The association between type 1 diabetes mellitus and autoimmune thyroid diseases has long been documented. Both are organ specific T-cell mediated disease, and have a similar pathogenesis, which involves T-cell infiltration resulting in dysfunction of the target organ. Moreover, two immune regulatory genes, HLA and CTLA-4, contribute to the susceptibility to both diseases (Leven and Tomer, 3002).

Type 1 diabetes and autoimmune thyroid diseases (AITDs) often coexist in the same individual and in the same family (González et al, 3002).

Autoimmune thyroid diseases (AITD) cover a large spectrum of disease from hyperthyroidism in Graves’ disease (GD) to thyroid destruction in Hashimoto’s thyroiditis (HT). In both GD and HD, autoantibodies (aAbs) specific of thyroid autoantigens, such as thyroglobulin (Tg), thyroperoxydase (TPO) and/or the TSH receptor (TSHr), are present. Besides the role of AITD marker, these antibodies could be implicated in the pathogenic mechanisms of these diseases. TSH receptor “stimulating or blocking” antibodies influence the action of TSH and may lead to a hyper- or a hypo-thyroidism (Reffubat et al, 7002).

Autoimmune thyroid disorders are the most common immunological disorders in patients with type 1 diabetes. A high prevalence of thyroid autoantibodies in children with type 1 diabetes mellitus has been found in many studies, but most of the antibody-positive diabetic patients were clinically and biochemically euthyroid.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Clinical Guidelines 3000 suggest that thyroid
function and thyroid antibody tests should be considered close to the time of diagnosis and repeated if clinical circumstances suggest the possibility of thyroid disease. The guidelines make no statement on screening of asymptomatic patients.

There is general agreement on the utility of systematic screening ofAITD in the type 1 diabetes population given its high prevalence, but procedure and frequency remain controversial (Glastras et al., 2001). Screening may improve the diagnosis of thyroid disease in an early stage and thus prevent complications and compromise of health especially growth (Jaeger et al., 2001; Kordonouri et al., 2001).

The prevalence of thyroid autoimmunity in type 1 diabetic children (in the form of positive antibodies) varies with different racial groups, age groups, sex, geographical regions and type of autoantibody measured. It is reported to range from 7% to 30%, whereas hypothyroidism has a lower prevalence of 5–1% according to most studies (Perros et al., 1996; Badman et al., 2001; Mohn et al., 2001; Hansen et al, 2001).

The aim of the present study was to detect the frequency of thyroid autoimmunity and thyroid dysfunction in a cohort of Type 1 diabetics randomly selected from the Diabetic Endocrine Metabolic Pediatric Unit at the Children's Hospital of Cairo University. Patients were included in the study as they presented to the unit. We also aimed to study possible epidemiologic risk factors, including family history of autoimmune disease, parental consanguinity, age, sex, and duration of diabetes.

We screened one hundred Type 1 diabetic children of different ages, variable diabetes duration and without prior symptoms suggestive
of thyroid disease and of unknown thyroid status, and one hundred age
and sex-matched normal children and adolescents were screened for
thyroid autoimmunity (as reflected by the presence of thyroid antibodies)
and thyroid dysfunction. Diabetic children were also screened for the
presence of celiac disease.

The diabetics included 57 females and 44 males with a female to
male ratio of 1.04 to 1. Patient ages were a mean of 10.1 ± 7.9 years
(range 1-14 years). They had a mean duration of diabetes of 7.1 ± 7.8
years and their mean height SDS was –0.1 ± 1.7 (range –5.07 to 7).
On examination, fifteen had a goiter ranging from grade I to grade III.

Laboratory screening for thyroid antibodies (anti-TG-Ab and anti-TPO-
Ab) in all revealed thyroid autoimmunity in 51 patients of the diabetic
group (71%) (TPOAb and/or TGAb) and 10 of the control group (10%).
This difference was statistically significant p valu < 0.005.

The frequency of thyroid autoimmunity in our study of children with type
1 diabetes is comparable to that reported in China and Taiwan (71,8%) (Chang et al., 3003) and in the Czech Republic (77%) (Prazny et al,
1999). However, our frequency is higher than that reported in Brazil by
Mantovani et al (3002) (74,7%), and lower than that reported by Barker
et al, (3000) (79%).

