BENGHAZI UNIVERSITY – FACULTY OF MEDICINE
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Auto-immune Disorders in Diabetic children from north- eastern part of Libya

الأمراض ذاتية المناعة المصاحبة لمرض السكري لدى الأطفال في شمال شرق ليبيا

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بسم الله الرحمن الرحيم

رَ ۡفَعَرُ َات ٖمَنَشۡ َاءُ ۗوَفَوۡ كَلِ ُ ذِيعِلۡ ٍ َلِيمٌ ﴿٧٦﴾

سورة يوسف

TO MY MOTHER, HUSBAND & MY DAUGHTER

ACKNOLEDGEMENT

I thank God and praise Him so much that helped me to complete this work.

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ABBREVIATIONS

DM Diabetes mellitus

T1D.M. Type 1 diabetes mellitus

CD Celiac disease

EMA Endomysial antibodies

tTG Tissue transglutaminase

AGA Antigliadin antibodies

ARA Antireticulin antibodies

HbA1c Glycosalatedhemoglobulin

TFT Thyroid function test

TSH Thyroid-stimulating hormone

TPOAb Thyroperoxidase antibodies

TG-Ab Thyroglobulin auto antibodies

21OH Ab 21hydroxylase antibodies

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C O N T E N T S

1. SUMMARY

Objectives: To estimate the % percentage of common autoimmune disorders in patients with type 1D.M. from north eastern part of Libya.

Patients and method: It is a retrospective study including 387 Libyan type 1 diabetic children aged (1-15 years old), from January 2002 to December 2012.this study was conducted in Benghazi Children Hospital, which is a main referral hospital of north- eastern part of Libya from Tobruq to Ejdabia. Data collected: Name ,age & date of birth, sex, residence ,date & age at diagnosis of type 1 D.M., mode of presentation of type 1 D.M., family history of type 1 or type 2 D.M. ,family history of auto-immune disorders, HbA1C, TFT , development of auto-immune disorders ,date & age of development of autoimmune disorders .Data was statistically analyzed.

Results:16 cases from 387 patients had autoimmune disorders which represent 4.2% of all cases of diabetic patients , 8 cases had celiac disease (3.5%), 5 cases had hypothyroidism (1.4%), 2 cases had hyperthyroidism (0.6%), 1 case had Alopecia totalis (0.3%).

Conclusion and Recommendations: There is an association between type 1 D.M. & autoimmune disorders, the % percentage of thyroid disorders & celiac disease much less than reported in literature .we recommend early screening of autoimmune disorders to prevent long term morbidity & mortality.

2. I N T R O D U C T I On

Diabetes mellitus (DM) is a common, chronic, metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature.

Type 1 DM characterized by low or absent levels of endogenously produced insulin. The onset occurs predominantly in childhood, with median age of 7 to 15 yr, but it may present at any age.

T1DM results from autoimmune destruction of the insulin –producing beta cells (islets) of the pancreas. Both genetic susceptibility and environmental factors contribute to the pathogenesis. It is also associated with auto antibodies to islet cell cytoplasm (ICA), insulin (IAA), antibodies to glutamic acid decarboxylase (GADA or GAD65), and ICA512 (IA2).

The incidence of T1DM is rapidly increasing in specific regions and shows a trend toward earlier age of onset. T1DM accounts for about 10% of all diabetes, affecting about 15 million in the world.
T1DM is associated with other autoimmune diseases such as thyroiditis, celiac disease, multiple sclerosis, and Addison disease.

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is frequently associated with T1DM in children .As many as one in 5 insulin-dependent diabetic patients may have thyroid antibodies in their serum; the prevalence is 2–20 times greater than in control populations. Only a small proportion of these patients, however, acquire clinical hypothyroidism; the interval between diagnosis of diabetes and thyroid disease averages about 5 yr. Periodic palpation of the thyroid gland is indicated in all diabetic children, if the gland feels firm or enlarged, serum measurements of thyroid antibodies and thyroid-stimulating hormone (TSH) should be obtained. A confirmed TSH level of greater than 10 μU/mL indicates existing or incipient thyroid dysfunction that warrants replacement with thyroid hormone.

Hyperthyroidism affects 1% of children with diabetes; the condition is usually discovered at the time of diabetes diagnosis.

Addison disease is uncommon, affecting less than 1% of children with diabetes.

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Celiac disease ,is another autoimmune disorder, which is due to hypersensitivity to dietary gluten, that occurs with significant frequency in children with type 1 DM. It is estimated that about 7.0% of children with type 1 DM develop celiac disease within the 1st 6 yr from the diagnosis. Additionally, the incidence of celiac disease is significantly higher in children under 4 yr of age and girls. Young children with type 1 DM and celiac disease usually present with gastrointestinal symptoms (abdominal cramping, diarrhea, and gastro esophageal reflux), growth failure due to suboptimal weight gain, and unexplained hypoglycemic reactions due to nutrient malabsorption, adolescents may remain asymptomatic. The diagnosis of celiac disease is considered if serum antiendomysial and/or tissue transglutaminase antibody titers are positive in the presence of normal serum total IgA level. The diagnosis is confirmed on endoscopic evaluation and biopsy of small bowel revealing characteristic atrophy of intestinal villi. Therapy consists of a gluten-free diet.(1)

This study was conducted in Benghazi Children Hospital ,including patients diagnosed withT1 D.M. from north- eastern part of Libya.
Data collected from Diabetic & Endocrine clinic ,a retrospective study including all Libyan type 1 diabetic children between 1-15 years of age from January 2002 to December 2012 referred to Diabetic clinic.
The aim of this study was to estimate the % percentage of common Autoimmune disorders in Diabetic children.

3.LITERATURE REVIEW

In one retrospective study conducted in Medwin hospital, in India in 2012. patients of T1DM from May 1997 to December 2011 were retrospectively analyzed in context of associated clinical profile.
Among 260 patients diagnosed as T1DM, 21 (8%) had hypothyroidism, 4 (1.5%) had hyperthyroidism and 2 (0.7%) had primary adrenal insufficiency. Eighteen patients (7%) had celiac disease, Down's syndrome present in 2 patients (0.7%).
1 patients had myasthenia gravis. Systemic lupus erythematosus and rheumatoid arthritis were present in 3 and 1 patients respectively. Mean age of study patients was 20.8±9.8 years (range, 3-23 years).(2)

Soyucen E1& others conduct a study in the Thrace region of Turkey in 2010. the population studied consisted of 33 children with insulin-dependent diabetes mellitus and 41 healthy children with demographic features similar to the study subjects. Free triiodothyronine, free thyroxin, thyroid-stimulating hormone, anti-thyroid peroxidase antibody, anti-thyroglobulin antibody, IgA, anti-endomysium IgA, and anti-gliadin IgA were measured in all cases and controls. In this study the serum levels of free triiodothyronine and free thyroxin were within the normal range in all cases. However, in one patient who had anti-thyroid peroxidase and antithyroglobulin antibodies, the thyroid-stimulating hormone level was high despite a normal free triiodothyronine and free thyroxin value. Ultrasonographic findings confirmed thyroiditis in this patient. Anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies, anti-endomysium IgA and anti-gliadin IgA were detected in 15.4%, 6%, 9.1% and 3% of the diabetic cases, respectively. None of these antibodies was detected in the control group. In the diabetic group, the seroprevalences of the antithyroid peroxidase antibodies and the anti-endomysium IgA were statistically higher than in the control group ($p<0.05$).(3)

Another study was conducted in Germany in 2008. Data from 31,104 patient <18 yr of age (52% males, mean age 13.1 yr) with T1DM from 177 pediatric centers in Germany and Austria from 1995 until 2007 were analyzed.
In this study eleven per cent of the patients had positive antibodies for CD. Patients with positive antibodies were significantly younger at diabetes onset and had a significantly longer duration of diabetes ($p < 0.001$). Fifteen per cent of the patients had positive thyroid antibodies.(4)

In a study was published in 2004. Conducted on 63 children aged 2-14 years who were treated in the Department of Pediatrics of the Virgen de las Nieves University Hospital in Granada (Spain) from 1998-2002. Antibodies to glutamic acid decarboxylase-65 (GADA), anti-insulin (AIA), thyroperoxidase (anti-TPO), thyroglobulin (anti-TG), thyroid-stimulating immunoglobulins (TSI) and endomysial antibodies (EmA-IgA) were measured and documented. A total of 55.5 % of these patients were girls and the mean age was 7.9 +/- 3.2 years.
In this study the prevalence rates were: GADA 65.1 %; AIA 68.3 %; anti-TPO 11.1 %; anti-TG 9.5 %; TSI 4.8 % and EmA-Ig A 3.1 %. Children with thyroid antibodies (anti-TPO1) were significantly older and developed diabetes later in life ($P < 0.05$) than those without antibodies. Thyroid-stimulating hormone levels, goiter and thyroid dysfunction were higher in children who were anti-TPO1 than in diabetic children without thyroid autoimmunity.(5)

