

Association between Pediatric T1DM and Autoimmune Diseases in Misurata Diabetic Center

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Abstract:

Objective: This study aimed to assess the prevalence of autoimmune diseases (AID) associated with Type 1 Diabetes Mellitus (T1DM) in Misurata Diabetic Center and analyze their impact on the course of T1DM.

Methods: A retrospective single-center study of 592 children diagnosed with T1DM between 2007 and 2022 at Misurata Teaching Hospital, Libya, was conducted. Data on prevalence, age of onset, and timing of diagnosis of AID and T1DM were collected and analyzed.

Results: AID was identified in 30 (5.07%) children with T1DM. Celiac disease (CD) was the most prevalent AID (4.22%), followed by hypothyroidism (<1%). No significant difference in the age of onset of T1DM was observed between children with CD and hypothyroidism. However, the time between T1DM and AID diagnosis differed significantly, with hypothyroidism requiring a longer period. Interestingly, only 20% of CD cases were diagnosed during symptomatic episodes, while the remaining 80% were identified through serological testing during non-episodic periods. All hypothyroidism cases presented with clinical symptoms. Notably, 56.7% of children with T1DM and AID were underweight at diagnosis.

Conclusion: This study indicates a relatively low prevalence of AID associated with T1DM in Libyan children. Among identified AID, CD predominates over hypothyroidism. While the age of onset of T1DM is similar for both AID, the timing of diagnosis and presentation differ significantly. These findings highlight the importance of routine screening for CD in children with T1DM, even in the absence of symptoms.

Keywords: Diabetes Mellitus Type 1, Autoimmune disease, Thyroid disorder, human leukocyte antigens.

الملخص

الأهداف: هدفت هذه الدراسة إلى تقييم شيوع الأمراض المناعية الذاتية المصاحبة لمرض السكري من النوع الأول في مركز مصراتة لمرضى السكري وتحليل تأثيرها على مسار المرض.

الطرق: تم إجراء دراسة استرجاعية أحادية المركز على 592 طفلاً تم تشخيصهم بالسكري من النوع الأول بين عامي 2007 و 2022 في مستشفى مصراتة التعليمي في ليبيا. تم جمع البيانات حول الانتشار، والعمر عند بداية المرض، وتوقيت تشخيص امراض المناعة الذاتية والسكري لدى هؤلاء الأطفال.

النتائج: تم تحديد امراض المناعة الذاتية لدى 30 طفلاً (5.07%) مصابين بالسكري من النوع الأول. كان مرض حساسية القمح هو النوع الأكثر شيوعاً (4.22%)، يليه قصور الغدة الدرقية (أقل من 1%). لم يُلاحظ أي فرق ذي دلالة إحصائية في العمر عند بداية الإصابة بالسكري من النوع الأول و بين الأطفال المصابين بحساسية القمح وقصور الغدة الدرقية. ومع ذلك، اختلف الوقت بين تشخيص مرض السكري وامراض المناعة الذاتية بشكل ملحوظ، حيث يتطلب قصور الغدة الدرقية فترة أطول. ومن المثير للاهتمام، أنه تم تشخيص 20% فقط من حالات حساسية القمح خلال النوبات العرضية، بينما تم تحديد الباقي (80%) من خلال الفحص المصل خلال الفترات غير العرضية. ظهرت جميع حالات قصور الغدة الدرقية بأعراض سريرية. وتجدر الإشارة إلى أن 56.7% من الأطفال المصابين بالسكري من النوع الأول وامراض المناعة الذاتية كانوا يعانون من نقص الوزن عند التشخيص.

الاستنتاج: تشير هذه الدراسة إلى انخفاض نسبي في شيوع امراض المناعة الذاتية المصاحبة للسكري من النوع الأول لدى الأطفال الليبيين. وبين أنواع امراض المناعة الذاتية المحددة، يسيطر مرض حساسية القمح على قصور الغدة الدرقية. في حين أن عمر بداية الإصابة بالسكري متشابه لكلا النوعين من امراض المناعة الذاتية، فإن توقيت التشخيص والعرض يختلفان بشكل كبير. تسلط هذه النتائج الضوء على أهمية الفحص الروتيني لحساسية القمح عند الأطفال المصابين بالسكري، حتى في حالة عدم وجود أعراض.

