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Unusual CD4 CD28 T Cells and Their Pathogenic Role in Chronic Inflammatory Disorders

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ABSTRACT:

Background: CD28 is an essential co-stimulatory receptor and is essential for successful T cell activation, proliferation, and survival. While it is ubiquitously expressed on naïve T cells, the level of CD28 expression on memory T cells is largely dependent on the stage of T cell differentiation in humans. Expanded CD4+CD28–T cells can produce large amounts of proinflammatory cytokines such as IFN- γ and TNF- α and also have cytotoxic potential, which may cause tissue damage and advance the pathogenesis of several inflammatory disorders. Here we review the characteristics of CD4 + CD28 - T cells in addition to recent developments that highlight the contribution of these cells to many pathological conditions.

Objective: To estimate the percentage of T-cell, the pathogenesis of several inflammatory. **Methods:** 58 pregnant women with diabetes participated in the study, including 24 pregnant women with T1DM and 34 pregnant women with T2DM. C-peptide levels.

Results: All pathological samples showed a decrease in CD4+ Tcell concentration compared to control. Samples taken from T1DM patients also showed a decrease in the presence of other diseases and bacterial infections compared to T2DM patients and the absence of bacterial infections. They also showed CD28 did not appear and there were no statistically significant differences.

Conclusion: There was a positive correlation between CD4 + T-cell, CD28 immunoreactivity

Keywords: CD28, Co-stimulatory receptor, CD4+CD28– T cells, Chronic inflammatory diseases, Cytotoxic potential.

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1. Introduction

CD4 T cells play a critical role in orchestrating immune responses by helping humoral and cellular immune cells ⁽¹⁾. Successful CD4 T-cell activation is guaranteed by two signals; TCR stimulation as the primary signal (signal 1) and antigen-independent costimulation as the secondary signal (signal 2) ^(2,3). CD28 is a primary co-signaling receptor that transduces a costimulatory signal 2 and is essential for successful T cell activation, and survival ^(3,4). Furthermore, the CD28 molecule is constitutively expressed on naive and memory T cells. However, in humans there is a marked loss of CD28 expression on terminally-differentiated effector memory T cells ⁽⁵⁾. Repeated antigenic stimulation over a lifetime results in the generation of this terminally-differentiated T-cell subset following extensive division ⁽⁶⁾. Thus, CD28 is progressively lost after replicative senescence with advancing age ⁽⁷⁾. similar in both T-cell subsets, but the age-associated accumulation of CD28⁻ T cells is more prominent in CD8 T cells than CD4 T cells ^(8,9). Expansion of CD8+CD28⁻ T cells in part reflects the infectious burden from latent viral infections such as CMV and EBV and leads to generating memory inflation in the elderly ⁽¹⁰⁾. Accumulating evidence reveals that there is a significant age-inappropriate expansion of cytotoxic CD4+CD28⁻ T cells in patients with a variety of chronic inflammatory diseases, suggesting that these cells might play a role in the pathogenesis of these immune disorders ⁽¹¹⁻¹⁵⁾. Despite the lack of CD28 expression on these cells, they are not anergic, but rather respond to stimulation in a stimulation independent nature. Moreover, loss of CD28 is closely linked to changes in the transcriptional program resulting in production of potent effector cells exhibiting atypical cytotoxic capacity and inflammatory cytokine producing potential ^(7,11,16). The biological role of CD8+CD28⁻ T cells has been extensively reviewed elsewhere. Therefore, this review will focus on physiological and pathological characteristics of CD4+CD28⁻ T cells and recent advances in the understanding of the role of CD4+CD28⁻ T cells in several disease conditions. The molecular mechanisms controlling CD28 expression and loss appear to be Accumulation of CD28⁻ T cells was initially considered a hallmark of age-associated changes in the human immune system. However, loss of CD28 on CD4 T cells also occurs in patients with chronic autoimmune diseases in an age-inappropriate manner (Fig. 1). Despite their restricted TCR diversity, shorter telomeres and