Significant titres of thyroid antibodies (anti-TG-Ab and/or anti-TPO-
Ab) were found in 19 diabetics (19%), while borderline elevation of one
or two of the 7 antibodies tested was detected in 7 patients (7%). For
the purpose of this study, and as suggested by many authors (who are
they?), subjects with borderline results for thyroid antibodies have been
considered as being positive for thyroid autoimmunity as this may represent the early stage of the autoimmune process.

The worldwide prevalence of anti-TPO antibodies in type I diabetic patients who are clinically euthyroid have been reported to vary from 7% in Germany, the Netherlands and Northern Europe (Rees, 1987, Kordonuri, 1993 and Hansen, 1997), 11% in Spain (Lopez, 1998), 14% in South Germany (Holl, 1999), 14% France (Maugendre, 1999), 11% in Turkey and Taiwan (Okten, 1999 and Chang 1999) and 7% in Iran (Moayeri 1998).

The wide range of prevalence in various reports may be due to differences in ethnic groups, geographic area, iodine intake, population size and methodology. For example, some of the studies measured antibodies after onset of puberty; others measured antibody levels only when suspicious symptoms appeared (Kordonouri et al, 1999).

In our study the percentage of children positive for Anti-TPO Ab was 14% in diabetics while 4% of the controls. Although the prevalence of antibodies was higher in the diabetic children than in the controls, this did not reach significance. However, when we measured the actual mean levels of Anti-TPO Ab in the two groups, we found these to be significantly higher in the diabetic children than in the controls (18±4, range 7-21, compared with 18±3, range 7-30, 0).

Previous studies reported elevation of Anti-TPO Ab in a higher percentage (Kordonouri et al., 1999).
Progression to overt thyroid disorders in individuals with significant titers of anti TPO occurs in about \( \approx 50\% \) of children and adolescents with DM within \( \tau - \xi \) years \( (\text{Kordonouri et al., } \tau \cdot \xi) \).

On the other hand, \( \xi \) diabetics were positive for anti-TG-Ab (\( \xi \% \)) while only \( \xi \) of the controls were positive. This difference was significant. Also, mean levels of this antibody were significantly higher in diabetics than in controls (\( \tau \xi, \xi \pm \tau \gamma, \gamma \) versus \( \tau \gamma, \gamma \pm \tau \gamma, \gamma \) in controls).

Prevalence of anti-TG antibodies in type I diabetic patients who are clinically euthyroid have been reported \( \tau \% \) in Germany \( (\text{Kordonouri et al., } \tau \cdot \xi) \) and \( \tau, \gamma \% \) in Spain \( (\text{Lopez et al., } \tau \cdot \xi) \).

Of note in our group of diabetic children was that thyroid autoantibodies were more prevalent in the female children than in the males.

Anti-TG in diabetics was positive in \( \xi \) males \( (\tau, \gamma \%) \) and \' \cdot females \( (\tau, \gamma \%) \)

Anti-TPO in diabetics was positive in \( \xi \) males \( (\tau, \gamma \%) \) and \' \cdot females \( (\tau, \gamma \%) \)

The incidence of thyroid autoantibodies in the general population has previously reported by the \( \tau \cdot \text{-year Whickham survey} \). In that survey, antibodies were more frequent in women than in men, and there was no age-related distribution.

In a follow-up study \( \text{Li et al., } (\tau \cdot \xi) \) reported the prevalence of positive Anti-TPO and Anti-TG in the general population from \( \tau \cdot \tau \gamma \).
Ten of the controls were positive for thyroid autoantibodies, \(^*\) of whom were female and \(^*\) were male. Six of these children were positive for Anti-TPO alone, one was positive for Anti-TG alone, while \(^*\) were positive for both antibodies. Eleven of the diabetic children in our study were positive for both antibodies. The latter difference showed a \(P\) value of \(0.005\).

Antibody testing is not widely available for routine clinical practice in Africa, and few studies have measured thyroid antibodies in African general population. Anti-TG prevalence vary from \(0.7\) in Cameroon (Njemini et al., \(2003\)), \(1.0\) in Sudan (Magzoub et al., \(2992\)), \(7.7\) in South Africa (Omar et al., \(2992\)) to \(12\) in Nigeria (Okosieme et al., \(2002\)) while Anti-TPO prevalence vary from \(0.7\) in Cameroon (Njemini et al., \(2003\)) to \(7.7\) in Nigeria (Okosieme et al., \(2002\)).