الكلمات المفتاحية: داء السكري النوع الاول، أمراض المناعة الذاتية، مرض الدرقية، مضاد الكريات البيضاء البشرية.

1. Introduction

An array of chronic illnesses known as autoimmune diseases (ADs) occur when the target organs are damaged or cease to function as a result of the immune system's reaction to self-antigens. Since many ADs have similar immunologic mechanisms and genetic predispositions, they frequently coexist in the same person or in the same family (1). Being one of the important autoimmune diseases characterized by an autoimmune reaction directed against pancreatic beta cells, Type 1 diabetes mellitus (T1DM) often coexists with other autoimmune diseases, and anti-islet autoantibodies develop prior to the disease's clinical manifestation. (2)

T1DM is most commonly linked to autoimmune thyroid diseases (17–30%), especially Graves' disease and Hashimoto's thyroiditis; it is also linked to Addison's disease (0.2%), celiac disease (8%), autoimmune gastritis (5–10%), rheumatoid arthritis (1.2%), and systemic lupus erythematosus (1.15%) (3-6). Existing data suggests that celiac disease and hypothyroidism are the most commonly observed additional ADs in type 1 diabetes (T1D) among the over 80 different ADs. (4,7)

Based on other researches, it appears that the increased frequency of new ADs in people with T1DM is mostly caused by a shared genetic background. Thus, it is not surprising that the HLA area and ADs have a strong correlation, as this locus encodes many molecules essential to the functioning of the immune system (8). Outside of the HLA area, T1DM and other ADs share some genetic commonality (9), but clustering of ADs in the same individuals and families suggests that it is impossible to rule out the possibility of common environmental factors or other pathophysiological mechanisms (10). Although a number of environmental factors—including viral infections, cow's milk proteins, and vitamin D3 deficiency—have been suggested as being initiators of the autoimmune process in genetically predisposed people; however, none of them have been positively connected to diabetes (11). Additionally, a higher incidence of multiple ADs is often associated with female sex (12-13), older age, and longer duration of diabetes (12).

As these coexisting autoimmune conditions may have a significant impact on the disease's natural course and make managing diabetes more challenging, we aimed to evaluate the prevalence of autoimmune disorders associated with type 1 diabetes in children and how they affect the progression of the disease.

2. Aim and objectives:

To assess the prevalence of T1DM associated autoimmune diseases and their impact on the course of T1DM. Timing of diagnosis of other autoimmune disease relevant of time diagnosis of diabetes mellitus.

3. Methodology:

Study design:

An observational retrospective cross sectional single center study.

Setting and duration:

The study was conducted at the pediatrics department at Misurata's Diabetes Center over a four months period from the 1st of April 2023 until the 30th of July 2023.

Study population:

The study included 592 children who were diagnosed with T1DM during from 2007 until 2022 at Misurata Diabetic Center which is a center established to provide specialized healthcare services for diabetic patients and covers over 675 thousand residents of the central region of Libya according to the Libyan bureau of census and statistics.

Inclusion criteria:

All cases diagnosed with T1DM during the target study period in the pediatric age group.

Exclusion criteria:

Cases with incomplete, or missing information that could not be obtained or verified.

Study variables:

The study included: age, sex, anthropometry and Body Mass Index (BMI) -for suitable age groups-. Also, family history of autoimmune disease and diabetes was included in the study. As well as the age of onset of the autoimmune disease, the method of diagnosis symptoms, and comorbidities were included.

Data collection:

The data was collected from the paper based records of the patients who were diagnosed with T1DM or were treated for it at the study location and during the targeted study period. The authors first filtered all the files of T1DM cases registered during the study period. The filtered files were then reviewed by the authors in scheduled sessions, and evaluated for clarity and completion according to the inclusion and exclusion criteria (see above).

Data analysis:

The data was analyzed using IBM SPSS version 25 for Windows. Descriptive statistics were used to interpret and present that results. Frequencies and percentages were used to describe categorical variables, and chi-square test was used to compare them. The means and standard deviations were calculated for the numerical data, and t-test was used to compare them. All tests were considered significant at $p < 0.05$.