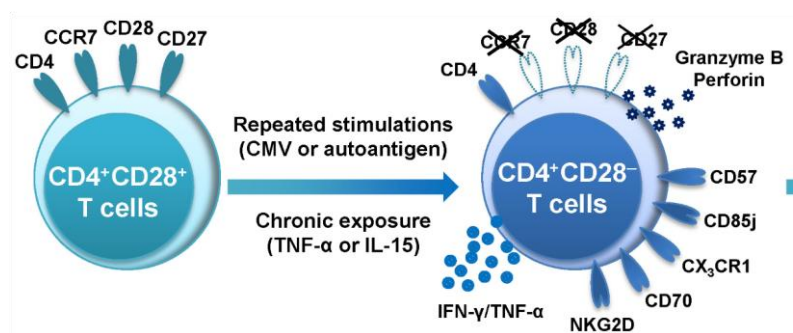


Figure 1. Immunological role of expanded CD4⁺CD28⁻ T cells in chronic inflammatory disorders. CD28⁺ T cells lose CD28 expression after repeated stimulation with latent viral infections or autoantigen. Additionally, the loss of CD28 occurs when T cells are exposed to proinflammatory cytokines. Expanded CD4⁺CD28⁻ T cells produce large amounts of proinflammatory cytokines (e.g. IFN- γ and TNF- α) and cytotoxic mediators (e.g. granzyme B and perforin), which cause tissue damage and development of pathogenesis in many inflammatory disorders such as DM, cardiovascular diseases. abundance at the inflamed site, it remains questionable whether the autoreactive T cell response is a major contributing factor

for expansion of CD4+CD28⁻ T cells. Rather, recent studies suggest that repeated antigenic stimulation of T cells by chronic inflammation or latent CMV infections causes them to proliferate more rapidly and extensively resulting in the loss of CD28. Although most studies of CD28⁻ T cells have been conducted in humans, which are much more sensitive to loss of CD28 than mice are, development of an appropriate animal model will be required in order to investigate the underlying mechanisms of this phenomenon and its biological relevance in vivo. In this context, recent CD28 co-stimulation blockade therapy might provide invaluable information regarding the biological role of CD4+CD28⁻ T cells in physiological settings. Moreover, it is necessary to understand how CD28 loss is linked to the transcriptomic shift into pathogenic T cells. Better understanding of the molecular and functional features of CD4+CD28⁻ T cells will open new avenues to explore potential targets for intervention in a variety of chronic inflammatory diseases. Future research will be needed to investigate whether the accumulation of CD4+CD28⁻ T cells is generalized for various chronic inflammatory disorders and to evaluate their usefulness as a biomarker or a prognostic factor. Recovery of CD28 expression by TNF- α inhibition or selective depletion of CD4+CD28⁻ T cells by targeting specific surrogate molecules on their surface will be promising approaches for therapeutic intervention in various inflammatory disorders.

2. Material and methods

Statement of Ethics

As a mandatory step for taking samples from patients, this study is approved by the ethical committees, which include: Imam Hussein Medical Center Committee for Diabetes and Endocrinology (No. 112 on 4/11/2022), Karbala Health Directorate/Holy Karbala Governorate - Iraq. Written consent was obtained from the patients.

