Research: Complications

Risk factors for necrobiosis lipoidica in Type 1 diabetes mellitus

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Abstract

Aims To compare the clinical and metabolic characteristics of patients with Type 1 diabetes and necrobiosis lipoidica with those of patients with Type 1 diabetes who do not have necrobiosis lipoidica. A multicentre analysis was performed.

Methods Clinical and laboratory data were obtained from 64 133 patients (aged 0–25 years) with Type 1 diabetes with and without necrobiosis lipoidica who were registered in the German/Austrian Diabetes Prospective Documentation Initiative registry. Data were analysed using multivariable regression modelling. Age, diabetes duration, treatment year and sex were considered as confounding factors.

Results Results adjusted for demographic variables are presented. In patients with necrobiosis lipoidica, metabolic control was worse (HbA1c 72 vs. 67 mmol/mol, 8.7% vs. 8.3%; \( P = 0.0065 \)) and the duration of diabetes was longer [6.24 (3.28–9.97) vs. 5.11 (2.08–8.83) years; \( P = 0.014 \); not adjusted]. Patients with necrobiosis lipoidica required higher insulin doses than those without (1.02 vs. 0.92 U/kg/day; \( P < 0.0001 \)). There was no significant difference in the frequency of microvascular complications (microalbuminuria and retinopathy) between the groups. Furthermore, 24.8% and 17.5% of patients with Type 1 diabetes with and without necrobiosis lipoidica, respectively, had elevated thyroid antibodies (\( P = 0.051 \)). Necrobiosis lipoidica was correlated with coeliac disease in patients with Type 1 diabetes (3.4% vs. 1.0%; \( P = 0.0035 \)).

Conclusions Our data indicate a strong correlation between hyperglycaemia and the development of necrobiosis lipoidica. We postulate that the underlying pathogenic processes differ from those leading to microalbuminuria and retinopathy, and additional immunological mechanisms may play a role.

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Introduction

Necrobiosis lipoidica is a chronic, cutaneous, granulomatous condition with degenerative connective tissue changes of unknown aetiology. In > 80% of cases, the pretibial area is the typical site of presentation. The lesions are well demarcated, exhibit yellowish or brownish plaques, and are slowly enlarging, often with central atrophy. The first report of necrobiosis lipoidica in a person with diabetes was by Oppenheim in 1932 [1]. Data suggest that 0.3% of people with diabetes mellitus develop necrobiosis lipoidica [2,3], whereas 90% of those with necrobiosis lipoidica have diabetes and are predominantly female [4]. Different therapeutic approaches exist, and all demonstrate limited efficiency. Topical or systemic application of corticosteroids or calcineurin inhibitors is used as the first line treatment option [5–7]. Topical retinoids, topical psoralen ultraviolet A, photodynamic therapy and biologicals have also been described as being successful in some people [6–12].

Various aetiological factors have been proposed and are discussed in the literature. Poor metabolic control may also play a role in necrobiosis lipoidica development in patients with diabetes [13], although there is still controversy [5]. Some studies propose a higher prevalence of microvascular complications in patients with diabetes and necrobiosis lipoidica [14–16], whereas other studies do not describe this correlation [17]. Glycoprotein deposition as a major cause of microangiopathy in diabetes has also been discussed as a trigger of necrobiosis lipoidica lesions [18]. However, deposits of immunoreactants, such as immunoglobulins and...
complement factor 3 have been demonstrated in necrobiosis lipoidica lesions using dermatopathological examination [19], which supports an immunological aetiology [20]. However, these immunological phenomena might also be secondary and a consequence of a primary collagen defect [19] or metabolic tissue changes. In addition to these various aetiological theories, associations with other autoimmune disorders and necrobiosis lipoidica are described. An increased incidence of thyroid function disorders in patients with necrobiosis lipoidica was reported in one study [4], and there are case reports about the coincidence of autoimmune thyroid disease and necrobiosis lipoidica [21,22]. Furthermore, lifestyle behaviours, such as smoking, are considered a potential risk factor for necrobiosis lipoidica development [15].

Because necrobiosis lipoidica is a rare condition, studies involving associated diseases and risk factors are usually based on a relatively small number of patients. Thus, the aim of this survey was to compare groups of patients with Type 1 diabetes and Type 1 diabetes plus necrobiosis lipoidica in a large cohort in order to learn more about the relevant aetiological and/or associated factors in necrobiosis lipoidica development. Analysis of a German/Austrian multicentre diabetes registry was performed.

What’s new?