Ethical considerations:

The approval for the study was obtained from the Committee of Scientific Affairs at Misurata's Diabetic Center. The patients' personal information and details were not collected and data was stored anonymously.

4. Results

During the target period, a total of 592 cases of T1DM were identified among individuals aged 0 to 16 years. Among these cases, 30 (5.07%) were found to have an associated autoimmune disease. Figure 1 presents a chart illustrating the distribution of autoimmune diseases within the identified cases. Figure 1 highlights that celiac disease was the most prevalent autoimmune condition, accounting for 25 cases (4.22%) of the total study sample and representing (83.33%) of the cases with autoimmune diseases. In contrast, hypothyroidism was relatively less common, with only 5 cases (<1%) identified, making up 16.67% of the cases with autoimmune conditions.

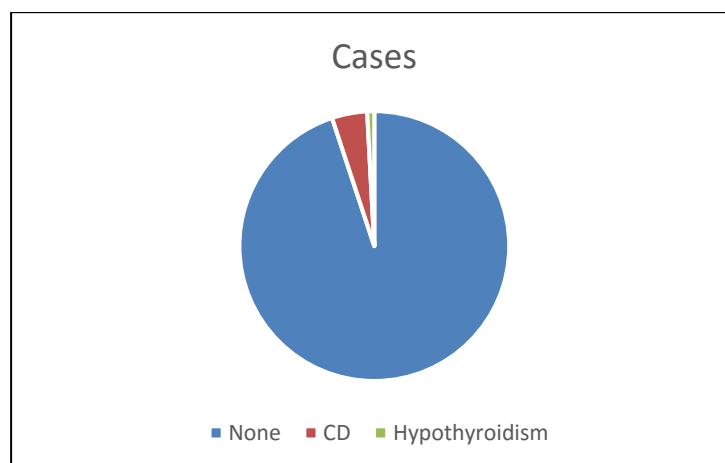


Figure 1. Distribution of Auto-immune Disease

The prevalence of autoimmune diseases displayed a slight variation between males and females, with 13 cases observed among males compared to 17 cases among females (56.67% vs. 43.33%, respectively). Notably, from Figure 2 there is a difference in sex distribution for the two autoimmune diseases identified in this study. Celiac disease (CD) showed a similar occurrence in

both sexes, with 12 cases among males and 13 cases among females. However, hypothyroidism was exclusively reported in females, with 4 cases identified, while 1 case were reported among females. It is worth noting that none of the 30 cases with autoimmune diseases exhibited comorbidities. Furthermore, a family history of either CD or hypothyroidism was reported in 8 cases (26.67%) among all individuals with autoimmune diseases.

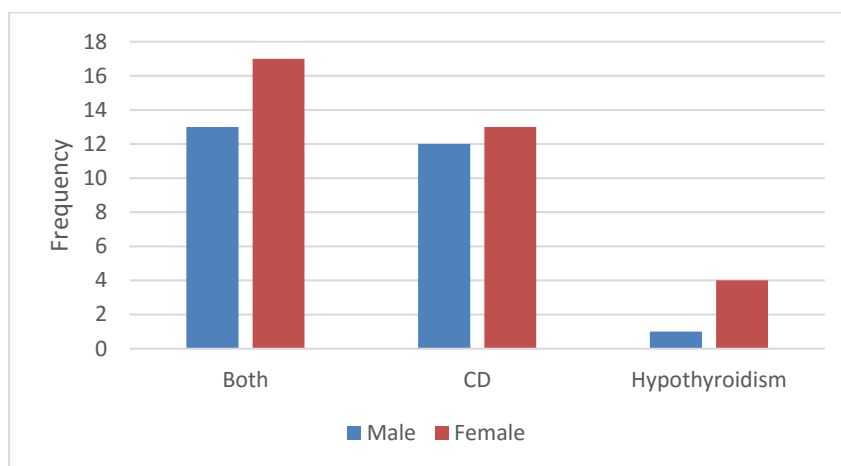


Figure 2. Sex distribution of Auto-immune Disease

The average age of onset of Type 1 Diabetes (T1D) in the 30 cases with an autoimmune disease was found to be 5.17 ± 3.4 years. Interestingly, there was no significant difference in the age of onset of T1D between the cases with hypothyroidism and those with Celiac Disease (7.8 years ± 2.72 vs. 4.64 ± 3.27) (p -value = 0.053). Figure 3 visually represents the contrast in the age of diagnosis between the two groups.