Topics of Research and Clinical Parameters

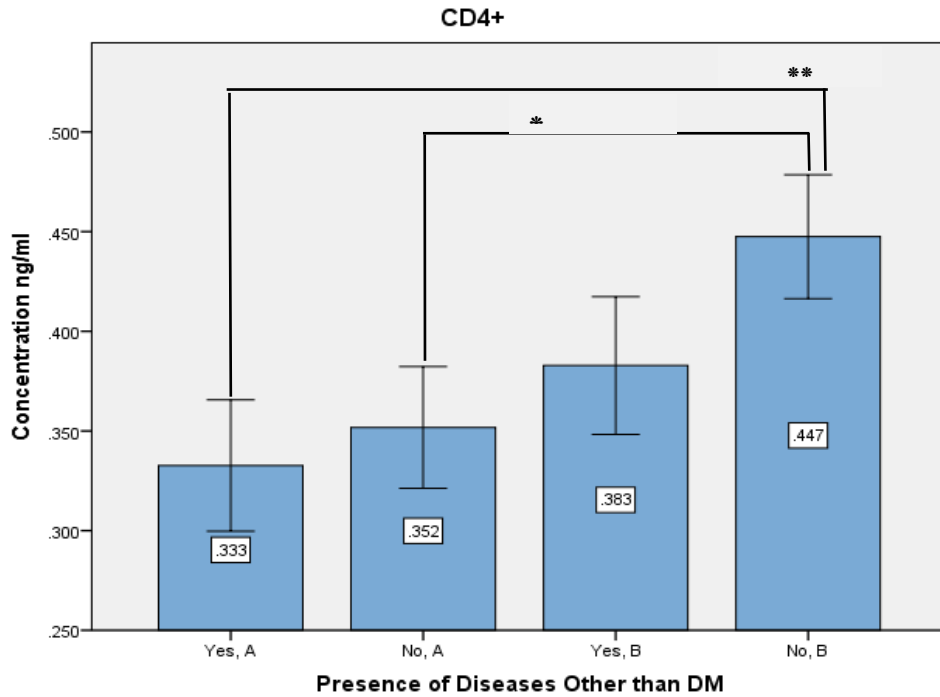
Samples were collected from Karbala Hospital for Obstetrics and Gynecology and Al-Hassan Center for Endocrinology and Diabetes in Karbala during the period from November 2022 to January 2023. This cross-sectional research included six groups: A1 pregnant women with type 1 diabetes with bacterial infection, A2 pregnant women with type 1 diabetes without bacterial infection, B1 pregnant women with type 2 diabetes with bacterial infection, B2 pregnant women with bacterial infection. Type 1 diabetes with bacterial infection, Type 2 without bacterial infection, C1 healthy pregnant women without diabetes and without bacterial infection, C2 non-pregnant women without diabetes without bacterial infection. The bacterial isolates from urine were identified using the Vitec 2 automated compact system, a GN-ID card, and 64 biochemical tests. 30 Samples were collected in Karbala (Imam Hassan Center for Endocrinology and Diabetes) and (Gynecology and Obstetrics Hospital, Holy Karbala) in accordance with the directives of the World Health Organization (WHO). Diabetes was determined in order to estimate glucose and C levels. Peptide: Blood samples were collected from patients and controls, and T cells were evaluated using the immunological markers CD4 T cell and CD28 in people who were diagnosed with diabetes, while ensuring that they had not eaten for at least 8 hours. The C rate was calculated Peptide.

Statistical Analysis

The statistical program for social sciences (S.P.S.S.) version 25 was used to enter and evaluate data from the study samples. The outcomes were reported as mean Standard Error (Mean S.E.). An independent-sample T-test was used in the statistical analysis to determine whether differences in the quantitative data were significant. One sign P 0.05, two signs P 0.01, three signs P 0.001, and four signs P 0.0001 were used to denote the probability levels.

3. Results

In comparison to the control, the concentration of Anti-GAD increased in every patient sample. We discovered that the concentrations of anti-GAD were lower in overweight individuals compared to normal weight people in the pathological samples. As indicated in figure 1. Samples of patients with diabetes for 5 years or more showed a decrease in Anti-GAD concentration compared to patients with diabetes for less than five years, but the decrease was not significant, as shown in figure 1



Figur1 -: Concentration of CD4+ in groups C1, C2, A1, A2, B1 and B2. The significance value was indicated as D between C1 and A1 groups, E between C1 and B1 groups, F between C2 and A1 group, G between C2 and B1 groups, and H between A1 and B1 groups. The level of probability was 0.05 ($P \leq 0.05$).