Szypowska A1& others conduct a study in 2008 in Poland. included 260 children (124 girls, 136 boys) aged 1.3-18 years (mean 11+/-4.01), the diabetes duration 3.99+/-3.7 years. Endomysial antibody (EMA) was measured and all patients with positive EMA had small-bowel biopsy. Antibodies against thyroperoxidase (a-TPO), thyroglobulin (a-Tg), TSH, fT4, HbA1c and ultrasound examination of thyroid glands were assessed.
The prevalence of EMA was 10% (27/260) and 9% (25/260) had biopsy-proven celiac disease. The median age of T1DM at onset was significantly lower in patients with EMA than those without EMA 6.2+/-5.6 vs. 7.7+/-4.2 $p=0.04$. 20% of children diagnosed with type 1 diabetes at age <4 years had celiac disease $p=0.001$. The prevalence of thyroid antibodies was 29% (75/260). In the group with positive thyroid antibodies, in 28% (21/75) thyroid ultrasonography showed scattered hypoechogenicity and 23% (17/75) required treatment with thyroxine. Children with positive a-TPO had higher TSH level (2.87+/-2.1 vs. 1.95+/-0.9) $p<0.01$ and HbA1c level (8.32+/-1.64 vs. 7.59+/-1.67) $p=0.03$ than children without thyroid antibodies. More frequently thyroid antibodies were positive in girls than in boys.(6)

Another study was conducted in 2009 in Portugal . forty individuals underwent an interview and blood was drawn for anti-thyroperoxidase (anti-TPO), anti-21OH, TSH, free T4 and cortisol measurement.
Anti-21OH was found in 7.5% ($n = 3$), none with adrenal dysfunction. This antibody was not exclusively seen in patients with anti-TPO (+). Anti-TPO was positive in 25% and associated with higher TSH levels ($p = 0.034$) and older age ($p = 0.009$).(7)

Triolo TM1, Amstrong TK & others conduct a study in 2011 on 491 children diagnosed (USA) with type 1 diabetes at the Barbara Davis Center for Childhood Diabetes were screened for autoimmune thyroid disease (thyroid peroxidase autoantibodies [TPOAb]), celiac disease (tissue transglutaminase autoantibodies [TTGAb]), and Addison disease (21-hydroxylase autoantibodies [21OHAb]).
122 (24.8%) were positive for TPOAb, and 15 of the 122 (12.3%) had autoimmune thyroid disease. there were 57 (11.6%) who were positive for TTGAb, of whom 14 (24.6%) had celiac disease. Five (1.0%) were positive for 21OHAb, of whom one had Addison disease.(8)

In one cohort study conducted on prevalence of celiac disease in Libyan children with type 1 diabetes mellitus in 2003 .
In this study 234 Libyan children with DM (121 males and 113 females) aged between 2 and 25 years and 50 healthy school children were screened for CD using the enzyme-linked immunosorbent assay (ELISA) for IgA and IgG antigliadin (AGA), anti-tissue transglutaminase (tTG), and anticalreticulin antibodies. An IgA antiendomysial antibody (EmA) was determined by immunofluorescence.
Fifty patients (21.3%) were positive for IgA- and/or IgG-AGA, tTG, and anticalreticulin antibodies. Nineteen of these patients were EmA positive and seven were EmA negative. From the EmA negative patients we found that five sera with IgA deficiency had high IgG class in antigliadin, anti-tissue transglutaminase, and anticalreticulin antibodies. All these patients underwent intestinal biopsy. Twenty-four had clear histological (atrophy) evidence of CD including the EmA negative patients with IgA deficiency; prevalence of CD in this study was thus 10.3%.(9)

Mankaï A1 & other sconduct a study in 2007 was designed to evaluate the frequency of CD among Tunisian children with DM1.
A total of 205 diabetic children (92 girls, 113 boys, age range 6 months-15 years, median 11 years) were screened for CD by determination of IgA anti-endomysium antibodies (EMA).
EMA were positive in 17 out of 205 (8.3%) children with DM1. The median age of DM1 at onset was significantly lower in patients with EMA than those without EMA ($P<10(-7)$). In 13 of 17 EMA-positive patients, duodenal biopsy could be performed and a destructive type of CD was confirmed in 11 of them: 8 patients showed total villous atrophy, 3 patients showed a partial villous atrophy. The other two patients showed a normal histological picture with normal number of intraepithelial lymphocytes. Parents of the remaining EMA-positive children refused endoscopy. Thus the prevalence of biopsy-proven CD was 5.3% (11/205). It was 7.6% (7/92) in girls and 3.5% (4/113) in boys but the difference was not statistically significant. Seventy three percent of patients with CD were asymptomatic.(10)

Another retrospective study conducted at the Pediatric Diabetes Clinic of King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia (KSA) between October 2002 and June 2011.
A total of 430 children with T1DM were screened by anti-tTG antibody. The median age at screening was 10.7 years (range; 1.1-18). The study cohort included 232 (54%) Saudi patients, and females constituted 58.8% of the total number. Anti-tTG antibody screening was positive in 91 (21.2%) patients. Forty-eight (11.2%) out of 430 children screened had biopsy-proven CD. Forty-two patients with CD (87.5%) were asymptomatic .There was no difference in the mean glycosylated hemoglobin level (p=0.38), or insulin requirements (p=0.74) between the 2 groups.(11)

In a prospective cross-sectional study was published in 2012 about the prevalence of celiac disease among Saudi children with type 1 diabetes.
One hundred and six children with T1D have been screened for CD over a two-year period (2008-2010), by doing anti-TTG, EMA, and total IgA. Children with positive anti-TTG titres (>50 U/ml) and/or EMA and children with persistently low positive anti-TTG titres (two readings 20-50 U/ml; within 6 months intervals) had upper endoscopy and 6 duodenal biopsies.
Age ranged between 8 months to 15.5 years (62 females). Nineteen children had positive anti-TTG and/or EMA, however only 12 children had biopsy proven CD (11.3%). Five of 12 had gastrointestinal symptoms (42%). The sensitivity and specificity of anti-TTG were 91.6% and 93.6%, with a positive and negative predictive value of 64.7% and 98.8%, respectively.(12)

Al-Sinani S1& others conduct a cross sectional study, Children with type 1 diabetes mellitus were prospectively screened for celiac disease, at Sultan Qaboos University Hospital, Muscat, Oman over a period of one year (June 2011 - May 2012). Serum anti tissue transglutaminase IgA, endomysial IgA antibodies and total IgA were measured for screening of celiac disease. Children with positive anti-tissue transglutaminase and/or endomysial IgA antibodies underwent endoscopy.
A total of 103 children with type 1 diabetes mellitus were initially included. Ten patients were lost to follow up. Ninety-three patients aged 2-17 years underwent screening for celiac disease. Sixteen patients had positive anti-tissue transglutaminase (17%). Fourteen patients underwent endoscopy with duodenal biopsies, while two were lost to follow-up. Five patients with positive anti-tissue transglutaminase had intestinal biopsy proven celiac disease. The prevalence of celiac disease is 5.5% in our cohort of children and adolescents with type 1 diabetes mellitus.(13)

A prospective study was conducted on 83 diabetes mellitus type 1 children from the south of Iran in 2013. They were tested for the presence of anti-tissue transglutaminase immunoglobulin A antibody and total immunoglobulin A level. The patients testing immunoglobulin A anti-tissue transglutaminase-positive were offered small bowel biopsy.
Eighty-three children with diabetes mellitus type 1 (49 females, 34 males) aged 10.38±4.7 years were enrolled. None of the patients was immunoglobulin A deficient. Twelve diabetic children had a high titer of anti-tissue transglutaminase immunoglobulin A (14.4%). In four patients, biopsy was in favor of celiac disease (4.8%).(14)

Greco D & others conduct a study published in 2013 . The aim of this study was to assess the prevalence of celiac disease in patients with type 1 diabetes in western Sicily (Italy).
The records of 492 consecutive patients with type 1 diabetes mellitus referred in a period of 5 years were analyzed. During the period of the survey, out of 492 patients with type 1 diabetes, 22 (4.5 %) had a previous diagnosis of celiac disease. There were 14 females and 8 males; these patients showed a mean age of 13 years at diabetes onset. Diagnosis of celiac disease was often simultaneous or subsequent to that of diabetes.(15)

