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Evaluation of Surface Morphological Changes in B Cells Using Flow Cytometry in Children with Type I Diabetes

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Abstract

Background: Type 1 diabetes (T1D) is one of the most common chronic diseases among children and adolescents, characterized by an autoimmune reaction that destroys insulin-producing beta cells in the pancreas. B cells play a more complex role than just antibody production in T1D; they are involved in antigen presentation and regulation of the immune response.This study aimed to identify the immunophenotypic heterogeneity of CD19+CD27+ , CD19+CD80+, and CD19+CD24+ B cells in T1D patients and compare their proportions with those in healthy individuals.

Patients and Methods: The study was conducted on 44 peripheral blood samples from male children aged 5 to 10 years. It included 24 patients with T1D and 20 healthy children as controls. Peripheral blood mononuclear cells were isolated, and B cells were then labeled using monoclonal antibodies conjugated to fluorescent dyes and analysis was performed using Flow Cytometry.

Results: The results showed a statistically significant decrease in the proportions of all studied B cells types CD27+ , CD80+, and CD24+ in children with T1D compared to healthy children. This decrease in surface expression suggests a potential imbalance in immune balance and cellular regulation in patients.

Conclusion: The variation in the normal balance of B cells, which play an important role in regulating the immune response, suggests that these cell types may be early indicators of the onset or progression of the disease, making them potential targets for the development of immunotherapies that target modifying these cells to slow or halt the progression of diabetes.

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1. Introduction

B cells are a major component of the adaptive immune system and are traditionally known for their role in producing antibodies in response to antigens.[1] However, recent research has revealed additional complex functions performed by these cells, such as antigen presentation, regulating immune responses through interaction with T cells, and participating in the secretion of regulatory cytokines. [2] This multifaceted role is particularly important in the context of autoimmune diseases, most notably type 1 diabetes (T1D). [3]

Type 1 diabetes is an autoimmune disease characterized by the destruction of insulin-producing beta cells in the pancreas, resulting from a dysregulated immune response against self-components. [4] Immune B cells play a role beyond the production of autoantibodies in type 1 diabetes patients. It is believed that quantitative and qualitative changes in the distribution of B cell types, as well as differences in the expression of surface markers and activation, contribute to the initiation and progression of the disease.[5] The main B cell types linked to type 1 diabetes include transitional B cells ($CD24^{hi}$ B cells), which some studies have shown to be decreased in newly diagnosed patients;[6] activated plasmablasts ($CD19^{+}IgD^{+}CD27^{-}$ naïve B cells), which have been observed to be elevated in patients and their at-risk relatives;[7] memory B cells ($CD27^{+}$ B cells); and regulatory B cells ($IL\text{-}10^{+}$ B cells), including interleukin-10-producing B10 cells, which are associated with the body's ability to control autoimmune responses. [8][9]

In type 1 diabetes, B cells exhibit impaired immunosuppressive mechanisms, leading to enhanced autoreactive T cell activation and exacerbated immune-mediated destruction of pancreatic beta cells. [10] According to the Hilliard *et al.* study, B cells not only produce antibodies but also actively contribute to the presentation of self-antigens and the secretion of inflammatory cytokines such as IL-6 and TNF-α, with a decrease in regulatory B cells that produce IL-10. The study also revealed a significant presence of B cells within the islets of Langerhans in the early stages of the disease, especially in young patients, suggesting their direct role in accelerating the inflammatory response. These findings demonstrate that the loss of balance between the regulatory and activating functions of B cells is a central driver of disease progression and highlight the importance of studying the phenotypic changes in these cells as a gateway to understanding disease mechanisms and proposing new therapeutic targets.[11]

B cells that express CD27 are commonly known as memory B cells. This molecule belongs to the tumour necrosis receptor superfamily and promotes the maturation of memory B cells into antibody-secreting cells.[12] CD80 (also known as B7-1) is a co-stimulatory signaling molecule expressed on the surface of cells such as B cells and antigen-presenting cells (APCs). CD80 is involved in regulating immune homeostasis by interacting with the CD28 receptor to stimulate T cells, or with CTLA-4 to inhibit this response [13]. CD24 is expressed on the surface of B cells in the early stages of their development (immature B cells), where it contributes to regulating cell differentiation and activation. [14] It also promotes interaction with complement receptors on T cells, such as Siglec-10, acting as a "brake" to limit excessive immune activation [15,16].