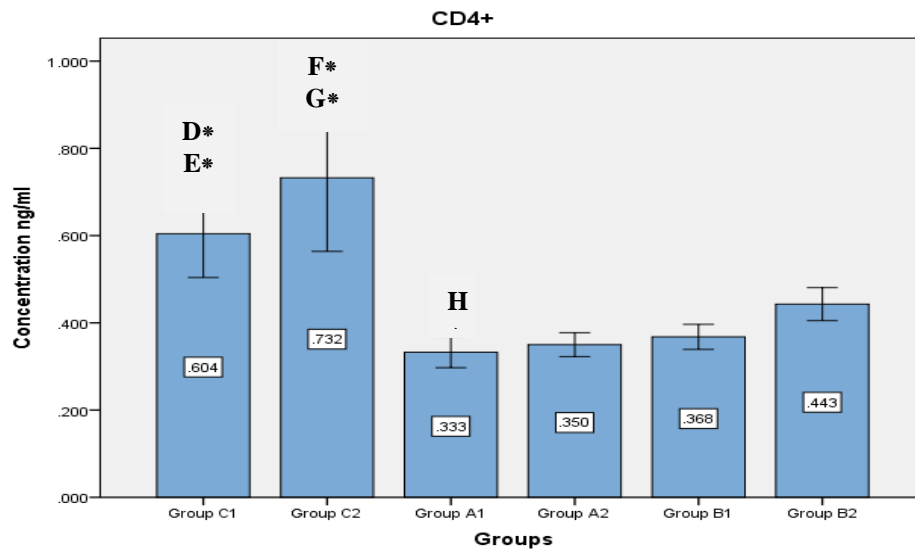


Figure 2: Concentration of CD4+ in patients of A and B groups. The significance value was indicated as * The level of probability was 0.05 ($P \leq 0.05$).

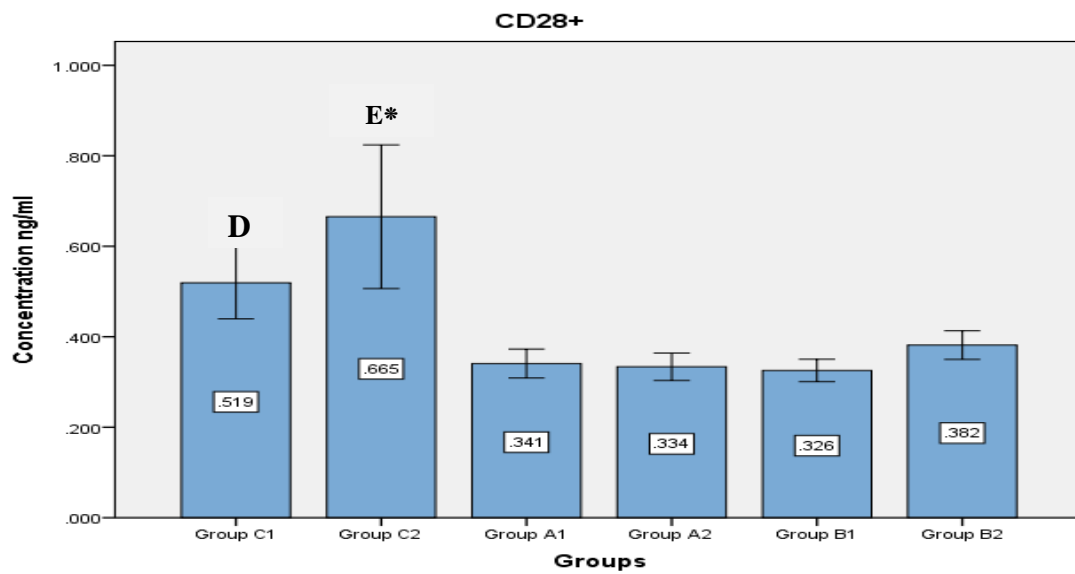


Figure 3: Concentration of CD28+ in patients of A and B groups. The significance value was indicated as * The level of probability was 0.05 ($P \leq 0.05$).

