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Lipoatrophy Is Associated with an Increased Risk of Hashimoto's Thyroiditis and Coeliac Disease in Female Patients with Type 1 Diabetes

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Key Words

Type 1 diabetes · Lipoatrophy · Hashimoto's thyroiditis · Coeliac disease · Diabetes Patienten-Verlaufsdokumentationssystem

Abstract

Background/Aims: Lipoatrophy (LA) is a rare, possibly underrecognised side effect of insulin treatment of unclear aetiology. The aim of this study was to describe the characteristics of patients with type 1 diabetes (T1D) who have LA and to explore the relationship between LA and other autoimmune diseases based on the hypothesis that additional autoimmune phenomena are more prevalent in T1D patients with LA. ***Methods:*** This was a cross-sectional observational study of T1D patients with LA in comparison to T1D patients without LA who are registered with the Diabetes Patienten-Verlaufsdokumentationssystem database of 241,650 patients in Germany and Austria. ***Results:*** Hashimoto's thyroiditis and coeliac disease were more prevalent in patients with LA ($p < 0.001$ for both). LA was associated with an increased risk of Hashimoto's thyroiditis and coeliac disease in female patients [odds ratio (OR) 2.5, $p = 0.003$, and OR 3.1, $p = 0.02$, respectively]. This relationship persisted after adjustment for current age, duration of diabetes and calendar year of treatment (OR 2.7, $p = 0.002$, and OR 3.5, $p = 0.01$, respectively). ***Conclusion:*** These findings support the hypothesis that an immune complex-mediated inflammatory process may be important in the development of LA.

Introduction

Lipoatrophy (LA) is a relative loss of subcutaneous adipose tissue. In the early years of insulin therapy, up to 50% of patients with diabetes showed evidence of LA, possibly due to a reaction to impurities in the insulin

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preparations. With the development of recombinant insulins and highly purified injection solutions, LA has become a rare side effect with any type of insulin. The aetiology remains unclear and there is no solid evidence base for an optimal treatment strategy. An underlying immunological mechanism was originally proposed by Paley [1] in 1953. Peters and Winkelmann [2] suggested that transitory lymphocyte-mediated panniculitis is the primary lesion that progresses to LA, which has recently been called into question [3].

Given the apparently higher prevalence of LA in female patients with type 1 diabetes (T1D) [4–11], we hypothesised that Hashimoto's thyroiditis and coeliac disease would be more common in T1D patients with LA. Our exploratory objectives were to undertake a cross-sectional observational study of patients with LA and to determine the relationship between LA, gender, Hashimoto's thyroiditis and coeliac disease.

Subjects and Methods

Study Population

Subjects were identified through the Diabetes Patienten-Verlaufsdokumentationssystem (DPV), a prospective database of currently 241,650 patients with any type of diabetes who are registered across 371 centres in Germany and Austria. Each centre updates their patients' anonymised data every 6 months, which are processed at a central administrative unit at the University of Ulm, Germany. Inconsistent data are reported back to the respective centre for correction. The DPV has ethical approval at the University of Ulm.

A total of 91 subjects (46 males and 45 females) with T1D (mean age 12.1 years, range 2.8–48.1 years) who showed any degree of LA (LA+) were compared to 53,754 age-matched T1D subjects (28,167 males and 25,587 females) without LA (LA–; mean age 12.4 years, range 2.7–21.0 years).

Current thyroid auto-antibody levels were available for 69 LA+ subjects. Thyroid auto-antibody positivity was defined as anti-thyroid peroxidase ≥100 U/ml and/or thyroglobulin antibody ≥100 U/ml [12]. Hashimoto's thyroiditis was diagnosed according to the individual treating centres' clinical guidelines. Current coeliac antibody levels were available for 66 LA+ subjects. Coeliac disease was diagnosed according to the national guidelines [13]. A severe hypoglycaemic episode was defined as hypoglycaemia that required help from someone other than the patient [14].

Calculations

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in metres. Using lambda, mu and sigma model methods, age- and sex-specific standard deviation scores for BMI were calculated with reference data from the German Adiposity Society [15]. Glycated haemoglobin (HbA_{1c}) values were adjusted to the Diabetes Control and Complication Trial reference range (4.05–6.05%). The total daily insulin dose was calculated as units per weight in kilograms.