In a multicenter cohort study conducted in 25 Italian centers for childhood diabetes in 2004. Yearly screening for celiac disease was performed using IgA/IgG anti-gliadin and IgA anti-endomysium antibodies.
Of the 4,322 children and adolescents (age 11.8 +/- 4.2 years) identified with type 1 diabetes, biopsy-confirmed celiac disease was diagnosed in 292 (prevalence 6.8%, , with a higher risk seen in girls than in boys. In 89% of these, diabetes was diagnosed before celiac disease. In logistic regression analyses, being younger at onset of diabetes, being female, and having a diagnosis of a thyroid disorder were independently associated with the risk of having diabetes and celiac disease. (16)

A 6-year prospective longitudinal study conducted in Milan (Italy) in 2002.We prospectively studied, by repeated serologic screening, 274 consecutive patients at the onset of type 1 diabetes (age [mean +/- standard deviation]: 8.28 +/- 4.65 years) for 6 subsequent years. One patient had a diagnosis of celiac disease before the onset of diabetes. The immunoglobulin A-antiendomysium antibody test was selected as the screening test; patients with positive results (++ or +++) or with 2 consecutive weak positive tests (+) were considered appropriate for the jejunal biopsy.
At diabetes onset, 15 (5.5%) of 273 patients tested positive with the antiendomysium test; jejunal biopsy was performed in 10, and celiac disease was diagnosed in 9. The prevalence of biopsy-confirmed celiac disease at the manifestation of diabetes was 3.6% (10 of 274 patients). Twelve more patients with a negative antiendomysium antibody test at diabetes onset tested positive during the follow-up within 4 years; 10 of them had biopsies performed, and 7 had celiac disease. Therefore, the overall prevalence of biopsy-confirmed celiac disease in the entire cohort of patients was 6.2%. The age at diabetes onset in patients with and without celiac disease was not different (7.88 +/- 5.69 vs 8.3 +/- 4.58 years). The majority of cases of celiac disease were asymptomatic in their presentation, and no signs of overt malnutrition were documented.(17)

In another study in 2007 in London, UK .All patients with T1DM attending a pediatric diabetes clinic, were screened for celiac disease by serological testing for celiac antibodies (antiendomysial and either/both tissue transglutaminase and antigliadin). Antibody positive patients were reviewed and their presenting symptoms, tissue biopsy result and coexisting morbidities investigated.
Of the 113 patients with T1DM, 7 (6.2%) tested antibody positive. Jejunal biopsy confirmed celiac disease in 5 of the 7 (4.4%) patients. Celiac disease presented atypically or silently in the majority of cases with an unpredictable interval between diagnosis of diabetes and celiac disease presentation. two suffered other autoimmune diseases.(18)

Retrospective cohort study published in 2007 in France .950 children with type 1 diabetes seen between 1994 and 2001. Antibodies to gliadin, reticulin, endomysium and transglutaminase were looked for one to seven times in each patient.
Fifteen patients (1.6%) had biopsy-confirmed celiac disease. Symptoms led to the diagnosis in six patients (mean age, 7 years) and screening tests in nine patients (mean age, 11 years). Anti-endomysium antibodies were consistently positive.Anti-endomysium antibody seroconversion was seen in two patients, 2 and 6 years, respectively, after the diagnosis of diabetes. In another patient, the biopsy became abnormal 6 years after the first positive anti-endomysium antibody test (latent form). (19)

Arató A1& others publish a study in 2003. was designed to evaluate the frequency of coeliac disease among Hungarian diabetic children. A total of 205 diabetic children (age range 2.0-17.0 years, median 11.6 years) were screened for coeliac disease by determination of IgA-endomysium (EMA) antibodies. In the positive cases, a jejunal biopsy was performed . IgA-EMA was positive in 24 cases, 17 of them (8.3% of all diabetic children) had a subtotal villous atrophy and thus coeliac disease was diagnosed. Of the remaining seven patients with positive EMA but normal villous structure, five (2.4%) had elevated number of epithelial gamma/delta T-cells, indicating probable latent coeliac disease.(20)

In a population-based study in 2001. was conducted to determine the prevalence of coeliac disease (CD) in 106 Danish children (age 2-18 y) with type I diabetes mellitus compared with 106 age- and sex-matched healthy controls. Serum samples were analysed for immunoglobulin A (IgA) and IgG gliadin antibodies by enzyme-linked immunosorbent assay (ELISA), for IgA endomysium antibodies (EMA) by immunofluorescence and for IgA tissue transglutaminase antibodies (tTGA) by ELISA. None of the controls had EMA or tTGA. Two diabetics previously diagnosed with CD were antibody negative on a gluten-free diet. Ten diabetics had both EMA and tTGA. Intestinal biopsy was performed in nine of them. All biopsies showed a histological picture of partial or total villous atrophy confirming the diagnosis of CD .the over all prevalence of CD was10.4%. Diabetics with CD were significantly younger ($p = 0.026$). had an earlier onset of diabetes ($p = 0.005$).(21)

In 2010.a study conducted in Serbia to determine the prevalence of Celiac disease in children and adolescents with type 1 diabetes.
One hundred and twenty-one patients (70 girls, 51 boys; mean age, 10.8 years) with T1DM (mean duration of diabetes, 3.4 years) and 125 control group participants (75 girls, 50 boys; mean age, 10.4 years) were tested for CD on tissue transglutaminase antibodies (tTG). In seven serologically positive T1DM patients endoscopic small bowel biopsies were taken and examined on histopathology.
Nine patients with T1DM were positive on IgA tTG antibodies. In seven of them small bowel biopsy was performed, and all were proven to have CD on histopathology. The prevalence of biopsy-proven CD in children and adolescents with T1DM was significantly higher in the study group compared to controls (5.79%. vs 0.8%, $P < 0.05$).(22)

Uibo O1& others conduct a study in2010.the study aimed to determine the prevalence and characteristics of celiac disease in children with type 1 diabetes in Estonia.
Altogether, 271 patients with diabetes were studied over 12 years (1995-2006): 122 at diagnosis and 149 patients 0.1-14.8 years after diagnosis. In addition, 73 patients were followed up over 1-6 years. Immunoglobulin A type endomysium and tissue transglutaminase antibodies were determined. Patients with antibodies and/or with celiac-disease-related symptoms were invited for a small-intestinal biopsy.
At the primary screening, celiac disease was histologically confirmed in nine patients (all without symptoms), that is, in 3.3% (95% confidence interval: 1.63-6.42) of type 1 diabetes cases. At follow up, celiac disease was additionally detected in two (2.7%) of 73 diabetic patients, that is, in 0.016 (95% confidence interval: 0-0.072) celiac disease cases per follow-up year.(23)

Another study in 2013. was conducted to estimate the prevalence of celiac disease (CD) in children and adolescents with type 1 diabetes mellitus (T1DM) treated in the Children's Division of Endocrinology, at the Universidade Federal de Minas Gerais Hospital das Clínicas in Portugal .
Children and adolescents diagnosed with T1DM, aged 0 to 18 year, were included in this study performed from March 1999 to April 2009. All patients were screened for CD at their first visit and, again, annually. The investigation was performed through the measurement of IgA (AGAA) and IgG (AGAG) antigliadin antibodies. Patients with values of AGAA and/or AGAG above two times the cutoff mark undertook intestinal biopsy.
A group of 21 patients were excluded from the initial total of 384 patients. Out of the remaining, 50 patients had positive serology and 29 underwent intestinal biopsy. The prevalence index was 3.1%.(24)

In 2001 in British Columbia (Canda) .prospective study conducted to establish the prevalence of celiac disease (CD) in children with type 1 diabetes.
Two hundred thirty-three children with type 1 diabetes were screened for CD using immunoglobulin A endomysium antibody (EmA), and the novel immunoglobulin A tissue transglutaminase (tTG) antibody. Those children with positive results were offered small bowel biopsy.
At least 14 new cases of CD were detected in addition to four known cases, yielding an overall biopsy-confirmed prevalence of CD of 7.7% (18 of 233). The study confirms that CD is as prevalent in the pediatric type 1 diabetic population in British Columbia as it is in Europe. (25)

Mont-Serrat C1& others In 2008 conduct a study. this study was performed to determine the prevalence of celiac disease in children and adolescents with type 1 diabetes mellitus (DM1) in attendance in InstitutoEstadual de Diabetes e Endocrinologia Luiz Capriglione (IEDE) (Brazil).
Blood samples were analyzed in 120 children and adolescents with DM1 from IEDE Diabetes Clinic for the IgA antitissue-transglutaminase antibody and dosage of the seric IgA. Those with positive serology were guided for upper endoscopy with small-bowel biopsy to confirm the celiac disease.
The antibody was positive in 3 of the 120 patients. The small-bowel biopsy was confirmatory in all of the positive patients, leading to a prevalence of celiac disease of 2.5% in the studied group.(26)