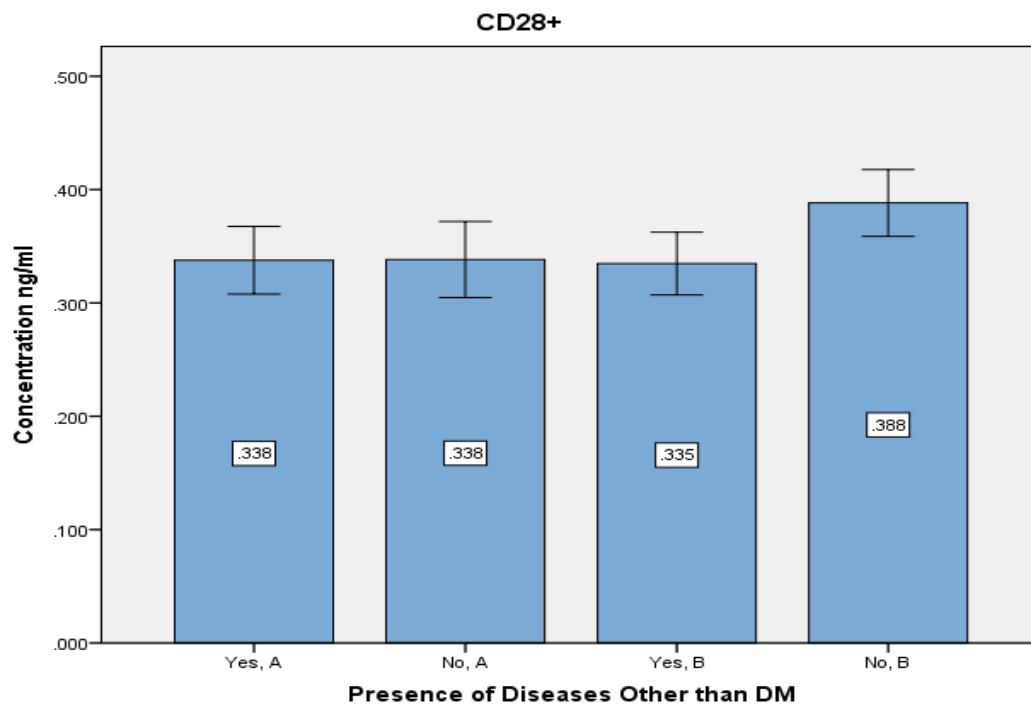


Figure 4: Concentration of CD28+ in groups C1, C2, A1, A2, B1 and B2 . The significance value was indicated as D between C1 and B1 groups, E between C2 and B1 groups . The level of probability was 0.05 ($P \leq 0.05$).

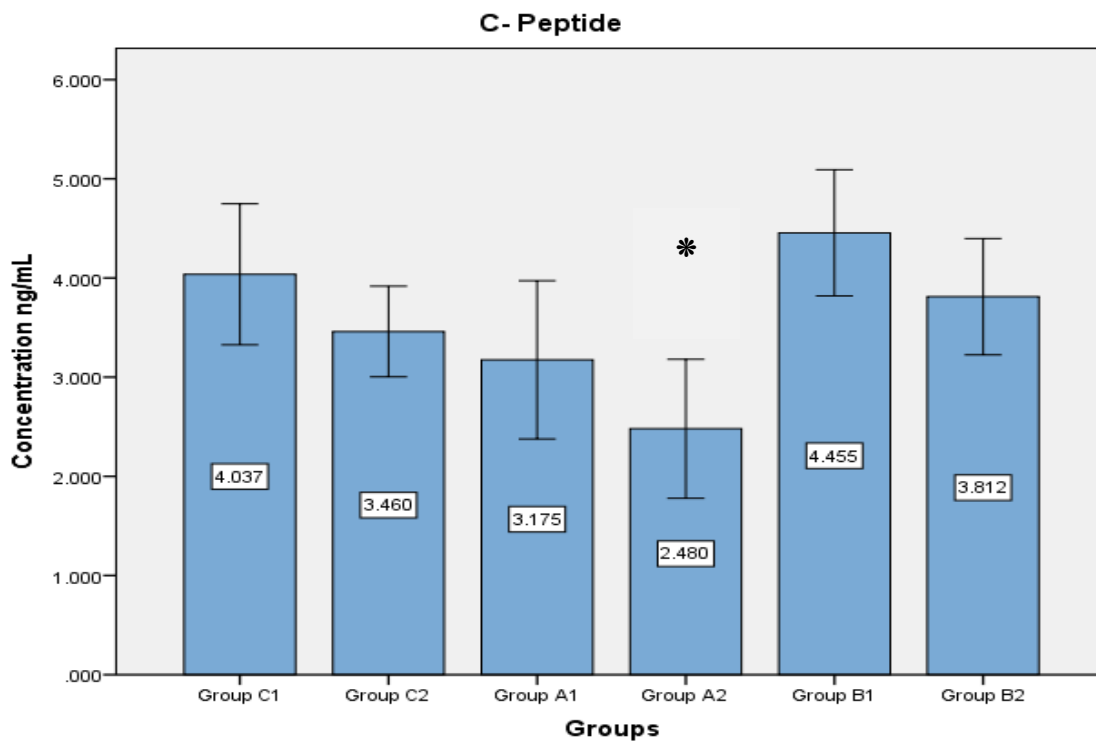


Figure4: Concentration of C. Peptide in groups C1, C2, A1, A2, B1 and B2 . The significance value was indicated as * between A2 and B1 groups. The level of probability was 0.05 ($P \leq 0.05$).

