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Incidence and prevalence of thyroid dysfunction in type 1 diabetes

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ABSTRACT

Aims: To estimate prevalence and incidence of auto-immune thyroid disease and thyroid auto-antibodies in an unselected cohort of patients with DM1, including stratification by age, gender and duration of diabetes.
Methods: Patients with T1D visiting our outpatient clinic between 1995 and 2011 were included. We calculated the prevalence of AITD at first screening and estimated prevalence and incidence rates during follow-up.
Results: A total of 1304 patients were included, 48.9% being female. Mean age of diabetes onset was 18.7 years. Of all patients without known thyroid disorder first screened for AITD, 10.3 % (n = 104) was diagnosed with hypo- or hyperthyroidism. The average prevalence of AITD in our population was 112/1000 patients. We found 128 new cases of AITD, 101 cases of hypothyroidism and 27 of hyperthyroidism between 1995 and 2011 with accompanying incidences of 11.2/1000 person–years (95% CI 9.5–13.4), 8.9/1000 person–years (95% CI, 7.3–10.8) and 2.4/1000 person–years (95% CI, 1.6–3.5), respectively. Age-stratified incidence of AITD was comparable at all ages in both males and females, with an approximately two times higher incidence in females.
Conclusions: The incidence of AITD among T1D patients is high, but stable among all ages and independent of diabetes duration.

1. Introduction

Type 1 diabetes (T1D) is caused by an auto-immune reaction against insulin producing pancreatic beta cells. It is associated with higher risk of other auto-immune diseases such as auto-immune thyroid diseases (AITD) and celiac disease (Crone, Rami, Huber, Granditsch, & Schober, 2003; Lorini, d'Annunzio, Vitali, & Scaramuzza, 1996; Radetti et al., 1995; Shun, Donaghue, Phelan, Twigg, & Craig, 2014; Warncke et al., 2010). The prevalence of antibodies against thyroid tissue such as anti-thyroid peroxidase (TPO) antibodies is markedly higher (up till 25 percent) in patients with T1D (Araujo et al., 2008; Betterle, Zanette, & Pedini, 1984; Bilimoria, Pescovitz, & DiMeglio, 2003; Frohlich-Reiterer et al., 2008; Holl et al., 1999; Kakleas et al., 2009; McCanlies et al., 1998; Radetti et al., 1995) compared to the general population (10 percent) (Hollowell et al., 2002). Of antibody positive T1D patients 3–55 percent will develop auto-immune thyroiditis (Dagdelen, Hascelik, & Bayraktar, 2009; Franzese, Buono, Mascolo, Leo, & Valerio, 2000; Frohlich-Reiterer et al., 2008; Radetti et al., 1995; Umpierrez et al., 2003). The larger part of these patients develops hypothyroidism, but hyperthyroidism (M. Graves), characterized by antibodies against the TSH receptor, is also associated with T1D (Franzese et al., 2000; Prazny et al., 2005).

Patients with T1D are often screened for auto-immune thyroid disease at regular intervals (Frohlich-Reiterer et al., 2008; Prazny et al., 2005). Protocols for screening for AITD are generally based on measurement of TSH levels and anti-thyroid antibodies (Kordonouri et al., 2002; Lombardo et al., 2011). These antibodies are considered the best predictor for development of auto-immune thyroiditis. Treatment however is based on thyroid stimulating hormone (TSH) levels, as the sole presence of antibodies has no clinical consequences yet. In the past decades clinicians tended to screen for AITD and antibodies more frequently and over time various screening strategies are proposed (Frohlich-Reiterer et al., 2008; Kakleas et al., 2009; Karavanaki et al., 2009; Kordonouri et al., 2002; Perros, McCrimmon, Shaw, & Frier, 1995; Prazny et al., 2005). With regard to cost-effectiveness, and selection of patients with increased risk for AITD the optimal screening strategy is not known yet (Shun et al., 2014).

Although the prevalence of AITD in patients with T1D increases with age, it is not clear if risk to develop AITD depends on age or duration of diabetes. Detailed information on the incidence of AITD is of direct relevance for clinical practice and might guide the improvement of screening-strategies. In this study we aimed to estimate prevalence and incidence rates of auto-immune hypo- and

Declaration of interest: Nothing to declare.

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hyperthyroidism in patients with diabetes type 1 in more detail. Secondly, we aimed to assess whether incidence rates depended on age, sex or duration of diabetes.

2. Subjects, Materials and Methods

2.1. Study population

We included all patients with type 1 diabetes who visited the outpatient clinic of internal medicine, endocrinology or the pediatrics department of the Leiden University Medical Center in the Netherlands at least once between January 1995 and December 2010. To secure that visits were diabetes related, we excluded patients without any HbA1c measurement. We assessed clinical records of each patient, containing information on outpatient visits as well as medical correspondence and diagnostics. We extracted available information on the diagnosis of diabetes, the diagnosis of hypo- or hyperthyroidism, presence of other thyroid (related) diseases including use of (iodine containing) medication and diagnosis of multinodular goiter or thyroid carcinoma, diabetes related co-morbidity and death. Patients were excluded if the date of T1D diagnosis could not be retrieved (n = 11).