In another study in 2005.was conducted to determine the prevalence of CD in Brazilian children and adolescents with DM 1.
One hundred and four children and adolescents with DM 1 (52 males and 52 females; age range 22 months - 19 years) and 105 age and gender-matched control participants were screened for CD using the IgA anti-endomysial antibody test (IgA-EmA) and total serum IgA. A small bowel biopsy was performed in all patients with positive IgA-EmA.
Nine of 104 diabetic patients (8.7%) had a positive IgA-EmA. Biopsies were normal in four patients, two had partial or subtotal villous atrophy with elevated intraepithelial lymphocyte (IEL) counts, and three showed partial villous atrophy but with IEL counts under the maximum limit adopted (40 IEL/100 enterocytes). EmA-IgA positive patients had mild, non-specific gastrointestinal complaints including dyspepsia, abdominal pain, flatulence and constipation. All control participants had negative results for IgA-EmA.
The prevalence of CD in a group of Brazilian pediatric DM 1 patients was at least 4.8%.(27)

In 2012. a clinic-based observational cohort study of 4379 people aged ≤ 18 years (49% male) between 1990 and 2009 from Sydney, Australia. Screening for coeliac disease was performed at diagnosis and 1-2 yearly using anti-endomysial and/or anti-tissue transglutaminase immunoglobulin A (IgA) antibodies. Coeliac disease was diagnosed by small bowel biopsy based on Marsh score ≥ III.
Coeliac disease was confirmed by biopsy in 185; of these, 61 (33%) were endomysial or tissue transglutaminase IgA antibody-positive at diabetes diagnosis. Mean age at diabetes onset was 6.6 ± 4.0 vs. 8.4 ± 4.1 years in those without coeliac disease ($P < 0.001$). Mean incidence was 7.7 per 1000 person years (95% CI 6.6-8.9) over 20 years. Incidence was higher in children aged < 5 years at diabetes diagnosis (10.4 per 1000 person years) vs. ≥ 5 years (6.4 per 1000), incidence rate ratio 1.6 (95% CI 1.2-2.2, $P = 0.002$). Coeliac disease was diagnosed after 2, 5 and 10 years of diabetes in 45, 78 and 94% of cases, respectively. Median time to coeliac disease diagnosis was longer in children aged < 5 years at diabetes onset (3.3 years) compared with older children (0.7 years, $P < 0.001$).(28)

In one study in 2011. was conducted to define the prevalence of thyroid autoimmune disease in Libyan patients with type 1 diabetes mellitus (T1DM.) Blood samples were collected from 218 patients with T1DM who are followed by the Pediatric Department, Tripoli Medical Center, Libya. All sera were analyzed in Italy (Laboratory of Immunopathology and Allergy, Udine). The patients were composed of 123 females (56.4%) and 95 males (43.6%), mean age 12.2□±□4.6 years (range 2.1-24.5 years), mean duration of diabetes 4.7□±□4.0 years (range 0.1-17.5 years). Sera were tested for anti-thyroperoxidase (TPO) and anti-thyroglobulin antibodies (TG). TSH and FT4 concentrations were measured in all subjects. GAD, IA-2 was also measured. Of the diabetic children, 23.4% were positive for anti-microsomal peroxidase antibodies (TPO-Ab) and 7.8% for antithyroglobulin antibodies (TG-Ab); whereas 6.9% of the patients were positive for both TPO-Ab and TG-Ab. Of the T1DM patients who were positive for TPO-Ab, 66.6% were females. The majority (57%) of the patients who were positive for TPO had diabetes for longer than 5 years. Five patients (2.3%) had evidence of subclinical hypothyroidism whereas two patients (0.9%) had overt hypothyroidism. Two patients had subclinical hyperthyroidism and two (0.9%) had overt hyperthyroidism. Interestingly, 16.2% of patients were positive for both thyroid and pancreatic antibodies.(29)

Cardoso C & others conduct a study in Nigeria in 1995. The aim of this study was determined thyroid function and the prevalence of thyroid autoimmunity in IDDM Africans. The results are compared with those of a nondiabetic group and a group with non-insulin-dependent diabetes mellitus (NIDDM). Thyroid hormone levels were significantly lower in IDDM patients than in the control population and the NIDDM population. Subclinical hypothyroidism was present in 21% of the 28 IDDM patients. One patient was hypothyroid and another hyperthyroid. Of the 60 NIDDM patients, 5 (8.3%) had subclinical hypothyroidism. Forty-six percent of the IDDM patients had significant levels of serum thyroid autoantibodies (TAAB). This was significantly higher than the 1.4% and 1.7%, respectively, in the controls and NIDDMs. Presence of TAAB in the patients was strongly associated with thyroid dysfunction, female preponderance, and duration of diabetes mellitus. (30)

Radaideh A1& others conduct a study published in 2003 . carried out at the National Center for Diabetes, Endocrinology and Genetics, Jordan University, Amman, Jordan between 2000 and 2001.
Seventy-nine type 1 diabetic patients were recruited in the study, and underwent complete investigations for thyroid function, which included free thyroxine, free tri-iodothyronine, and thyroid stimulating hormone, of those only 64 patients had performed thyroid autoantibodies (TAb); anti- thyroid peroxidase antibodies (TPOAb) or antimicrosomal antibodies and thyroglobulin antibodies (TgAb). They were compared with 127 healthy subjects matched for sex and age.
In the diabetic group, 7 cases (8.9%) of thyroid dysfunction were detected, 4 of these were diagnosed as subclinical hypothyroidism, whereas the other 3 had overt hypothyroidism and were on thyroxine replacement therapy. In the control group, 6 (4.7%) subjects were diagnosed as subclinical hyperthyroidism. There was a significant difference in thyroid function variables between diabetics and controls. Among type 1 diabetic patients, 7 (9.2%) had thyroid autoantibodies, 5 with positive TPOAb only and 2 with positive TAb; TPOAb or antimicrosomal antibodies and TgAb; compared with 8 (6.3%) in the control group, 4 with positive TPOAb only and 4 with positive TAb; TPOAb or antimicrosomal antibodies and TgAb P=0.68.(31)

A study was conducted in 2011 in Isfahan ,Iran.One hundred patients with T1DM who were referred to Isfahan Endocrine and Metabolism Research Center and 184 healthy schoolchildren matched for age and sex were included. They were examined for goiter by two endocrinologists. Thyroid function test and serum thyroid antibodies (anti-TPO Ab and anti-Tg Ab) were measured. The prevalence of subclinical hypothyroidism was high in both groups (18%). T1DM patients had lower frequency of goiter (21% vs. 38%, P=0.001), and higher prevalence of positive AIT (22% vs. 8%, P=0.001), anti-TPO Ab positivity (19.3% vs. 5.3%, P=0.000), and anti-Tg Ab (11.1% vs. 6.4%, P=0.1) in comparison with the control group.(32)

In a study done in Regional Children's Hospital, Kielce, Poland in 2011. This study included 382 children, who in the years 2001 to 2010 were diagnosed with type 1 diabetes. The concentrations of antibodies against thyroid peroxidase (anti- TPO), TSH and FT4 were measured and thyroid ultrasound examinations were performed. Children who had not initially shown the presence of anti-TPO had the test repeated at yearly intervals for 2-8 years. At the time of diagnosis of diabetes, elevated anti-TPO titres were found in 14.4% of patients, more often in girls than in boys, $p<0.01$. Children with a positive anti-TPO titre were on average older than those whose anti-TPO levels were within the normal range, $p<0.05$. The incidence of elevated titers of anti-TPO increased with age, 20,5% of children above 10 years old had positive anti-TPO, compared to 8.3% of children less than 10 years old, $p <0.001$. At the time of the onset of diabetes, hypothyroidism was diagnosed in 14.5% of children with elevated anti-TPO, and in 2.1% of the whole group. 4.5% of patients whose levels of anti-TPO were initially normal, within the next 1-8 years had positive antibody titers.(33)

Roldán MB1& others conduct a study in Madrid, Spain in 1999. Two hundred and four diabetic patients, less than 20 years old, were studied in order to diagnose thyroid autoimmunity. The prevalence of thyroid autoimmune disorders was 17.6% and, of those, chronic autoimmunethyroiditis was the most frequent. Microsomal autoantibodies correlated more accurately with the presence of chronic autoimmune thyroiditis than thyroglobulin autoantibodies. The thyroid status of most of the patients with positive markers was euthyroidism (77%), but subclinical hypothyroidism (11%), overt hypothyroidism (3%), subclinical hyperthyroidism (3%) and overt hyperthyroidism (6%) were also present. Autoimmune thyroid disorders were the most prevalent immunological processes affecting diabetic patients.(34)