The heterogeneity of B cell phenotypes in patients with type 1 diabetes is crucial for understanding the immunological mechanisms underlying disease progression. Changes in the surface expression of exogenous molecules may reflect an imbalance in B cells between

regulatory and immune-stimulating patterns, contributing to the acceleration or exacerbation of the autoreactive response against pancreatic beta cells. Based on the above, this study aims to evaluate the morphological changes represented by the expression of CD27, CD80, and CD24 on the surface of B cells in peripheral blood cells of male children with type 1 diabetes using flow cytometry technology. This contributes to expanding the understanding of the mechanisms of disease progression and may, in the future, help in developing early diagnostic or therapeutic strategies based on cellular immune changes.

2. Materials and Methods

2.1. Study Design and Participants

This cross-sectional study was conducted on two groups of children: the first group consisted of 24 children newly diagnosed with type 1 diabetes, aged 5–10 years. The second group consisted of 20 healthy children of the same age who had no history of immune or chronic diseases. Ethical approval was obtained from the Medical Ethics Committee, along with written parental consent for participation in the study.

2.2. Sample Collection

Blood samples were collected from the children participating in the study. 3–5 ml of venous blood was drawn from each child using special tubes containing an anticoagulant (EDTA). The samples were transported directly to the laboratory and processed within two hours of the draw to maintain cell viability and sample quality. To ensure accurate classification of participants into the type 1 diabetes group, the following diagnostic tests were performed: 1-Fasting and postprandial blood glucose levels were measured. 2-Measuring HbA1c (glycated hemoglobin) levels to assess the extent of long-term hyperglycemia. 3-Qualitative and quantitative analysis of autoantibodies associated with type 1 diabetes, namely anti-GAD (glutamic acid decarboxylase antibodies). The results of these tests were used as criteria to confirm inclusion in the type 1 diabetes group [17,18].

2.3- B-cell Isolation and Preparation for Analysis

Mononuclear cells were isolated from venous blood using Ficoll-Hypaque gradient centrifugation, following established protocols for isolating peripheral blood mononuclear cells (PBMCs). After separating the mononuclear cell layer, the cells were washed three times with physiological PBS to remove plasma and red blood cells. Cell counts were then performed using a manual cell counter (hemocytometer) under a microscope. The cells were resuspended at an appropriate concentration (1×10^6 cells/ml) in PBS, prior to staining and flow cytometry analysis.[19]

2.4- Fluorescent Antibody Staining (Staining for Flow Cytometry)

B cells and their subtypes were characterized using a panel of monoclonal antibodies conjugated to specific fluorescent dyes.anti-CD19-PE-CY7 MAB (HIB-19) was used as the primary marker represented by CD19 to identify B cells, while anti-CD27PE (clone LEU-27), anti-CD24/FITC (clone ML5) and anti-CD80/APC-H7 (clone L307) were used as surface markers to classify the different functional types within these cells. Transitional B cells were characterized by CD24, memory cells by CD27, and CD80 was used to identify cells with a

stimulatory role in antigen-presenting B cells. Cells were incubated with these antibodies for 30 minutes in the dark at 4°C to ensure stable reactions and prevent dye degradation. After incubation, cells were washed thoroughly with PBS to remove unbound antibodies and then resuspended in PBS containing 1% human serum albumin, which helps stabilize cells and reduce adhesion during analysis.[20, 21]

2.5- Flow Cytometry Analysis

The analysis was performed using a BD FACSCanto II device, pre-calibrated according to the manufacturer's technical instructions. 50,000 live cells were analyzed for each sample to provide sufficient and accurate data for statistical analysis. FlowJo (version X) software was used to analyze the results and extract percentages for the studied cell types. The analysis began by identifying B cells based on their expression of CD19. The surface expression of CD24, CD27, and CD80 within this group was then evaluated using a specific gating strategy to ensure accurate discrimination between the different types [22]. The graphical analysis steps are documented in Figure (1) of the study results.