We collected laboratory measurements including thyroid function (FT4, TSH and TPO-ab) for all patients from January 1995 until December 2010. During that time interval thyroid function tests (TSH, FT4) were performed as part of a two-yearly routine screening protocol. This protocol included antibody measurements of associated diseases, including TPO-ab and TG-ab every two years, irrespective of results of TSH and FT4, although in clinical practice screening frequency varied. Besides thyroid function parameters, cholesterol levels and kidney function were measured. The study protocol was approved by the local ethical committee.

2.2. Disease definitions

In our study T1D was defined as insulin dependence within one year after diabetes diagnosis combined with either diagnosis before the age of 25 years, diabetic ketoacidosis at onset, low fasting c-peptide shortly after diagnosis or GAD positivity (Alberti & Zimmet, 1998; American Diabetes Association, 2012; The expert committee on the diagnosis and classification of diabetes mellitus, 2003). Definition of subclinical hypothyroidism was elevated TSH values and free thyroxine (FT4) values within normal range. Clinical overt hypothyroidism was defined as elevated TSH and FT4 values below 10.0 pmol/l. Hypothyroidism with accompanying TPO-ab positivity was considered Hashimoto's disease. Definitions of clinical overt and subclinical hyperthyroidism were decreased TSH values and FT4 values exceeding 24 pmol/l or decreased TSH values with FT4 values in the normal range, respectively. Graves' disease was defined as hyperthyroidism with positive antibodies against the TSH receptor. Definition of AITD included: 1. patients with thyroid dysfunction and positive thyroid antibodies (Hashimotho and Graves' disease) and 2. all patients with thyroid dysfunction not attributable to an alternative (not auto-immune mediated) disease irrespective of antibody positivity, because for a substantial part of the patients no antibody measurement was available in general or at presentation of thyroid dysfunction. Diagnosis of AITD, before 1995 was based on information from clinical files, including reported lab results and/or clinical opinion.

2.3. Laboratory assays

Until 10-'97 TSH was measured by IFMA *(Delfia, Perkin Elmer-Wallac Oy, Turku, Finland)*; reference values 0.4 to 4.0 mU/l. From 10-'97 a Modular Analytics E-170 system *(Roche Diagnostic Systems, Nederland BV, Almere, The Netherlands)* was used; reference values 0.3 to 4.8 mU/l. FT4 levels were measured with IMx until 10-'97 *(Abbott Laboratories, Abbott Park)* and from 10-'97 with a Modular Analytics E-170 system *(Roche Diagnostic Systems, Nederland BV, Almere, The Netherlands)*. Reference range: 10.0 to 24.0 pmol/l. Until 12-'05 TPO-ab were measured with an anti-TPO radioimmunoassay (RIA) kit *(Brahms, Germany)* and from 12-'05 with Immulite 2500 *(Siemens Medical Solutions Diagnostics)*. Values >30.0 kU/L and >35.0 kU/L respectively were considered positive. Antibodies against the TSH receptor were initially measured with a radioimmunoassay (RIA) kit *(Brahms, Germany)* >10.0 IU/L and later with a competitive radioreceptor assay (TRAK assay *Brahms, Germany)* > 1.0 IU/L).

2.4. Statistical analysis

2.4.1. Patient characteristics

Patient characteristics were reported as proportions (binary data) or means with accompanying 95% confidence intervals (95% CI) or interquartile range (IQR). Follow-up ended at death, last HbA1C measurement or the occurrence of a thyroid disease other than AITD that potentially could affect thyroid function (for example operation for goiter).

2.4.2. Prevalence

Prevalence of an outcome was calculated as number of patients with the outcome (AITD) at a specific time-point divided by the total number of patients at risk at yearly intervals.

2.4.3. Yield of first screening for AITD

We calculated how many patients screened for the first time for thyroid diseases had (sub)clinical thyroid disease. Patients diagnosed before 1995, or patients that had not been screened for thyroid disease during follow-up were excluded to estimate the yield of first time screening.

2.4.4. Incidence of AITD between 1995 and 2011

We estimated incidence rates for biochemically confirmed AITD in the period 1995–2011. Incidence rates were calculated as number of patients with newly diagnosed AITD per 1000 person–years (py) at risk. Incidence calculations were restricted to patients without 1) a previous diagnosis of AITD before 1995 2) subclinical thyroid dysfunction at first TSH screening in order to obtain a cohort of patients at risk for the outcome at baseline. The second group was excluded because with diagnosis of subclinical disease at first screening (with usually absence of clinical symptoms) in strict sense it is unknown how long thyroid dysfunction was present and what the specific time point should be for calculating the incidence. We stratified incidence rates by age (ten year intervals), duration of diabetes (ten year intervals) and sex. We tested for trends of the stratified rates using a Mantel–Haenszel method. Hereby we calculated an approximate estimate of the rate ratio for increase of one decade of age or duration of diabetes.

2.4.5. Prevalence of auto-antibodies

In the majority of the patients at least one TPO-ab and TG-ab measurement was done. We calculated prevalence of TPO-ab and TG-ab positivity in all patients with and without AITD.

Data were analyzed using *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP. Figures were made using GraphPad Prism 5.00 (GraphPad Software, Inc.).

3. Results

A total of 1304 patients (638 female, 48.9%) diagnosed with type 1 diabetes was included. All patients were on insulin treatment. Mean age at first diabetes related outpatient visit was 34 years (IQR 23.2 to 43.8), with an average duration of diabetes of 15.3 years (IQR 3.7 to 23.9). Mean age at time of diabetes diagnosis was 18.7 year (IQR 10.3 to 25.3). Based on either results from biochemical screening during