Another study in 2009.T1DM patients (493 pts., 268 males and 225 females) treated in the Juvenile Diabetes Tuscany Regional Centre at Meyer's Children Hospital (Italy) were enrolled to determine TSH, fT4, thyroid autoantibodies levels and to undergo thyroid ultrasound. Anamnestic data about T1DM onset, AIT onset, time frame between T1DM and AIT onsets were studied.
In the screened population 11.7% of patients presented with increased thyroid autoantibodies, and 63.6% of them showed positive thyroid ultrasound. AIT was significantly more frequent in females compared to males ($p < 0.01$). The mean age at AIT onset was 11.17 +/- 3.29 years (range 4.99-20, 30) and AIT onset before 12 yrs. of age was found in 54.5% of cases; The mean time between T1DM and AIT onset was 2.46 +/- 3.41 years (range 0-13, 41). The subgroup with increased thyroid autoantibodies was not statistically different from the whole population with regard to TDM1 duration and mean age at onset.(35)

In a longitudinal study was published in 2003 . analyzed the incidence of thyroid dysfunction over time in a cohort of 58 patients (26 men and 32 women) enrolled in the Diabetes Control and Complications Trial at the University of Tennessee Health Science Center (USA) in 1983 and prospectively followed for 18 years. Patients underwent measurement of thyroid function tests (thyroid-stimulating hormone [TSH], thyroxine, and triiodothyronine) every year and thyroid peroxidase (TPO) antibodies at 4-year intervals.

A total of 18 patients had hypothyroidism, and 1 patient experienced transient hyperthyroidism. Two subjects developed hypothyroidism 7 and 18 years before the development of diabetes and were excluded from the analysis. The mean age of diagnosis was 19 +/- 2 years for type 1 diabetes and 29 +/- 3 years for hypothyroidism. Hypothyroidism was more common in female (41%) than in male (19%) subjects and in patients with positive TPO antibodies. Patients who were TPO positive were 17.91 times as likely to develop hypothyroidism as patients who were TPO negative (95% CI 3.89-82.54). (36)

Comparison studies of prevalence of Auto-immune Disorders

Ref.	Study	Year	NO.	Thyroid Disorders	Celiac Disease	Addison Disease
(2)	**India** (Kota SK1& others)	2012	260	21 patients had hypothyroidism (8%) & 4 patients had hyperthyroidism (1.5%)	18 patients (7%)	2 patients (0.7%)
(3)	**Turkey** (Soyucen E1& others)	2010	33	15.4% had positive TPOAb&6% had positive TG-Ab	9.1% had positive EMA IgA & 3% ad positive antiglidin IgA	
(4)	**Germany** (Fröhlich-Reiterer EE1& others)	2008	31104	15% had positive thyroid antibodies	11% had antibodies for celiac disease	
(5)	**Spain** (López Medina JAI& others)	2004	63	11.1% had positive anti-TPOAb -9.5% had positive TG-Ab & 4.8% had positive thyroid stimulating immunoglobulin	3.1% had positive EMA IgA	
(6)	**Poland** (Szypowska A1& others)	2008	260	29% had positive thyroid antibodies& 23% require treatment with thyroxin	10% had positive EMA & in 9% CD proved by biopsy	
(7)	**Portugal** (Nunes RC1& others)	2009	40	25% had positive anti-TPOAb		Anti-21OH positive in 7.5% None with adrenal dysfunction
(8)	**USA** (Triolo TM1& others)	2011	491	122 (24.8%) had positive TPOAb&15 of 122 had autoimmune thyroid disease	57 (11.6%) had positive tTG& 14 (24.6%) had CD	Anti-21OH positive in 5 patients (1.0%) of whom 1 had Addison disease

comparison studies of prevalence of celiac disease

Ref.	Study	Year	NO.	Screen	positive serology	NO. biopsied	positive biopsy
(9)	**Libya** (Ashabani A1& others)	**2003**	234	tTG +AGA+ARA	50 (21.3%)	50	24 (10.3%)
(10)	**Tunisia** (Mankaï A1& others)	**2007**	205	EMA	17 (8.3%)	13	11 (5.3%)
(11)	**Saudi Arabia** (Saadah OI1& others)	**2011**	430	tTG	91 (21.2%)		48 (11.2%)
(12)	**Saudi Arabia** (Al-Hussaini A1& others)	**2012**	106	tTG +EMA+total IgA	19 (17.9%)	12	12 (11.3%)
(13)	**Oman** (Al-Sinani S1 & others)	**June 2011-may 2012**	93	tTG +EMA+total IgA	16 (17%)	14	5 (5.5%)
(14)	**South of Iran** (Honar N1 &others)	**2013**	83	tTG +total IgA	12 (14.4%)		4 (4.8%)
(15)	**Italy** (Greco D&others)	**2013**	492				22 (4.5%)
(16)	**Italy** (Cerutti F1 & others)	**2004**	4322	tTG +AGA			292 (6.8%)
(17)	**Italy** (Barera G1& others)	**2002**	274	EMA	27(9.8%)	20	16(+1) (6.2%)
(18)	**UK** (Goh C1, Banerjee K)	**2007**	113	tTG +EMA+AGA	7 (6.2%)		5 (4.4%)
(19)	**France** (Poulain C1 & others)	**2007**	950	tTG +EMA+AGA+ARA	9 (1.0%)		15(1.6%)
(20)	**Hungaria** (Arató A1& others)	**2003**	205	EMA	24 (11.7%)		17 (8.3%)
(21)	**Denmark** (Hansen D1& others)	**2001**	106	tTG +EMA+AGA	10 (9.4%)	9	9 (+2) (10.3%)
(22)	**Serbia** (Djurić Z1& others)	**2010**	121	tTG	9 (7.4%)	7	7 (5.79%)
(23)	**Estonia** (Uibo O1& others)	**2010**	344	tTG +EMA			11 (4.1%)
(24)	**Portugal** (Gonçalves CB1 & others)	**2013**	363	AGA	50 (13.7%)	29	3.1%
(25)	**Canada** (Gillett PM1 & others)	**2001**	233	tTG +EMA			14 (+4) (7.7%)
(26)	**Brazil** (Mont-Serrat C1& others)	**2008**	120	tTG+total IgA	3 (2.5%)	3	3 (2.5%)
(27)	**Brazil** (Baptista ML1& others)	**2005**	104	EMA +total IgA	9 (8.7%)	9	5 (4.8%)
(28)	**Australia** (Pham-Short A1&others)	**2012**	4379	tTG +EMA			185 (4.2%)

Comparison studies of prevalence of Thyroid disorders

Ref.	Study	Year	TPO-Ab (+)	TG-Ab (+)	Both TPO-Ab &TG-Ab (+)	Hypothyroidism	Hyperthyroidism
(29)	**Libya** (Ghawil M1&others)	2011	23.4%	7.8%	6.9%	5 patients (2.3%)had subclinical&2 patients (0.9%)had overt hypothyroidism	2 patients (0.9%)had subclinical& 2 patients (0.9%) had overt hyperthyroidism
(30)	**Nigeria** (Cardoso C& others)	1995	46%			21% had subclinical hypothyroidism& 1 patient had overt hypothyroidism	1 patient had overt hyperthyroidism
(31)	**Jordan** (Radaideh A1& others)	2003	5cases		2cases	7 patients (8.9%) had hypothyroidism 4 patients had subclinical hypothyroidism & 3 patients had overt hypothyroidism	
(32)	**Iran** (Ardestani SK1& others)	2011	19.3%	11.1%		18% had subclinical hypothyroidism	
(33)	**Poland** (Piątkowska E1, Szalecki M)	2011	14.4%			2.1% had hypothyroidism	
(34)	**Spain** (Roldán MB1& others)	1999			17.6%	11% had subclinical hypothyroidism & 3% had overt hypothyroidism	3% had subclinical hyperthyroidism& 6% had overt hyperthyroidism
(35)	**Italy** (Lenzi L1& others)	2009			11.7%		
(36)	**USA** (Tennessee) (Umpierrez GE1& others)	2003				18 patients had hypothyroidism	1 patient had transient hyperthyroidism

4.AIM OF THE STUDY

The aim of this study was to estimate the % percentage of common Autoimmune disorders in patients with type 1D.M. from north eastern part of Libya.

5. P A T I E N T S AND M E T H O D S

This study was conducted in Benghazi Children Hospital ,which is main referral hospital of north eastern part of Libya from Tobruq to Ejdabia.

