and dis-regulated immune responses are known to impair the ability of the human body to summon an effective immune response against infections in general, including viral infections like COVID-19. In addition, type 2 diabetes is accompanied by dysregulated oxidative stress flow that contributes to its pathophysiology. It has long been known that the production of interferons and other immune mediators is negatively affected in metabolic disorders, such as those in type 2 diabetes, due to the activation of chronic low-grade inflammation and metabolic signaling pathways such as NF-κB and JNK. This dysfunctional immune response may lead to viral persistence and increased susceptibility to COVID-19 complications such as pneumonia and acute respiratory distress syndrome (ARDS) , can result from this dysregulated immune response [25].

Previous studies Zhang *et al .,* [17], have suggested an association between type 2 diabetes and reduced interferon (IFN) production in response to viral infections. Moreover, another study revealed that patients with type 2 diabetes had reduced interferon beta after SARS-CoV-2 infection, which accounted for their susceptibility to developing severe disease outcomes and increased mortality. Our data also show that interferon beta levels are extremely low in patients of COVID-19 with type 2 diabetes compared to the controls, which coincides with our results, as illustrated in Table 5 and Figure 4. Reversed production of interferon beta may correspond to an inability that is impaired in controlling viral replication, augments virus load, and worsens clinical courses in these patients.

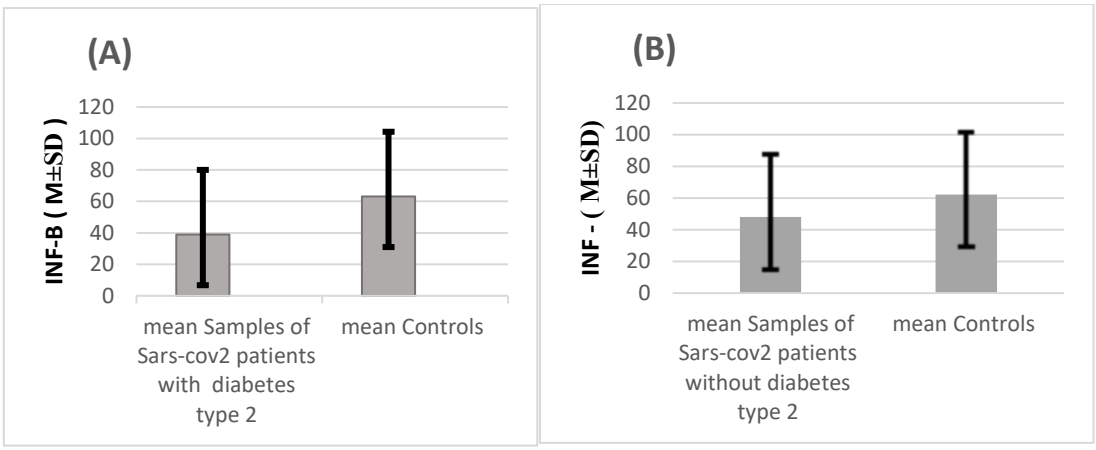
As illustrated in Table 5 and Figure 4. These data suggest that SARS-CoV-2 and/or the innate immune responses to this virus in patients without type 2 diabetes suppress or dysregulate interferon responses, enabling increased virus replication while avoiding appropriate recognition by neighboring cells.

Thus, SARS-CoV-2 infected patients with T2DM showed significantly decreased levels of IFN-α compared to non-diabetic patients. This could be related to chronic inflammation in diabetes, which is characterized by increasing pro-inflammatory cytokines (e.g., IL-6 and TNF-α) that may affect IFN-α production properly. Endogenous IFN-α was lower in low-risk diabetic patients, which has been associated with the severity of COVID-19—The weakened antiviral response that might decline virus replication is supposed to play a role in the heightened mortality and morbidity among individuals infected by SARS-CoV2 [19].

Table 5: Levels of INF-β in DMT2, without-DMT2, and control groups**.**

	Mean ± SD		***P*. Value**
	Control	***INF-β (pg/mL)***	
SARS-Cov-2 with DM2	63.13 ± 41.63	38.88 ± 32.55	0.0034
SARS-Cov-2 without DM2	63.13 ± 41.63	48.04 ± 33.42	0.109

For interferon beta levels, a significant difference was observed between control samples and those infected with SARS-CoV-2 for type 2 diabetes patients, while there was no significant difference between control samples and those infected with SARS-CoV-2 who did not have type 2 diabetes.