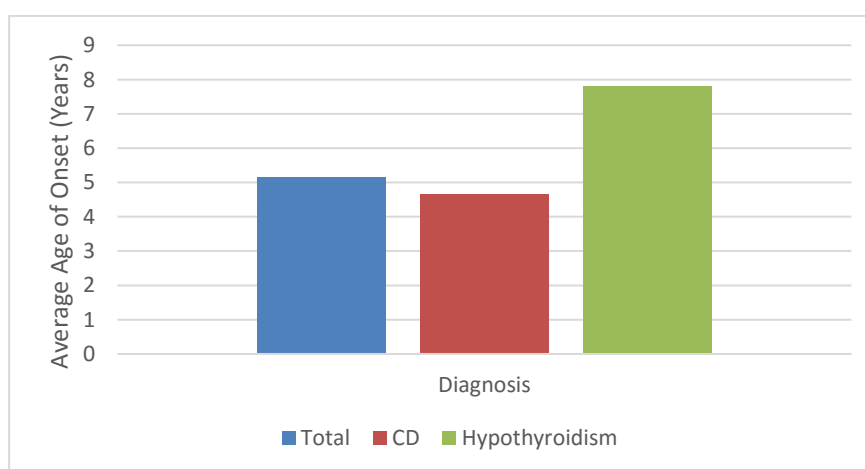


Figure 3. Age of Diagnosis with T1D According to the Co-existing Auto-immune Disease

In a similar vein, the average age of onset for the autoimmune disease in the 30 cases was determined to be 6.7 years \pm 3.4 years. Interestingly, the average age of onset for Celiac Disease (CD) was lower than that of hypothyroidism (6.32 years \pm 3.84 vs. 8.6 years \pm 1.96 years) ($p = 0.22$).

Furthermore, the average duration between the onset of Type 1 Diabetes (T1D) and the onset of the autoimmune disease was calculated to be 3.03 years \pm 2.63 years. It is worth noting that the occurrence of hypothyroidism required a significantly longer period compared to patients with CD ($p = 0.0000001$). A graphical representation of this difference can be observed in Figure 4.

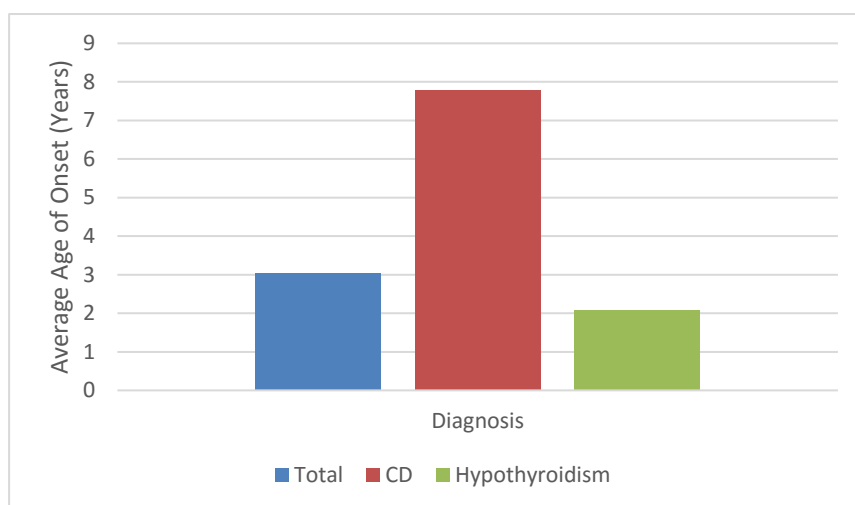


Figure 4. Period Between the Onset of T1D and the Auto-immune Disease

All of the five cases (100%) with hypothyroidism exhibited symptoms and sought medical attention with clinical manifestations of hypothyroidism. In contrast, only five out of the 25 cases (20%) with Celiac Disease (CD) were diagnosed during a celiac episode when they presented with symptoms related to CD. These symptomatic cases underwent an endoscopic biopsy procedure, which led to their diagnosis. On the other hand, the remaining 20 cases (80%) were diagnosed during non-episodic periods through serological testing.