Data collected from Diabetic & Endocrine clinic ,a retrospective study including all Libyan type 1 diabetic children between 1-15 years of age from January 2002 to December 2012 referred to Diabetic clinic.

From 551 files,164 files were excluded from our study because of poor registration , incomplete information & loss follow up of patients.

files of all cases reviewed for (Name ,age & date of birth, sex, residence ,date & age at diagnosis of type 1 D.M., mode of presentation of type 1 D.M., family history of type 1 or type 2 D.M. ,family history of auto-immune disorders, HbA1C, TFT , development of auto-immune disorders ,date & age of development of autoimmune disorders).

We exclude all non- Libyan, type 2D.M patients& age more than 15 years from this study.

Data was statistically analyzed using statistical packages of social sciences (SPSS).
Chi square was calculated & P value. P value less than 0.05 was considered significant.

6. R E S U L T S

A total of (387) type 1 Diabetic patients included in this study.

6.1 Demographic figures:

6.1.1 Age:

Their age ranged from 1 to 15 years with mean of 8 years**.**

6.1.2 Gender:

- 54.3% were female .
- 45.7 % were male .
- M : F ratio (1 : 1.2)

Table 1: Number of Diabetic patients according to gender

Gender	NO. of patients	%
Male	177	45.7%
Female	210	54.3%
Total	387	100%

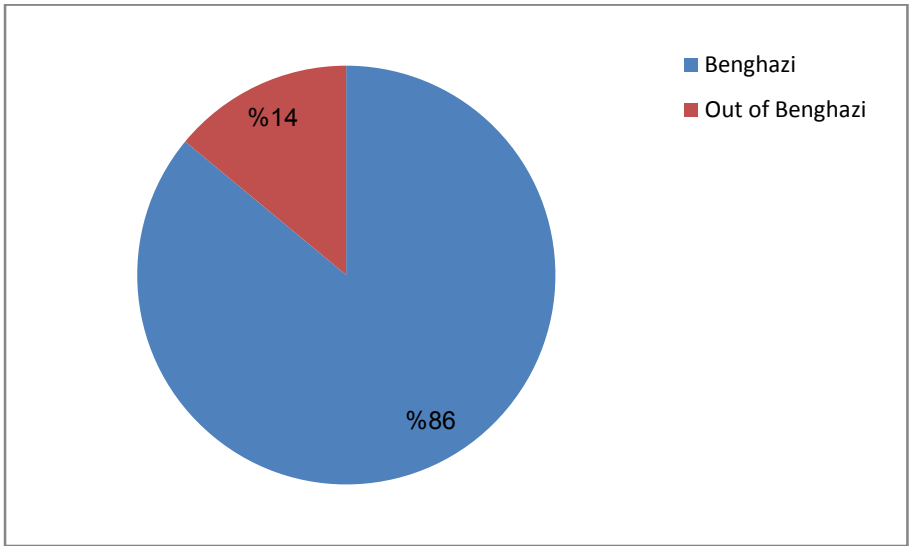
6.1.3 Residence:

- (86.3 %) were from Benghazi.
- (13.7%) out of Benghazi.

Table 2: Number of Diabetic patients according to Residence

Area of residence	NO. of patients	%
Benghazi	334	86.3%
Marj	20	5.2%
Ejdabia	11	2.8%
Derna	3	0.8%
Baida	4	1%
Briqa	5	1.3%
Raslanof	5	1.3%
Kufra	3	0.8%
Jalo	2	0.5%
Total	387	100%

Figure (1) Distribution of Diabetic patients according to Residence



6.1.4 Mode of presentation of type 1 D.M. :

Table 3: Number of Diabetic patients according to mode of presentation of type 1 D.M.

Presentation	NO. of patients	%
Diabetic Keto Acidosis	155	40.1%
Symptomatic hyperglycemia	230	59.4%
Not reported	2	0.5%
Total	387	100%

6.1.5 Family history of Diabetes mellitus :

- 51.4% had Positive family historyof D.M. (type 1 or type 2 D.M.)

Table 4: Number of Diabetic patients according to Family history of Diabetes mellitus

Family history	NO. of patients	%
Positive family history	199	51.4%
Negative family history	188	48.6%
Total	387	100%

6.1.6 Family history of Autoimmune Disorders:

- 10.3% had Positive family history of Autoimmune Disorders.

Table 5: Number of Diabetic patients according to Family history of Autoimmune disorders.

Family history	NO. of patients	%
Positive family history	40	10.3%
Negative family history	347	89.7%
Total	387	100%

6.1.7 HbA1C%:

- Mean value at time of diagnosis of D.M. was 10.8% .
- No association between control of HbA1C% & developing of Autoimmune Disorders.

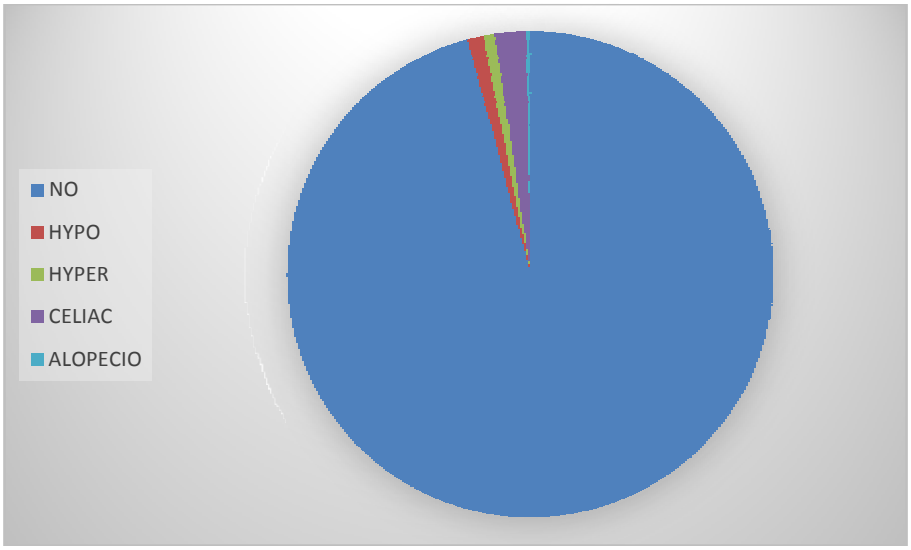
6.1.8presence of Autoimmune disorders:

- 4.2% of patients with type 1 D.M. had autoimmune disorders.

Table 6: Number of Diabetic patients according to presence of Autoimmune disorders.

Diagnosis	NO. of patients	%
No autoimmune disorder	371	95.8%
Hypothyroidism	5	1.3%
Hyperthyroidism	2	0.5%
Celiac disease	8	2.1%
Alopecia	1	0.3%
Total	387	100%

Figure (2) Distribution of cases according to presence of autoimmune disorders



6.1.9 Age:

- Age at diagnosis of autoimmune disorder range from 1 to 18.3 years with mean9.8 years.

6.1.10 Relationship between time of diagnosis of D.M. & Autoimmune Disorders:

- Diabetes preceding autoimmune disorders in 50% of cases.
- Diagnosis at the same time in 37.5%.
- Autoimmune disorders preceding diabetes in 12.5%.

Table 7: Temporal relationship between Diabetes and Autoimmune Disorders.

Temporal relationship	NO. of patients	%
At the same time	6	37.5%
Autoimmune disorder preceding	2	12.5%
Diabetes preceding	8	50%
Total	16	100%

6.1.11 Thyroid disorders:

- TFT was done in 353 from 387 type 1 Diabetic patients.
- 5 cases had hypothyroidism, 3 cases were male & 2 cases were female.
- 1 case of hypothyroidism was Down syndrome.
- TSH range from 6.6 to 60 with mean 22 MIU/L
- 2 cases had hyperthyroidism with M:F(1:1).
- No auto-antibodies (TPO-Ab & TG-Ab) done in patients with thyroid disorders.

Table 8: Number of Diabetic patients according to thyroid function test result.

Test result	NO. of patients	%	Valid %
Normal	346	89.4%	98%
Hypothyroidism	5	1.3%	1.4%
Hyperthyroidism	2	0.5%	0.6%
No result	34	8.8%	
Total	387	100%	100%

6.1.12 celiac disease:

- Celiac serology was done in 230 from 387 type 1 Diabetic patients.
- In 12 patients TTG done only & had positive result.
- In 2 patients anti- endomysial anti-bodies done only & had positive result.
- 6 patients had both positive TTG & anti-endomysial anti-bodies.
- The % of positive serology was 8.7% (suspected to be celiac disease)
- Duodenal biopsy done in 12 patients, 8 patients had biopsy proven celiac disease(3.5%), 7 show total villous atrophy & 1 show subtotal villous atrophy.
- 3 patients had normal histology, sample was inadequate in one patient.
- The remaining 8 patients refused doing intestinal biopsy.
- Patients with biopsy proven celiac disease ,their age range from 3 to 14 years with mean 7.8 years.
- All Patients with biopsy proven celiac disease were female.
- 6 patients from Benghazi& 2 patients out of Benghazi.
- 3 patients had positive family history of Autoimmune disorders.
- 3 cases diagnosed at same time of diagnosis of type 1 D.M., 5 cases diagnosed after diagnosis of type 1 D.M .(their diabetes duration was less than 5 years)
- 2 cases were asymptomatic, 3 cases had abdominal pain ,distension& diarrhea, 1 patient was anemic , 1 patient was under weight& anemic& last one was under weight& had abdominal distension.