Figures 4: The results of levels of INF-β between (A) SARS-COV2 patients with DMT2 and control, (B) SARS-COV2 patients without DMT2 and control.

Levels of INF-α in DMT2, Without-DMT2 Groups

As illustrated in Table 6 and Figure 5. SARS-CoV-2 infected patients with T2DM have significantly less IFN-α than non-diabetic patients. This disparity can be explained by the diabetic-specific inflammation, which is characterized as a low-grade chronic inflammation status along with enhanced pro-inflammatory cytokines (e.g., IL-6 and TNF-α) that may inhibit IFN-α production adequately. This defect in IFN-α response suggests a potential mechanism to explain the prolonged viral shedding of SARS-CoV-2 during COVID-19 and why diabetic patients have, overall, a more severe clinical presentation [23].

Plasma levels of INF-β in DMT2, without-DMT2 groups

Studies that compare IFN-β levels in SARS-CoV-2 infected patients with or without T2DM have reported generally no differences in its levels among these two populations [26,30]. IFN-β production may be more tightly regulated than IFN- α, either as a result of the metabolic and inflammatory disturbances found in T2DM having less effect on IFN- β production or that differences between populations are smaller for parameters associated with variability in IFN-β relative to those predicting differences in IFN-α production.

The equivalent disease concordance rate in IFN-α expression among diabetic and non-diabetic patients supports that aberrant IFN signaling is part of the T2DM immune-dissection story, whereas no meaningful differences in IFN-β levels with respect to its association with the development of diabetes. This is significant as, thus far, the targeting of IFN-β in therapeutic strategies (as part of SARS-CoV-2 was found to globally repress the type I interferon response overall) recommended due to this specific lack in IFN-α demonstrated by T2DM patients could signify a requirement for more precise therapeutics within this cohort [27,28].

However, when comparing patients with COVID-19 without type 2 diabetes, this difference was not significant, as illustrated in Table 6 and Figure 5. he variation in interferon beta levels among individuals may provide some explanation; however, the lack of significant difference could also result from an insufficient number of individuals or other unidentified variablesPrior research has also pointed to a lack of Interferon response in critically ill COVID-19 patients, particularly low levels of interferon beta, although it remains unclear as to whether this contributes toward uncontrolled viral replication and disease severity [19,31].

Table 6: Levels of INF-α and INF-β in diabetic, non-diabetic groups.

	Mean ± SD		*P*. Value
	SARS-Cov2 without DM2	SARS-Cov-2 with DM2	
INF-a	365.64 ± 190.88	263.25 ± 176.18	0.025
INF-b	48.04 ± 33.42	38.88 ± 32.55	0.253

While it was found that interferon alpha levels had a significant difference between SARS-CoV-2 infected type 2 diabetes patients and non-type 2 diabetes patients, it was found that interferon beta levels had no significant difference between SARS-CoV-2 infected type 2 diabetes patients and non-type 2 diabetes patients.

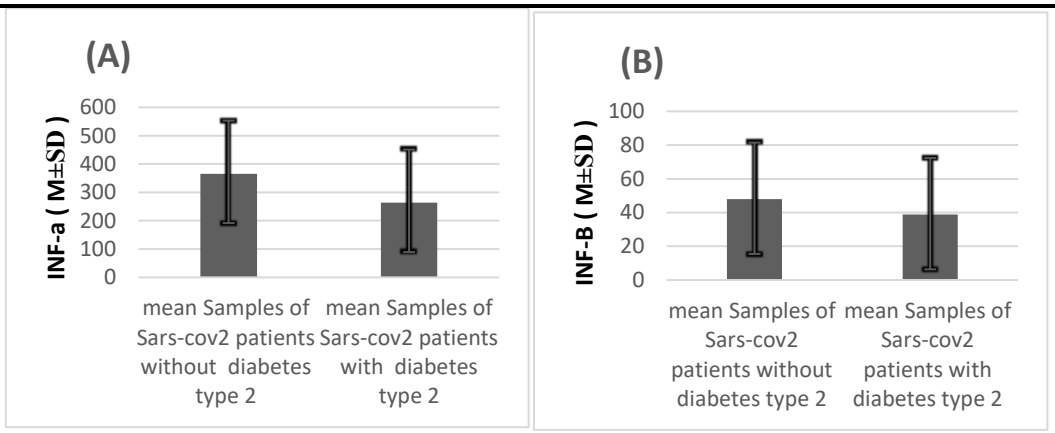


Figure 5: The results of INF-α and INF-β Levels. (A) levels INF-α between SARS-COV2 patients without DM2 and SARS-COV2 patients with DM2. (B) Levels INF-β between SARS-COV2 patients without DM2 and SARS-COV2 patients with DM2 .

