

Spectrum of Autoimmune Disorders in Type 1 Diabetes – A Cross-Sectional Clinical Audit

Barry Joffe, Larry Distiller*, Stanley Landau, Laura Blacking and Anna Klisiewicz

Centre for Diabetes and Endocrinology, 81, Central Street, Houghton, 2198, Johannesburg, South Africa

Abstract

Most cases of Type 1 diabetes mellitus (T1DM) are thought to result from selective autoimmune destruction of pancreatic beta cells. In keeping with the autoimmune aetiology, other autoimmune diseases occur with increased frequency. The purpose of this study was to determine the frequency of hypothyroidism, adrenocortical insufficiency, pernicious anaemia, coeliac disease, vitiligo and systemic autoimmune disorders in 504 patients with longstanding T1DM.

The prevalence of documented hypothyroidism, adrenal insufficiency, pernicious anaemia, coeliac disease, vitiligo and systemic autoimmunity was found to be 20.2%, 1.8%, 0.4%, 0.6%, 2% and 1.6% respectively – consistently higher in females ($p < 0.0002$ for hypothyroidism).

Screening for thyroid (and possibly related) autoimmune disease should routinely be performed in newly diagnosed T1DM subjects, particularly female patients.

Keywords: Autoimmune disorders; Type 1 diabetes; Hypothyroidism; Autoimmune polyendocrine syndromes

Introduction

The current estimated prevalence of diabetes worldwide is 285 million people [1], of which 5 – 10% are of the Type 1 variety. Most cases of Type 1 diabetes are thought to have an autoimmune basis, with various environmental factors interacting with an underlying genetic predisposition, leading to selective autoimmune destruction of pancreatic beta cells [2]. In keeping with the autoimmune aetiology, other (organ-specific) autoimmune diseases occur with increased frequency in this situation. These include Addison's Disease (adrenocortical failure), Grave's hyperthyroidism, hypothyroidism, hypogonadism, coeliac disease, pernicious anaemia and vitiligo [3]. The term autoimmune polyendocrine syndromes encompass some of these associations [4].

Few large-scale surveys of the prevalence of these co-existing autoimmune disorders have been reported. Therefore the aim of the present study was to establish their frequency in a large cohort of patients with Type 1 diabetes attending a diabetes clinic in Johannesburg, South Africa.

Patients and Methods

From the Centre for Diabetes and Endocrinology (CDE) in Johannesburg, we randomly surveyed the records of 504 patients with longstanding established Type 1 diabetes. This comprised about 20% of our total Type 1 diabetic database [5]. There were 258 males and 246 female subjects who were of Caucasian descent, except for 6 Asian and 4 African patients. The classification of Type 1 diabetes had been made on clinical grounds. All patients presented at a young age with classical osmotic symptoms and required insulin from the time of diagnosis.

Having pre-selected the autoimmune features to be analyzed, we recorded the number of subjects with a clinical diagnosis of: - hypothyroidism, adrenocortical insufficiency, pernicious anaemia, celiac disease, vitiligo or a systemic autoimmune disorder. A particular patient may have manifested more than one of these features. Where appropriate, the clinical diagnosis had been confirmed biochemically.

The number of patients manifesting each of these features was tabulated and the female:male distribution calculated. The Chi square test was used to determine significant differences between the sexes, when indicated.

Results

(Table 1) summarises the distribution (number and percentages) of autoimmune features in the 504 patients with Type 1 diabetes included in our survey. Noteworthy was the high prevalence (20.2% overall, 30.9% females and 10.1% males) of documented hypothyroidism in both sexes – but significantly higher in females ($p < 0.0002$). Other autoimmune disorders were much less common, but again consistently higher in female subjects.

Not shown in the table are the inter-relationships of various autoimmune features in individual patients. Six of them had both hypothyroidism plus adrenal insufficiency, 6 patients (all females) had both hypothyroidism and vitiligo while 5 subjects manifested both hypothyroidism and systemic autoimmunity.

Discussion

Our large cross-sectional audit has confirmed the previously described strong association between Type 1 diabetes and autoimmune hypothyroidism constituting the autoimmune polyglandular syndrome Type 3 variant [6,7]. Recent studies have shown a shared genetic susceptibility to both conditions, with most of the shared genes being involved in immune regulation [8].

***Corresponding author:** Larry Distiller, Centre for Diabetes and Endocrinology, 81, Central Street, Houghton, 2198, Johannesburg, South Africa, Tel: +27 11712-6000; Fax: +27 11728-9097; E-mail: larry@cdecent.co.za

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Group	Number	Hypothyroidism	Adrenal Insufficiency	Pernicious Anaemia	Coeliac Disease	Vitiligo	Systematic Autoimmune*
Total	504	102 (20.2%)	9 (1.8%)	2 (0.4%)	3 (0.6%)	10 (2%)	8 (1.6%)
Females	246	76 (30.9%) **	6 (2.4%)	2 (0.8%)	3 (1.2%)	7 (2.8%)	7 (2.8%)
Males	258	26 (10.1%)	3 (1.2%)	0	0	3 (1.2%)	1 (0.4%)

*Rheumatoid arthritis, scleroderma, systemic lupus erythematosis

**p<0.0002 compared to males

Table 1: Distribution of Auto-Immune features in 504 patients with Type 1 Diabetes attending the CDE. Numbers (%).

particular the CTLA – 4, HLA – class – 11 and FOXP3 genes were implicated. We have shown a somewhat higher prevalence than previous reports involving smaller patient numbers [9]. However, the assumption that all our cases of hypothyroidism were autoimmune in aetiology remains speculative since thyroid autoantibodies (thyroperoxidase and thyroglobulin) were not routinely documented.

The next, but much less frequent, endocrine association in our study was that of adrenocortical insufficiency; this occurring together with hypothyroidism supports a diagnosis of autoimmune polyglandular syndrome Type 2. An association with HLA – class – 11 genes has also been reported here, suggesting an enhanced susceptibility to certain viral infections [10]. Other, non-endocrine, associations were sporadically encountered, although consistently higher in females.

A number of limitations of the current survey should be mentioned. In common with many clinical audits, we lacked a control group of non-diabetic individuals. Since thyroid disorders are not uncommon in the general population [11], the magnitude of our association between Type 1 diabetes and hypothyroidism may have been over-estimated. More over antibody data were not always available to confirm the autoimmune aetiology, as previously mentioned.

From a practical standpoint, screening for thyroid (and perhaps related) autoimmune disease should become part of the routine investigation of newly diagnosed Type 1 diabetic patients and appropriate replacement therapy instituted at an early stage. According to recent guidelines proposed by the American Diabetes Association [12], this should entail measurement of thyroid autoantibodies at diagnosis and thyroid-stimulating hormone levels every 1 – 2 years if replacement therapy has been instituted.

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