Table9 : Number of Diabetic patients according to celiacserology result.

Test result	NO. of patients	%	Valid %
Normal	210	54.3%	91.3%
Positive serology	20	5.2%	8.7%
No result	157	40.5%	
Total	387	100%	100%

1 case diagnosed as alopecia totalis. was male , his age 1 year . diagnosed at same time of diagnosis of type 1 D.M.

No cases reported to have Addison disease or other autoimmune disorders rather than mentioned.

6.2 statistical analysis:

6.2.1 Gender of patients with autoimmune disorders:

- 11 cases were female.
- 5 cases were male.

Table 10: Distribution of autoimmune disorders according to gender.

Gender of the patient	Occurrence of autoimmune disorders		
	Without autoimmune disorders	With autoimmune disorders	Total
Male	172	5	177
	97.2%	2.8%	100.0%
Female	199	11	210
	94.8%	5.2%	100.0%
Total	371	16	387
	95.9%	4.1%	100.0%

Results of statistical analysis :distribution of autoimmune disorders according to gender.

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.411	1	.235

No significant statistical influence of sex of diabetic child on the occurrence of Autoimmune disorders.

6.2.2Age of patients with autoimmune disorders:

- 3 cases under five.
- 13cases were at school age.

Table 11: occurrence of autoimmune disorders according to age at diagnosis of diabetes.

Age category	Occurrence of autoimmune disorders		
	Without autoimmune disorders	With autoimmune disorders	Total
Under Five	76	3	79
	96.2%	3.8%	100.0%
School age	295	13	308
	95.8%	4.2%	100.0%
Total	371	16	387
	95.9%	4.1%	100.0%

Results of statistical analysis : occurrence of autoimmune disorders according to age at diagnosis of diabetes.

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.028	1	.866

No significant statistical influence of diabetes onset on the occurrence of Autoimmune disorders.

6.2.3Residence of patients with autoimmune disorders:

- 12 cases from Benghazi.
- 4 cases out of Benghazi.

Table 12: Occurrence of autoimmune disorders according to area of residence.

	Occurrence of autoimmune disorders		Total
	Without autoimmune disorders	With autoimmune disorders	
Benghazi	322	12	334
	96.4%	3.6%	100.0%
Out of Benghazi	49	4	53
	92.5%	7.5%	100.0%
Total	371	16	387
	95.9%	4.1%	100.0%

Results of statistical analysis : occurrence of autoimmune disorders according to area of residence.

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.805	1	0.179

No significant influence of residence of diabetic child on the occurrence of Autoimmune disorders.

6.2.4 Family history of D.M. in patients with autoimmune disorders:

- 7 cases had positive family history of diabetes (type 1 or type 2).

Table13: Occurrence of autoimmune disorders according to family history of diabetes.

	Occurrence of autoimmune disorders		Total
	Without autoimmune disorders	With autoimmune disorders	
Positive family history	192	7	199
	96.5%	3.5%	100.0%
Negative family history	179	9	188
	95.2%	4.8%	100.0%
Total	371	16	387
	95.9%	4.1%	100.0%

Results of statistical analysis : occurrence of autoimmune disorders according to family history of diabetes.

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.393	1	.531

No significant influence of family history of diabetes in diabetic child on the occurrence of autoimmune disorders.

6.2.5 Family history of autoimmune disorders in patients with autoimmune disorders:

- 5 cases had positive family history of autoimmune disorders.

Table14: Occurrence of autoimmune disorders according to family history of autoimmune disorders

	Occurrence of autoimmune disorders		
	Without autoimmune disorders	With autoimmune disorders	Total
Positive family history	35	5	40
	87.5%	12.5%	100.0%
Negative family history	336	11	347
	96.8%	3.2%	100.0%
Total	371	16	387
	95.9%	4.1%	100.0%

Results of statistical analysis : autoimmune disorders according to family history of autoimmune disorders.

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	7.877	1	.005

A very Significant association were verified between family history of autoimmune disorders in diabetic child and developing of autoimmune disorders in the same child.

6.2.6HbA1C & autoimmune disorders:

- HbA1C of more than 8 % found in 2 cases with autoimmune disorders.

Table15 : Control of diabetes & occurrence of autoimmunedisorders.

	Occurrence of autoimmune disorders		Total
	Without autoimmune disorders	With autoimmune disorders	
8% or less	12	1	13
	92.3%	7.7%	100.0%
More than 8%	77	2	79
	97.5%	2.5%	100.0%
Total	89	3	92
	96.7%	3.3%	100.0%

Results of statistical analysis: Autoimmune disorders according to level of HbA1C.

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.942	1	.332

No Significant association were verified between control pattern of diabetes and developing of autoimmune disorder in the same child.

6.3. Thyroid disorders:

- No significant statistical influence of sex, age, residence, family history of diabetes & family history of autoimmune disorder in Diabetic child on the occurrence of thyroid disorders.

6.4 Celiac disease:

6.4.1 Gender ofpatients with celiac disease:

- 8 cases were female.

Table16: Distribution of celiac disease according to gender.

	Occurrence of celiac disease		
	No celiac disease	With celiac disease	Total
Male	177	0	177
	100.0%	0%	100.0%
Female	202	8	210
	96.2%	3.8%	100.0%
Total	379	8	387
	97.9%	2.1%	100.0%

Results of statistical analysis :distribution of celiac disease according to gender

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6.885	1	.009

There is a very Significant statistical influence of sex of diabetic child on the occurrence of celiac disease.

6.4.2 Family history of autoimmune disorders in patients with celiac disease:

- 3 cases had positive family history of Autoimmune disorders.

Table 17: occurrence of celiac disease according to family history of Autoimmune disorders

	Occurrence of celiac disease		Total
	No celiac disease	With celiac disease	
Positive family history	37	3	40
	92.5%	7.5%	100.0%
Negative family history	342	5	347
	98.6%	1.4%	100.0%
Total	379	8	387
	97.9%	2.1%	100.0%

Results of statistical analysis : occurrence of celiac disease according to family history of autoimmune disorders.

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6.504	1	.011

A very Significant association were verified between family history of Autoimmune disorder in diabetic child and developing of celiac disease in the same child.

- No significant statistical influence of age, residence &family history of diabetes in diabetic child on the occurrence of celiac disease.

7.D I S C U S S I O N

Diabetes mellitus (DM) is a common, chronic, metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature. Type 1 DM characterized by low or absent levels of endogenously produced insulin. The onset occurs predominantly in childhood, with median age of 7 to 15 yr, but it may present at any age.
T1DM is associated with other autoimmune diseases such as thyroiditis, celiac disease, multiple sclerosis, and Addison disease.(1)

Our study which was conducted in Benghazi Children Hospital, Looked for % percentage of common autoimmune disorders in Libyan type 1 Diabetic children were diagnosed between January 2002 to December 2012. a total of 387 patients included in this study, their age ranged from 1 to 15 years with mean of 8 years, 54.3% were female &45.7 % were male With M : F ratio (1 : 1.2) & the majority (86.3%) were from Benghazi .
59.4% presented with symptomatic hyperglycemia, 40.1% presented with DKA. 51.4% had Positive family history of D.M., 10.3% had Positive family history of autoimmune disorders, Mean value of HbA1C was10.8% .

In one retrospective study conducted in Medwin hospital, in India in 2012. Among 260 patients diagnosed as T1DM, 21 (8%) had hypothyroidism, 4 (1.5%) had hyperthyroidism and eighteen patients (7%) had celiac disease, Down's syndrome present in 2 patients (0.7%).(2)
In our study , among 387 patients diagnosed as T1DM, 5 (1.4%) had hypothyroidism, 2 (0.6%) had hyperthyroidism, 1(0.3%) had alopecia and eight patients (3.5%) had celiac disease, Down's syndrome present in 1 patient (0.3%).