Recommendations on clinical practice and public health in Kirkuk

The results of this study have clear consequences for clinical practice and public health in Kirkuk. The immune response of T2DM patients is compromised, and more intensive monitoring and treatment strategies may be required for these individuals infected with SARS-CoV-2. Early therapy with antivirals and careful monitoring of blood sugars might blunt the effects of COVID-19 on diabetics. Based on their greater risk of severe disease, diabetic patients should be considered one of the public health priorities in selecting vaccines against COVID-19 and for booster doses.

Discussion

The aim was to assess the immune response among patients with Type 2 Diabetes Mellitus (T2DM) following infection with SARS-CoV-2 by measuring type 1 interferons (INF-α and INF-β), anti-SARS-CoV-2 specific antibodies levels (IgM and IgG). Interferons and antibodies levels in T2DM patients were significantly lower compared to non-diabetic status, the most important finding of the study. Of the 72 confirmed COVID-19 cases, 43 were diabetic, while 29 were non-diabetic. Diabetic patients, and especially those poorly controlled (HbA1c > 7%), had even lesser immune responses related to interferons alongside antibodies. In contrast, non-diabetic patients demonstrated a more robust immune response, as indicated by higher levels of IgM and IgG antibodies, essential for effective viral neutralization and immunity.

A perspective on the crosstalk between interferons, SARS-CoV-2 response, and Type 2 Diabetes

These interactions implicate a fundamental aspect of the immune dysfunction observed in diabetic individuals. They are some of the earliest observations regarding type 1 IFNs during COVID-19 that have been associated with virus-neutralizing antibodies (including those to SARS-CoV-2). This study highlights that T2DM severely compromised both the innate and adaptive immune responses, rendering these patients more vulnerable to severe disease manifestations. The suboptimal release of INF-α and INF-β indicated that SARS-CoV-2 escaped the first antiviral line in patients with diabetes, allowing for rapid viral replication and an immense inflammatory response. Similarly, fewer IgM and IgG antibodies are produced in diabetics; which shows an inability to get rid of the virus naturally, and long-term immunity will also not be present if they were able to clear the virus, for it increases the risk of sustained illness and complications.

Recommendations: Real-world recommendations based on study results

These are some clinical recommendations for the management of COVID-19 in Type 2 Diabetic patients according to the study:

Vaccination in patients T2DM: Due to the impaired immune overall response noted in patients with T2DM, COVID-19 vaccination and boosters should be a priority for this population. Here, it was described the importance of being fully vaccinated, especially among patients with diabetes in order to have excellent immune protection and even prevent severe outcomes. Better surveillance and timely prescription intervention: Patients with diabetes, especially those whose blood sugar levels are not well controlled, should be under closer monitoring if infected by the new coronavirus. In cases where severe inflammation can lead to complications, early intervention with antiviral therapies that target the virus itself and other supportive treatments may be needed.

Preventive: Glycaemic control of optimal blood glucose level is necessary to avoid COVID-19 complications (eg. severe risks with diabetes). This is the time when healthcare providers should focus on ensuring that people with high blood sugar levels are meticulously monitored and treated to improve their immune status and facilitate better outcomes during this pandemic. Specific cellular immunodeficiencies in T2DM patients to be targeted by therapeutic strategies understanding the role of B cell subpopulations in generating either protective or pathogenic antibodies and optimizing protocols to develop immunity post-infection, infection-induced humoral responses or vaccination could pave novel paths for improving COVID-19 severity in this at-risk population through the research of potential immunomodulatory treatments that augment interferon production increase antibody response.

Public Health Awareness and Education: Public health campaigns to highlight that people with diabetes are particularly vulnerable during the COVID-19 pandemic. Education programs should target these patients in order to inform them about vaccination, glucose control, and the promptness of medical intervention in case of infection.

Conflict of Interest

The authors have no conflict of interest.

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