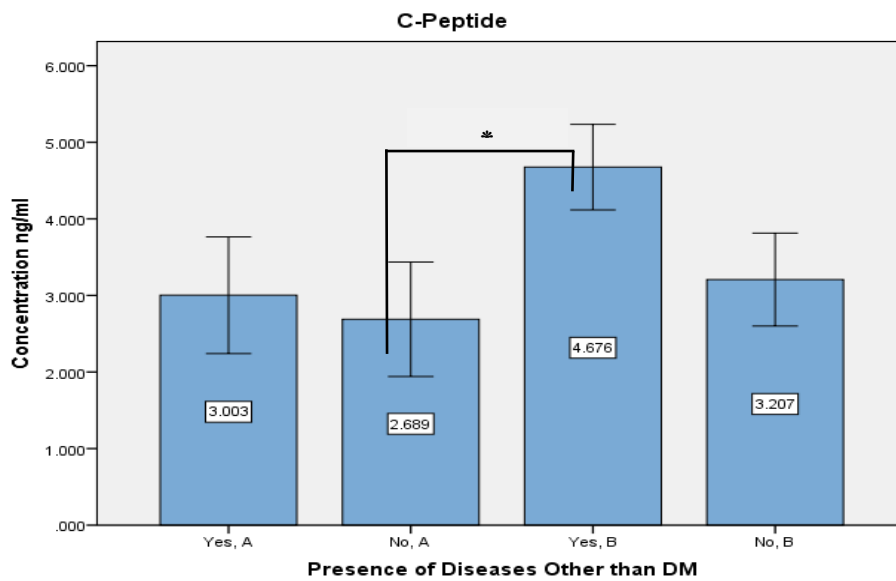


Figure 5: Concentration of C--Peptide in patients of A and B groups. The significance value was indicated as * The level of probability was 0.05 ($P \leq 0.05$)

In the current study, it was observed that 55.1% of those had a urinary tract infection, which was distributed as *E. coli* 46.9%, 25% with *K. pneumonia*, 6.3% with *Enterobacter cloacae*, and 9.3% with *Staphylococcus epidermidis* and 12.5% with *Staphylococcus haemolyticus*

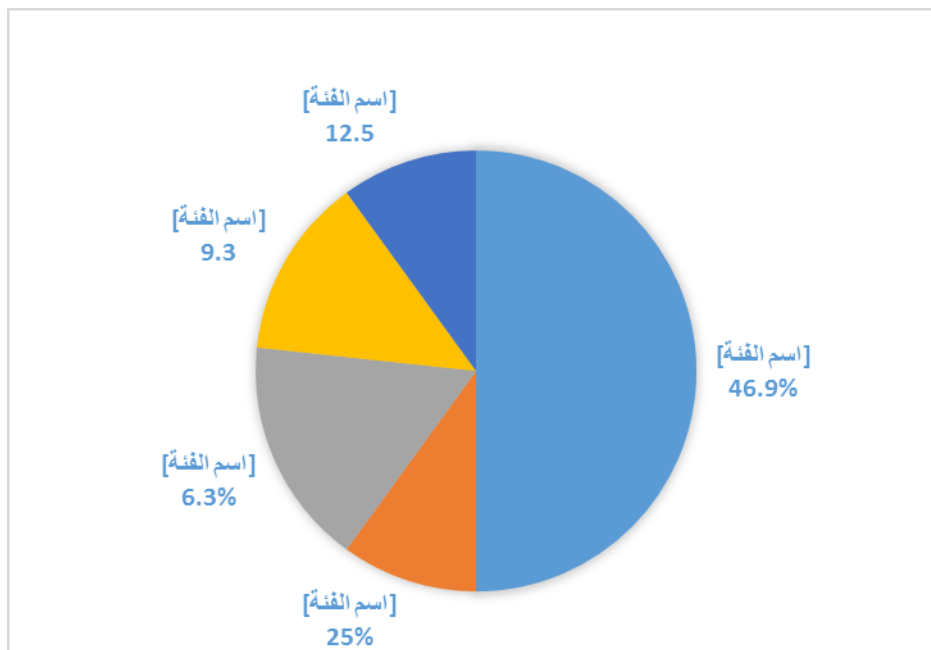


Figure7: shows the types of bacteria frequencies

Table 4-1: Bacterial etiology of UTI in diabetic individuals

No.	Types of bacteria	Number of strains		Total	%
		group A1 T1DM	group B1		
					Percentage of each type