17 (56.7%) of cases were underweight when diagnosed with diabetes, while 12 (40%) had normal BMI, and only one case (3.3%) was overweight.

Table 1. BMI categories of the 30 Cases

BMI	Number of cases
<18	17
18-25	12

25-30	1
Total	30

5. Discussion

As previously mentioned, celiac disease and hypothyroidism are the most commonly observed ADs associated with T1DM. (4,7) This was the case in our study with all cases being either associated with celiac disease (CD) or hypothyroidism, also known as Hashimoto's or autoimmune thyroiditis.

Female predominance among autoimmune diseases, including CD and hypothyroidism, is well known and was seen in our study too, which correlates with most other studies as well for CD (14-18) and hypothyroidism (18-21). The suggested explanation behind this feminine risk is having two X chromosomes. As the X chromosome has larger number of genes, this puts the female at significantly higher possibility of mutations. (22) Also, in autoimmune thyroiditis, study suggests that females are 3 times more prone to the disease because of the estradiol hormone which helps an important role in progression of the disease. (23)

Celiac disease was the most prevalent autoimmune disease seen in our cases with a percentage of 4.22% among children with T1D. A similar result with prevalence of 4.95% was seen in a research by Abosmaha et al (2014) in Libya (14) and of 4.8% in a Greek study by Karavanaki et al (24). Prevalence of celiac disease in other studies fluctuates between 1% to 16%. (23, 25) This variation might be a result of geographical difference which can be explained through multiple genetic, environmental and immunological factors which can trigger CD. (23,26)

For the diagnosis of CD, serological investigations are crucial as most of the cases are asymptomatic. (23, 27-28) and the majority of them are diagnosed at the phase of subclinical or silent CD where no or only mild symptoms are present. (29) This applies to our cases as only 5 of them (20%) were symptomatic while the rest were asymptomatic and were diagnosed through serological testing.

In our study, in all cases, T1DM preceded CD. Results from other studies suggest that the time between the diagnosis of T1DM and CD varies. It is suggested that CD may precede, follow or develop at the same time as T1DM. (23) This difference might also be the result of silent CD where patient don't exhibit any symptoms and are only discovered on screening. (30-31) In particular, it has been proposed that gluten, the main antigen in latent or silent CD, may act as an immunological trigger and cause diabetes and/or thyroid issues (32). Accordingly, the age of

diagnosis, or the amount of time spent exposed to gluten, is closely associated with the prevalence of type 1 diabetes in CD (33-34). In the other hand, other studies indicate that T1DM was present at the outset and that CD developed later. (23)

Hashimoto's disease is the most common autoimmune thyroiditis associated with T1DM (23,27) with a prevalence ranging from 12.1% to 23.4%. (35-36) The prevalence in our study also fall in between this range. Unlike CD, all cases with the disease exhibited symptoms prior the diagnosis. It is also worth noting that the average age of onset for hypothyroidism was older and hypothyroidism needed longer time to develop. This result correlates with other studies which suggest that the number of thyroid auto-antibodies is positively correlated with age and diabetes duration. Moreover, these auto-antibodies are not present at the time of diagnosis with T1DM but they develop later. (23)

As for the BMI, in our study most of the cases were either underweight (56.7%) or had normal BMI (40%). Most of our cases had CD, which is associated with lower BMI and patients are usually not only weighing less but also being shorter (37-38). Additionally, studies did not find a significant relation between having low BMI and the risk of developing CD, while being overweight was found to be a protective factor. (37) In contrary, studies suggest a significant relation between hypothyroidism and overweight, indicating that obesity might be a risk factor contributing for the onset autoimmune thyroid diseases. (39-40).

6. Conclusion:

This study indicates a relatively low prevalence of AID associated with T1DM in Libyan children. Among identified AID, CD predominates over hypothyroidism. While the age of onset of T1DM is similar for both AID, the timing of diagnosis and presentation differ significantly. These findings highlight the importance of routine screening for CD in children with T1DM, even in the absence of symptoms.

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