The discrepancy between our findings and other African studies may in part be due to differences in methodology. Some of the studies in Africans measured thyroid antibodies using agglutination methods, which are less sensitive than more recent ELISA and radioimmunoassay techniques. However, it is unlikely that methodological factors alone account for these differences. These differences may reflect regional as well as temporal differences between the groups studied. Thyroid autoimmunity is uncommon in iodine-deficient areas but becomes more prevalent with improvements in iodine nutrition (Laurberg et al., \(1998\), Doufas et al., \(1999\), Erdogan et al., \(2004\) Okten et al., \(2005\), Yushu et al., \(2005\)).
Therefore, differences in nutrition between different groups studied worldwide may be a significant factor accounting for differences in prevalence.

Diabetics with thyroid autoimmunity had comparable age and duration of diabetes with no significant difference compared to diabetics without thyroid autoimmunity. Our results are similar to those reported by several authors (Gray et al., Hansen et al., Menon et al.), who found no difference in diabetes duration between diabetics with and without thyroid autoimmunity. On the other hand, Kordonuri et al. found that patient with thyroid antibodies were significantly older, had a longer duration of diabetes, and developed diabetes later in life than those without antibodies. Holl et al. found that the prevalence of elevated thyroid antibodies increased dramatically with age. Other authors also reported similar results.

We compared diabetic girls with diabetic boys. First we compared the two groups as a whole regardless of size of thyroid gland and then we compared those with a goitre.

Goiter was found in fifteen diabetic children (one fifth of the females and one tenth of males), of whom were female (one fifth of the females and one tenth of males) and were male (one fifth of the females and one tenth of males). However, the difference did not reach statistical significance. In fact, the sex of the child appeared to have no impact on thyroid status as regards mean \( fT4 \), \( fT3 \), TSH or antibody levels. No significant difference was found in height standard deviations either.
Comparison between diabetics with and without goiter revealed statistically significant differences regarding mean level of Anti-TPO Ab (\(P < \cdot \cdot \cdot\)), mean level of Anti-TG Ab (\(P < \cdot \cdot \cdot\)), TSH (\(P < \cdot \cdot \cdot\)). All were significantly higher in those with goiter. However there was no significant difference regarding age or duration of diabetes. Although mean heights in both groups were within the normal range, there was a difference of \(\cdot \cdot \cdot\) SD between the two groups, with heights being less in the group of diabetics with goiter. This difference was significant (\(P < \cdot \cdot \cdot\)). There was no difference in levels of \(fT^4\) and \(fT^7\) between the two groups.

Eleven of those with goiter (\(\cdot \cdot \cdot\)) had laboratory evidence of thyroid autoimmunity in the form of a high level of Anti-TPO Ab and/or Anti-TG Ab. The percentages of diabetic children without goiter who were positive for one or both antibodies were significantly less than those who were negative for antibodies. Mean levels of antibodies were also significantly lower in those without a goiter than in those with a goiter. This finding is similar to that of Malachi et al. (\(\cdot \cdot \cdot\)) who reported significantly higher frequency of thyroid autoimmunity in presence of goiter.

Looking at it the other way round, goiter was found in a significantly higher percentage of diabetics with thyroid autoimmunity (\(\cdot \cdot \cdot\)), compared to those with negative autoimmunity (\(\cdot \cdot \cdot\)).

However, in our study goiter was also detected in \(\cdot\) diabetics with no evidence of thyroid autoimmunity.

Chronic lymphocytic thyroiditis is the most common cause of goiter in children and adolescents, and its diagnosis by pathology in absence of detectable antibodies has been previously reported (Hansen et al., \(\cdot \cdot \cdot\)).
Ultrasonographic evaluation and biopsy with pathologic evaluation are, therefore needed to verify the cause of goiter in those goitrous diabetics without evidence of thyroid autoimmunity.

Since thyroid autoimmunity is not necessarily associated with goiter in diabetics, then we cannot consider goiter as a reliable indicator for the need to screen for thyroid antibodies and on the other hand thyroid autoimmunity cannot be excluded in the absence of goiter. Ultrasonographic evaluation of those with thyroid autoimmunity in absence of a clinical goiter might reveal increase in the size or abnormality in the structure of the thyroid gland.