		NO.24	T2DM NO. 34		Bacteria
1	<i>Escherichia coli</i>	7	8	15	46.9%
2	<i>Klebsiella pneumonia</i>	3	5	8	25%
3	<i>Enterobacter cloacae</i>	1	1	2	6.3%
4	<i>Staphylococcus epidermidis</i>	1	2	3	9.3%
5	<i>Staphylococcus haemolyticus</i>	2	2	4	12.5%
		14	18	32	

Regarding the aim of this study, there was a need to know the role played by autoimmune diseases Type 1 and Type 2 diabetes, especially gestational diabetes, in the recurrence of bacterial infections. We found that infection and diabetes are equal because they both cause immune system reactions, but one function protects the body while the other allows harm to the body¹⁰

4. Discussion

The results showed a significant decrease in CD4+ T-cell in the pathological samples of pregnant women with type 1 diabetes in the presence of bacterial inflammatory factor compared to the control. This is consistent with the previous study. The level of CD4+ T-cell increased in control unmarried women as in Figure (1), and this is consistent with the study. With the increase in the duration of diabetes, the data revealed a decrease in the levels of T cells, which weakens the immune system and this helps to develop other diseases associated with diabetes, as in the figure (2), and this is the result It is consistent with the study. 6 The CD 28 percentage did not show any significant differences in the study. It only showed that the pregnancy factor has a role in the decrease or increase of these cells, as the CD 28 percentage was a significant decrease in the pregnant control compared to the unmarried control, as in the figure (3). This study agreed 7 .The study also showed that the percentage of C-peptide decreased significantly in type 1 diabetic patients with the absence of accompanying diseases, and increased in type 2 diabetes patients with the presence of diseases, as in the figure (4). This fact is consistent with the study 11. Community samples have been used in many studies on C-peptide levels as they eliminate the need for insulin testing even before diabetes becomes clinically apparent. They can also predict the need for insulin in people with type 2 diabetes. A subgroup of diabetic individuals known as latent autoimmune diabetes of adults (LADA) has also been defined by their characteristics. Generalized T-cell deficiency is known to be positive in more than 70% of people with type 1 diabetes who have just developed the disease, and its level appears to decline as the disease progresses and with fewer beta cells remaining. To obtain a more accurate knowledge and diagnosis of type 1 diabetes, it is important to know how frequently these autologous cells are present in the population. Recent research has found that CD4 and CD28 promote the incidence of autoimmune diseases, and the pregnancy factor has a major role in the high incidence of gestational diabetes.

The American Diabetes Association has recommended glycated hemoglobin (C-peptide) as a potential alternative to fasting blood glucose for diagnosing diabetes. C-peptide is a vital biomarker for long-term blood sugar control because it can reflect overall blood sugar history better than insulin. Because it is in the blood for a longer period than insulin, in addition to

being a reliable marker of chronic hyperglycemia, C-peptide also shows an association with Important with the possibility of long-term effects due to diabetes. A stand-alone risk factor for people with and without diabetes for coronary heart disease and stroke is high C-peptide levels, which has also been estimated. The useful information from the C-peptide test has made it a reliable biomarker for diabetes diagnosis and prognosis¹². All patient groups had significantly higher C-peptide values than the control group, according to the data, with overweight diabetic patients with bacterial infections having The biggest increases. Elevated C-peptide levels can be tested in obese pregnant women to look for early indicators of insulin sensitivity and resistance.

5. Conclusion

We found a relationship between CD4 + T-cellulose in pregnant women with diabetes and a positive relationship between the increased levels of Si-peptide in pregnant women with diabetes and its relationship with other diseases.

Compliance with ethical standards

Disclosure of conflict of interest No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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