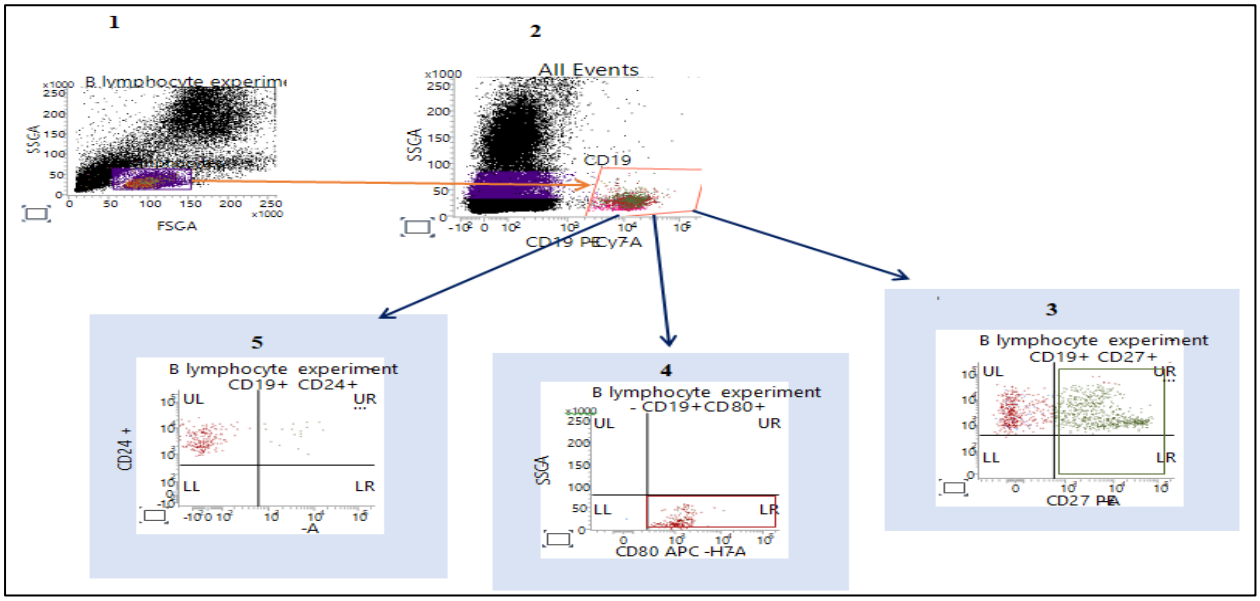

Fig.1: Flow cytometry analysis strategy for identifying B cells CD27+, CD24+, and CD80+. The figure illustrates the sequence of analytical gates used to characterize B cells in a blood sample: 1-Lymphocytes were first identified within peripheral blood mononuclear cells based on physical characteristics associated with forward scatter (FSC) and side scatter (SSC). 2-Next, B cells were identified by positive expression of the CD19 molecule. 3-The proportion of CD27-expressing B cells within the $CD19^+$ subset was evaluated, as an indicator of memory cells. 4-CD80-expressing B cells within $CD19^+$ were then identified. 5-Finally, the proportion of CD24-expressing B cells within $CD19^+$ was calculated, as these cells represent transitional or regulatory stages of B cell development.

2.6. Statistical Analysis

Data were analyzed using SPSS version 25. Values were expressed as mean ± standard error of mean (SEM) to assess the accuracy of the representation of the averages. To compare the two study groups (children with type 1 diabetes and healthy children), an independent samples t-test was used, as there was no relationship between the two groups being compared. Results were considered statistically significant when the probability value was $p < 0.05$ [23].

3. Results

3.1 Clinical Results of Participants

The study included 44 male children aged 5 to 10 years, equally distributed into two groups: 24 children with type 1 diabetes and 20 healthy children as a control group. Clinical analyses showed that the mean age of the patient group was 7.1 ± 1.6 years, compared to 7.3 ± 1.3 years in the control group, with no significant difference between the two groups ($p > 0.05$). The diabetic group showed a marked increase in HbA1c levels (9.8 ± 1.2%) compared to the control group (3.1 ± 0.4%), and the difference was highly significant ($p < 0.001$). The diagnosis of type 1 diabetes was confirmed in all patients by a positive anti-GAD autoantibody test. Children in the control group did not show any positive results for these antibodies. These data indicate that the selected sample accurately represents children with type 1 diabetes at the early stage of diagnosis.

3.2 Percentage of Memory B Cells (CD19+CD27+B cells)

Results of flow cytometry analysis showed a significant decrease in the surface expression of the marker CD27 on B cells in children with type 1 diabetes compared to healthy children (control group). The mean percentage of CD27-expressing B cells in the patient group was 0.38 ± 0.02, compared to 1.09± 0.07 in the control group **, as shown in Figure 2.** These results suggest a potential disturbance in B cell function or maturation in affected children, which may contribute to understanding the immune mechanisms associated with the development of type 1 diabetes.