In one cohort study conducted on prevalence of celiac disease in Libyan children with type 1 diabetes mellitus in 2003 , the prevalence of positive serology cases was 21.3% & CD proved by biopsy in 10.3%.of diabetic children(9)

In the Tunisian study ,the prevalence of positive serology was 8.3% by anti-endomysium antibodies & the prevalence of biopsy-proven CD was 5.3% (10)

In a prospective cross-sectional study in Saudi- Arabia , the prevalence of positive serology was 17.9% used TTG,EMA & total IgA as screening tests & 12 children had biopsy proven CD 11.3%. (12)

At Sultan Qaboos University Hospital, Muscat, Oman over a period of one year (June 2011 - May 2012). Children with type 1 diabetes mellitus were prospectively screened for celiac disease, Sixteen patients had positive anti-tissue transglutaminase (17%). Five patients with positive anti-tissue transglutaminase had intestinal biopsy proven celiac disease(5.5%)(13)

A 6- year prospective longitudinal study conducted in Milan (Italy) in 2002, the overall prevalence of biopsy – confirmed celiac disease was 6.2% (17)

In UK, the prevalence of biopsy proved CD was 4.4% (18)

In France , Fifteen patients (1.6%) had biopsy-confirmed celiac disease.(20)

In Portugal, 50 patients had positive serology and 29 underwent intestinal biopsy. The prevalence index was 3.1%.(24)

In Brazil, The antibody was positive in 3 of the 120 patients. The small-bowel biopsy was confirmatory in all of the positive patients, leading to a prevalence of celiac disease of 2.5% in the studied group.(26)

In our study, the % of positive serology was 8.7% & CD proved by biopsy in 3.5% which is much less than reported in Arabic studies but close to Portugal study & higher than France & Brazil studies.

In Tunisian study ,the prevalence of biopsy-proven CD was 5.3% (11/205). It was 7.6% (7/92) in girls and 3.5% (4/113) in boys, 8 patients showed total villous atrophy, 3 patients showed a partial villous atrophy, Seventy three percent of patients with CD were asymptomatic.(10)

In a prospective cross-sectional study in Saudi- Arabia, 12 children had biopsy proven CD (11.3%). Five of 12 had gastrointestinal symptoms (42%).(12)
In a multicenter cohort study conducted in 25 Italian centers for childhood diabetes in 2004. biopsy-confirmed celiac disease was 6.8%, , with a higher risk seen in girls than in boys. In 89% of these, diabetes was diagnosed before celiac disease. (16)

In our study. 8 patients (3.5%) had biopsy-confirmed celiac disease, it was 3.5% (8/230) in female ,7 patients showed total villous atrophy, 1 patient showed a partial villous atrophy, six of 8 had gastrointestinal symptoms75% & 5 patients diagnosed CD within average 2 years of Diabetes onset.

In one study in 2011. was conducted to define the prevalence of thyroid autoimmune disease in Libyan patients with type 1 diabetes mellitus (T1DM.). Five patients (2.3%) had evidence of subclinical hypothyroidism whereas two patients (0.9%) had overt hypothyroidism. Two patients had subclinical hyperthyroidism and two (0.9%) had overt hyperthyroidism.(29)

In study published in 2003 . carried out at the National Center for Diabetes, Endocrinology and Genetics, Jordan University, Amman, Jordan between 2000 and 2001. 7 cases (8.9%) of thyroid dysfunction were detected, 4 of these were diagnosed as subclinical hypothyroidism, whereas the other 3 had overt hypothyroidism and were on thyroxine replacement therapy.(31)
In Madrid, Spain in 1999. Two hundred and four diabetic patientsless than 20 years old, were studied in order to diagnose thyroid autoimmunity. subclinical hypothyroidism (11%), overt hypothyroidism (3%), subclinical hyperthyroidism (3%) and overt hyperthyroidism (6%) were present.(34)
In a longitudinal study was published in 2003 conducted in Tennessee. A total of 18 patients had hypothyroidism, and 1 patient experienced transient hyperthyroidism. Hypothyroidism was more common in female (41%) than in male (19%).(36)

In our study,5 cases had hypothyroidism which represent (1.4%).3 cases were male & 2 cases were female, 1 cases was Down syndrome. Their age range from 13 to 18 years.
4 cases diagnosed after diagnosis of type 1 D.M.(1 to 4 years), 1 case diagnosed at same time of diagnosis of type 1 D.M.
3 cases had overt hypothyroidism and on thyroxine replacement therapy,2 cases had subclinical hypothyroidism.
In our study, 2 cases had overt hyperthyroidism which represent (0.6%).1 case was male & 1 case was female, diagnosed before diagnosis of type 1 D.M. which is much less than reported in literature.

In our study. 1 case diagnosed as alopecia totalis. was male , his age 1 year , diagnosed at same time of diagnosis of type 1 D.M.

8.Conclusion

From our study we found that :

- There is an association between type 1 D.M. & Autoimmune disorders.
- The % percentage of autoimmune disorders were 4.2%.
- The % percentage of thyroid disorders were 2% which much less than reported in literature.
- The % percentage of celiac disease was 3.5% which much less than reported in literature.
- The % percentage of alopecia totalis was 0.3%.
- There is an association between family history of Autoimmune disorders & developing of Autoimmune diseases in the same patient.
- Our limitation:

❖ large sample size of patients.
❖ Poor registration of information in the files.
❖ Lack of results of investigations in the files.
❖ Loss follow up of patients.
❖ Serological screening of CD & thyroid auto-antibodies not available in the hospital.
❖ Cases with positive serology for CD refuse doing intestinal biopsy.

9.RECOMMENDATIONS

- Periodic palpation of the thyroid gland is indicated in all diabetic children, if the gland feels firm or enlarged, serum measurements of thyroid antibodies and thyroid-stimulating hormone (TSH) should be obtained.
- Each case diagnosed as type 1 D.M. must have regular screen for thyroid disorders starting from time of diagnosis of type 1 D.M then annually& this include (TSH & free T4).
- Each case diagnosed as type 1 D.M. must have regular screen for celiac disease by serological screening, those with positive results should undergo intestinal biopsy.
- Serological screening for CD should be available in Hospital for early detection of CD .
- Each case diagnosed as type 1 D.M. must have less frequent screen for Addison disease.
- Updating the data base in Diabetic & endocrine clinic in Benghazi children hospital is highly recommended to facilitate future studies.
- Prospective study is recommended to detect the actual prevalence of Auto-immune Disorders.

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ملخص الدراسة

أهدافالدراسة:

تقديرالنسبةالمئويةلاضطراباتالمناعةالذاتية الأكثر شيوعافيالمرضىالمصابينبالنوع الأول من مرض السكريفيالجزءالشماليالشرقيمنليبيا.

المرضى و أسلوب البحث:

هيدراسةتشمل387مريضا مصابون بالنوع الأول من مرض السكريالذينتتراوحأعمارهمبين (1-15 سنة)،خلالالفترةمنيناير 2002 إلىديسمبر 2012.
أجريتالدراسةفيمستشفىبنغازيللأطفال،وهوالمستشفىالمرجعيالرئيسيفيشمال شرقليبيامنطبرقإلىاجدابيا.
البياناتالتيتمجمعها: الاسموالعمروتاريخالميلادوالجنسوالإقامةوالتاريخوالعمرعندتشخيصالنوع الأول من مرض السكري ،وطريقةالمرضمنالنوع الأول من مرض السكري،التاريخالعائليمن النوعالاول أوالنوعالثاني من مرض السكري والتاريخالعائليللاضطراباتالمناعةالذاتية،نسبةالسكر التراكمي،تحليل وظيفة الغدة الدرقية,حصول اضطراباتالمناعةالذاتيةوالتاريخوالعمر عند حصولاضطراباتالمناعةالذاتية.
تمتحليلالبياناتإحصائيا.

نتائج الدراسة:

كانت 16 حالةمن387مريضا من مرضىالسكريأصيبت باضطراباتالمناعةالذاتيةوالتيتمثل4.2٪ منجميعحالاتمرضىالسكري،كانت 8 حالاتمرضالجواف (3.5٪)، 5 حالاتقصورالغدةالدرقية (1.4٪)، 2 حالاتفرطنشاطالغدةالدرقية (0.6٪)و 1 كانتحالةثعلبة (0.3٪).

الاستنتاجات والتوصيات:

هناكعلاقةبينالنوع الأول من مرض السكري واضطراباتالمناعةالذاتية،فإنالنسبةالمئوية٪
مناضطراباتالغدةالدرقيةومرضالجوافأقلبكثيرممانشرفيالدراسات الأخرى
ونحننوصيبالفحصالمبكرللاضطراباتالمناعةالذاتيةللوقايةمنالمراضيةوالوفياتعلىالمدىالطويل.