Statistics

The non-parametric Kruskal-Wallis test was used to compare current age, duration of diabetes, age at diagnosis of diabetes, BMI, HbA_{1c} and daily insulin dose between LA+ and LA– subjects. A χ^2 test was applied to the insulin treatment regimen and prevalences of Hashimoto's thyroiditis, coeliac disease and auto-antibody positivity. A Poisson regression model was used for event rates of severe hypoglycaemia and ketoacidosis. These comparisons between LA+ and LA– subjects then underwent Bonferroni correction (table 1). Odds ratios (ORs) derived from logistic regression estimated the risk of having Hashimoto's thyroiditis or coeliac disease in LA+ subjects (table 2). The ORs were also adjusted for current age, duration of diabetes and calendar year of treatment. Significance was set to $p < 0.05$. Analyses were performed with Statistical Analysis Software version 9.3.

Results

Table 1 summarises the characteristics of LA+ and LA– subjects for the current year. LA+ and LA– subjects had similar age, sex distribution, BMI and duration of diabetes, but LA+ subjects were younger at diagnosis of T1D ($p = 0.002$; table 1). HbA_{1c} and the incidence of ketoacidosis were similar in LA+ and LA– subjects (table 1). LA+ subjects had more frequent hypoglycaemic episodes that required assistance ($p < 0.001$; table 1). Daily insulin dose and the proportion of patients who used short- or long-acting insulin analogues were similar in LA+ and LA– patients (table 1).

Hashimoto's thyroiditis and coeliac disease were more common in LA+ subjects ($p < 0.001$ for both; table 1). Current thyroid and coeliac antibody status was similar in LA+ and LA– patients ($p = 0.2$ and $p > 0.9$; table 1). Following stratification of the cohort by sex, LA was associated with an increased risk of Hashimoto's thyroiditis and coeliac disease in female subjects only (OR 2.5, $p = 0.003$, and OR 3.1, $p = 0.02$, respectively; table 2). This relationship persisted after adjustment for current age, duration of diabetes and calendar year of treatment (OR 2.7, $p = 0.002$, and OR 3.5, $p = 0.01$, respectively; table 2).

Discussion

We used a large database of patients with T1D to determine the relationship between LA and additional autoimmune phenomena. The central finding is a higher prevalence of Hashimoto's thyroiditis and coeliac disease in LA+ patients, with an increased risk of these additional autoimmune diseases only in female LA+ patients.

Table 1. Cohort characteristics, glycaemic control, insulin treatment and prevalence of other autoimmune phenomena in LA+ and LA– patients with T1D

	LA+ (n = 91)	LA– (n = 53,754)	p
Age, years	11.2 (8.9–14.7)	13.0 (9.8–15.4)	0.3
Males, %	50.5	52.4	1.0
BMI, kg/m^2	18.4 (16.8–22.1)	19.7 (17.4–22.2)	0.2
BMI SDS	0.5 (–0.2 to 1.1)	0.4 (–0.2 to 1.0)	1.0
Duration of diabetes, years	3.9 (1.4–7.2)	2.9 (1.3–5.4)	0.07
Age at diagnosis of diabetes, years	6.3 (3.5–9.9)	8.7 (5.1–11.9)	0.002
Glycaemic control			
HbA_{1c}, %	7.5 (6.9–8.7)	7.9 (7.2–8.9)	0.2
Rate of severe hypoglycaemia, /100 patient-years	69.5 (4.7)	12.4 (2.2)	<0.001
Rate of ketoacidosis, /100 patient-years	2.7 (0.2)	4.2 (0.1)	1.0
Insulin treatment			
Daily dose, U/kg	0.8 (0.7–1.0)	0.8 (0.6–0.9)	0.4
Use of short-acting insulin analogue, %	44.4	31.4	0.2
Use of long-acting insulin analogue, %	24.2	27.5	1.0
Additional autoimmune phenomena			
Diagnosis of Hashimoto's thyroiditis, %	18.6	8.6	<0.001
Current thyroid auto-antibody positivity, %	30.4	19.1	0.2
Diagnosis of coeliac disease, %	6.6	3.2	<0.001
Current coeliac antibody positivity, %	30.3	22.3	1.0

In general, data represent medians (inter-quartile range) or percentages. Means (standard deviation) are shown for event rates of severe hypoglycaemia and ketoacidosis. SDS = Standard deviation score.