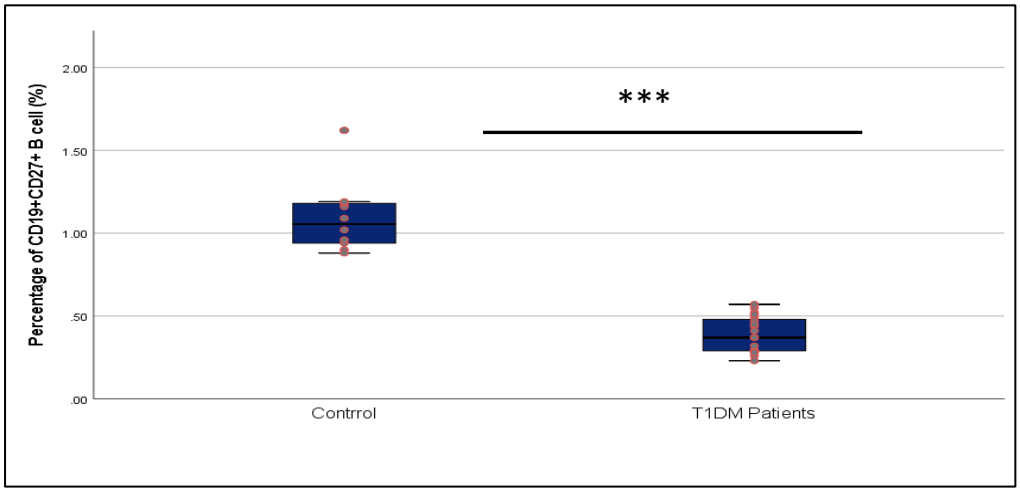

Fig.2: The percentage of CD19+CD27+B cells in control and Type 1 diabetes mellitus (T1DM) patients ,the significance value was indicated as * between the groups. The level of probability was indicated as *** $P \leq 0.001$. Data was presented as mean ± SE.

3.3 The co-stimulatory molecules CD80 expression on B Cells

The analysis results showed a significant decrease in the surface expression of CD80 on B cells in children with type 1 diabetes, compared to the control group. The mean ratio in the patient group was 3.33 ± 0.1, compared to 4.22± 0.9 in the control group**, as shown in Figure 3.**. This difference indicates a tendency toward decreased CD80 expression in patients, which may reflect changes in B cell function related to immune activation and participation in the autoreactive response.

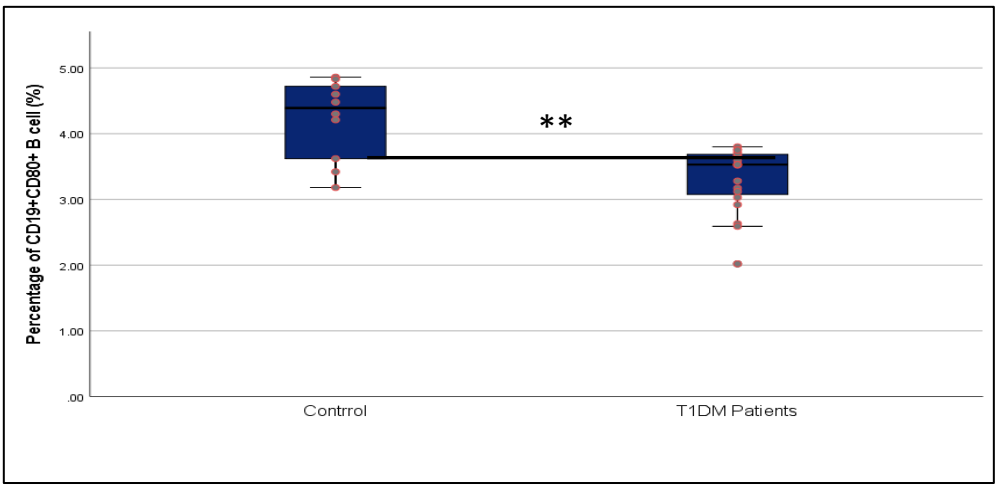

Fig.3: The percentage of CD19+CD80+B cell cells in and Type 1 diabetes mellitus (T1DM) patients ,the significance value was indicated as * between the groups. The level of probability was indicated as ** $P \leq 0.01$. Data was presented as mean ± SE.

3.4 Percentage of Transitional B Cells (CD19+CD24+B cells)

The study results showed a decrease in the proportion of transitional B cells expressing the surface marker CD24 in children with type 1 diabetes, compared to healthy children in the control group. The mean ratio in the patient group was 3.20 ± 0.9, compared to 4.85± 0.9 in the control group, as shown in Figure 4. This decrease suggests a possible defect in B cell differentiation or transition, which may affect the immune role of these cells in the disease.