The presence of an elevated TSH without a low level of fT4 indicates subclinical hypothyroidism (Kordonuri et al, 7007). The majority of patients (81%) were euthyroid, while nine of the diabetics (4%) had laboratory evidence of hypothyroidism in the form of elevated TSH. Of these, only two of them had low T4. Antibodies (one or both) were positive in 4 of these children (7 girls and 7 boys). In the ninth, no antibodies could be detected. Levels of both antibodies correlated positively with TSH levels. Only one of the controls had elevated TSH and this difference between patients and controls was significant. However only two of the diabetics with elevated TSH have low T4. one male and one female both of them were positive for both Anti-TPO and Anti-TG. None had clinical or laboratory evidence of hyperthyroidism

Chase et al. (1440) documented reduced speed of growth in diabetic children with elevated TSH values and thyromegaly but euthyroid serum
hormone levels. Treatment with L-thyroxine improved growth significantly in prepubertal children compared with age matched diabetic controls. In our study, we found a negative correlation between height SDS and fT₄ levels and a negative correlation between height SDS and TSH levels indicating growth impairment.

Similarly, levels of thyroid antibodies (Anti-TPO and Anti-TPO) correlated negatively with fT₄ levels and height SDS.

There is conflicting data in the literature as to the use of thyroid hormone treatment in those with autoimmune hypothyroidism with normal levels of thyroid hormones. For example, Padberg et al (3002) found a decrease in levels of thyroid antibodies and TSH when these patients received treatment, whereas others (Rother et al, 2992) found no change on treatment.

Twelve of the nineteen diabetic children positive for thyroid autoantibodies (777) were above 10 years. This finding is in agreement with George et al (2993) who reported a higher frequency of antibodies in children above 10 years of age and with Kordonouri et al (7007) who found that thyroid autoimmunity in the form of elevated TSH levels (indicating subclinical hypothyroidism) seemed to be particularly common in girls with diabetes during the second decade of life.

Celiac disease, also referred to as gluten-sensitive enteropathy, is characterized by immune-mediated damage to the jejunal mucosa, which is triggered by gluten, a protein complex found in wheat, rye, and barley. The diagnosis is based on classic findings on small bowel biopsy of villous atrophy and crypt hyperplasia. With maintenance of a gluten-free diet, multiple studies have documented reversal of the mucosal changes. There has been conflicting data on whether the duration of exposure to
gluten in those not following a gluten-free diet or with undiagnosed celiac disease correlates with a higher risk for subsequent autoimmune diseases, such as type 1 diabetes and thyroid disease.

Even though enterovirus infections are believed to trigger type 1 diabetes and gluten is the trigger of celiac disease, the increasing intake of gluten containing products all over the world could be the trigger for both diseases directly and indirectly. It has been shown that the duration of exposure to gluten is related to the prevalence of type 1 diabetes. It has also been shown that type 1 diabetes patients at onset have an inflammatory reaction in the gut. Hence, early diagnose of celiac disease followed by elimination of dietary gluten could lead to a decreased incidence of type 1 diabetes (Frisk et al, 2004).

Many cases of celiac disease are asymptomatic, or have features that are only recognized retrospectively. Classic symptoms of celiac disease generally include steatorrhea, flatulence, and the consequences of malabsorption, such as growth failure in children, weight loss, severe iron deficiency anemia, neurological disorders from vitamin B deficiencies, and osteopenia from vitamin D and calcium deficiencies (Fasy and Umpierrez, 2004).

The 2004 American Diabetes Association clinical practice recommendations state that antibody screening should be performed in patients with type 1 diabetes with suggestive symptomatology, such as iron deficiency anemia, weight loss, or unexplained fatigue. Patients with type 1 diabetes who become symptomatic for celiac disease should be tested by measuring tissue transglutaminase or anti-endomysial antibodies, with documentation of normal serum IgA levels. Patients with positive antibodies should be referred to a gastroenterologist for
confirmation and to a dietitian for instruction on a gluten-free diet (Fasy and Umpierrez, † † †)

Three patients in our study group of patients with IDDM had evidence of other autoimmune disorders in the form of positive celiac antibodies. Two of these were girls and the third was a boy. Of these, two (a boy and a girl) were also positive for both Anti-TPO and Anti-TG and the third was negative for both. The boy had a height of – 50.7 SDS (combined effect of thyroid affection and celiac disease) with elevated TSH and low FT4. The girl with celiac disease and thyroid antibodies had a height of –7.01 SDS, but normal thyroid functions. The third child had a height of –1.9 SD.