Table 2. Risk of Hashimoto's thyroiditis or coeliac disease in T1D patients with LA by sex

	Unadjusted OR	p	Adjusted OR	p
Hashimoto's thyroiditis				
Males	1.2 (0.5–2.8)	0.7	1.1 (0.5–2.7)	0.8
Females	2.5 (1.4–4.6)	0.003	2.7 (1.4–4.9)	0.002
Coeliac disease				
Males	0.8 (0.1–5.8)	0.8	0.7 (0.1–5.0)	0.7
Females	3.1 (1.2–7.9)	0.02	3.5 (1.3–8.9)	0.01

Data are mean ORs (95% confidence interval) adjusted for current age, duration of diabetes and calendar year of treatment where indicated.

LA has become a relatively rare side effect of insulin treatment. We identified 91 LA+ patients, with a similar number of cases in males and females. The age range of LA+ patients was relatively wide, and children as young as 3 years were affected. LA+ patients were younger at diagnosis of T1D, but the duration of diabetes was similar in LA+ and LA– patients. The insulin treatment regimen and average glycaemic control were similar in LA+ and LA– patients. However, LA+ patients had a higher incidence of severe hypoglycaemic episodes. This finding may have been biased by the subjective nature of the definition used to classify a hypoglycaemic episode as severe, particularly in young children.

An immune-mediated inflammatory response to insulin or excipients of the injection solution could underlie the development of LA. This is based on previously reported isolation of macrophages, lymphocytes, immunoglobulin (Ig) M, IgA, complement component 3, fibrinogen and fibrin from areas of LA and apparent reversal of the atrophic process upon local treatment with steroid [5–7, 11, 16–23]. In addition, there are case reports of increased circulating insulin antibody and IgG concentrations [6, 18, 20, 22, 24–26] where local cytokine release by macrophages may induce inflammation and thereby the dedifferentiation of adipocytes [11, 19, 27]. Higher numbers of eosinophils and tryptase-positive, chymase-positive degranulated mast cells have also been isolated from regions of LA. This is suggestive of a hypersensitivity reaction, which has led to attempts

to treat LA with the mast cell stabiliser sodium cromoglicate [25]. However, in their study of histological samples from 3 affected patients with T1D, Milan et al. [3] argued against an inflammatory process in the development of LA. They proposed that LA results from adipocyte delipidation secondary to local insulin resistance, but their analysis may have been limited by only sourcing samples from areas of established LA and not, for example, from the edges between normal and LA tissue [6].

The previously reported higher prevalence of LA in T1D than in type 2 diabetes and its apparent over-representation in female patients point to an immunological pathogenic process [4–11, 28]. Hashimoto's thyroiditis and coeliac disease were more common in LA+ patients. Moreover, only female LA+ patients had a significantly higher risk of these additional autoimmune phenomena.

We acknowledge that cause and effect are impossible to establish in an observational study like ours. Our study was also limited by the potential existence of unreported cases given the method of data collection, which relies on each participating centre's accurate and regular updating of patient details. This may have contributed to the low number of LA+ cases relative to the size of the DPV database. Furthermore, we were unable to look at the degree of LA in relation to patients' clinical characteristics given that LA+ is recorded as a binary variable.

In conclusion, Hashimoto's thyroiditis and coeliac disease were more prevalent in LA+ patients with T1D, with an increased risk of these additional autoimmune diseases only in female LA+ patients. We propose that these findings support the hypothesis that an immune complex-mediated inflammatory process may be important in the development of LA and suggest that the identification of LA in patients with T1D should prompt clinicians to screen for other autoimmune diseases. Affected patients may benefit from advice to avoid injecting insulin into or in close proximity to regions of LA in order to try and reverse the atrophic process. Based on case reports, local application of steroid and possibly sodium cromoglicate may be used as an adjuvant in the treatment of established areas of LA.

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