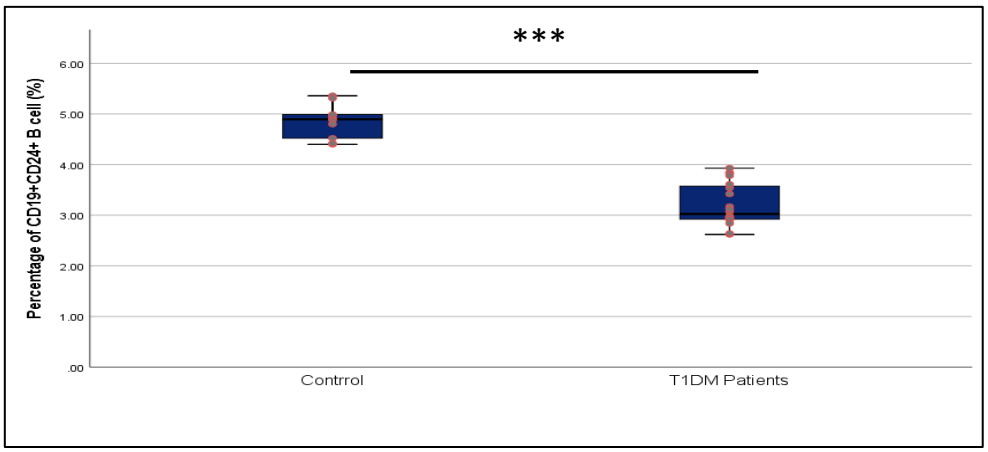

Figure 4 : The percentage of CD19+CD24+B cell cells in control and Type 1 diabetes mellitus (T1DM) patients , the significance value was indicated as * between the groups. The level of probability was indicated as *** $P \leq 0.001$. Data was presented as mean ± SE.

4. Discussion

The results of this study indicate clear changes in the phenotype of $CD19^+$ B cells in children with type 1 diabetes, represented by a significant decrease in the expression of the surface markers CD27, CD24, and CD80, compared to healthy children. CD27 is a typical marker of memory B cells, which play an important role in enhancing secondary immune responses upon re-exposure to antigens[24]. The decrease in the percentage of $CD19^+CD27^+$ cells in patients indicates a potential defect in the formation or survival of memory cells [25]. Previous studies, such as El-Mokhtar *et al*., 2020, have suggested that memory B cell dysfunction may lead to impaired immune autoregulation and, consequently, to persistent immune responses against pancreatic beta cells [26,27]. As for CD24, it is normally expressed on transitional and regulatory B cells, which play a role in suppressing inflammation and balancing autoimmune responses. The decreased $CD19^+CD24^+$ cells in diabetic patients in this study suggested a possible deficiency in regulatory B cells, which may contribute to the lack of immune balance necessary to prevent auto-destruction [28]. Studies such as Li *et al*., 2020, have supported this hypothesis, showing that low regulatory B cells in diabetes are associated with increased secretion of inflammatory cytokines such as IL-6 and TNF- [29] . CD80 is one of the co-stimulatory molecules expressed by B cells when they act as antigen-presenting cells (APCs). The decreased expression of CD80 in $CD19^+CD80^+$ cells in diabetic patients indicates impaired adaptive immune function[30]. Although this may be assumed to reduce the autoimmune response, some studies suggest that a specific imbalance in the expression of stimulatory molecules such as CD80 could lead to inappropriate antigen presentation, contributing to disease progression rather than preventing it [31]. Together, these findings are consistent with theories that assume that B cells contribute not only to antibody production but also to regulating immune balance, antigen presentation, and autoreactive T cell activation[32]. Thus, the clear phenotypic changes observed in this study support the active role of B cells in the development of type 1 diabetes, not only as a secondary factor, but as a pivotal factor in the initiation or maintenance of the autoimmune response. Furthermore, these findings may have future significance in the design of therapeutic strategies directed at B cells, whether by modifying their functions or influencing their differentiation, as is the case in some clinical studies that have tested the use of targeted therapies such as anti-CD20. However, it is important to note that this study is limited to a specific age group (5–10 years) and at an early stage of the disease, which may require additional studies including different stages of diabetes and multiple ages to understand the dynamic changes in B cells over the course of disease progression.

5. Conclusion

The results of this study highlight changes in the phenotype of B cells in children with type 1 diabetes, with significant decreases in the expression of CD27, CD24, and CD80 on the surface of these cells compared to healthy children. These changes indicate a disturbance in B cell function, including impaired memory and regulatory cells, as well as a defect in their ability to present antigens, which may contribute to the development of an autoimmune response and the destruction of pancreatic beta cells. These findings reflect the pivotal role of B cells in disease mechanisms and open the way for the development of therapeutic strategies that target modulating the functions of these cells to improve type 1 diabetes control and limit its progression.

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Conflicts of interest

No potential conflict of interest.

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