• This study of 64 133 patients, the largest on written record, is a further step towards describing the phenotype of people with necrobiosis lipoidica diabeticorum.
• There is conflicting evidence in the literature concerning the role of hyperglycaemia in the development of necrobiosis lipoidica diabeticorum. In our analysis, higher HbA1c and longer diabetes duration correlated with necrobiosis lipoidica.
• For the first time, we show that necrobiosis lipoidica in patients with Type 1 diabetes mellitus correlates with a higher daily insulin requirement and with coeliac disease. Necrobiosis lipoidica does not correlate with the application of insulin analogues or with BMI.

Patients and methods

Data collection

In total, 415 diabetes centres from Germany and Austria participated in a computerized follow-up programme called the Diabetes Prospective Documentation Initiative (DPV) [23]. The DPV registry started in 1995 on a nationwide basis, and today, 406 centres generate anonymized data from patients with Type 1 diabetes, which has contributed to our present analyses.

Routine visits to each participating centre form the basis of the data collection. Every 6 months, anonymous data for all patients with diabetes are transmitted to the central DPV registry. For the best data validity, inconsistent data are reported back to the corresponding centres for correction.

Study population

In total, 337 949 patients with any type of diabetes mellitus were registered between January 1995 and March 2014. Of these, 90 263 were documented as having Type 1 diabetes. We extracted 64 133 patients with Type 1 diabetes aged 0–25 years, and necrobiosis lipoidica was reported in 161 of them (0.25%).

We analysed the available data from 12 months prior to the documented diagnosis of necrobiosis lipoidica. We used the most recent data set if necrobiosis lipoidica was documented repeatedly. For the group with Type 1 diabetes but without necrobiosis lipoidica, data analyses were performed on the basis of the last 12 months of care.

Diagnosis of necrobiosis lipoidica

The diagnosis necrobiosis lipoidica was determined by each of the participating centres. It is mainly a clinical diagnosis, made by a dermatologist. Typically, a skin biopsy is only performed in awkward cases. Our database does not contain information about whether histological proof of the diagnosis necrobiosis lipoidica was available.

Measurements

Anthropometry

The “Study on the Health Status of Children and Adolescents in Germany” (KiGGS) reference data [24] were used to calculate BMI standard deviation scores.

Metabolic control

The multiple mean method was used for the mathematical standardization of HbA1c measurements from different centres to the Diabetes Control and Complications Trial reference range of 21–43 mmol/mol (4.05–6.05%).

Albuminuria

Persistent microalbuminuria was defined according to the guidelines of the International Society for Paediatric and Adolescent Diabetes as a minimum of two positive results from three consecutive urine specimens at least 4 weeks apart [25]; the definition of a normal albumin excretion rate was 20–200 μg/min in timed overnight urine collections or 30–300 mg/24 h in 24 h urine collections or an albumin-to-creatinine ratio of 2.5–25 mg/mmol (boys and men) or 3.5–25 mg/mmol (girls and women) in the morning spot urine. Each of the participating centres independently decided which method to use.
**Retinopathy**

According to the guidelines of the International Society for Paediatric and Adolescent Diabetes, an ophthalmological examination should be performed annually in children over the age of 10 years [25]. The gold standard for the detection of diabetic retinopathy is mydriatic ophthalmoscopy. Patients with a diagnosis of retinopathy during the course of their diabetes mellitus were defined as having retinopathy.

**Thyroid antibodies**

If either thyroglobulin antibodies or thyroidal peroxidase antibodies were above the normal laboratory reference range for each centre at any point between January 1995 and March 2014, the result was defined as ‘positive’.

**Coeliac disease**

For the diagnosis of coeliac disease, duodenal biopsies were performed by the participating centres. Each centre determined which patient had histologically proven coeliac disease, presumably according to the guidelines of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [26]. If coeliac specific antibodies were positive, then a Marsh classification grade ≥ 2 defines histologically proven coeliac disease.

**Statistical analysis**

For data analysis, the SAS statistical software package (version 9.4; SAS Institute Inc., Cary, NC, USA) was used. Data were presented as the median and interquartile range or as a percentage. For group comparisons, a non-parametric statistical test (Kruskal–Wallis test) was performed, with adjustment for multiple comparisons (method of Holm). For categorical variables, the $\chi^2$ test was performed to demonstrate differences in frequencies. A P-value ≤ 0.05 was considered statistically significant. We considered age, sex, diabetes duration and year of necrobiosis lipoidica diagnosis as confounders. Thus, multivariable regression analysis was performed. Adjusted mean values were provided for one standard person (15 years old, diabetes duration 5 years, equal distribution male and female).

### Results

**Clinical data**

Tables 1 and 2 display the anthropometric and clinical data of patients with Type 1 diabetes and those with the additional diagnosis of necrobiosis lipoidica. The age in the two groups (Type 1 diabetes with and without necrobiosis lipoidica) was similar, but patients with necrobiosis lipoidica had a longer diabetes duration [6.24 years (3.28–9.97)] than those who did not have necrobiosis lipoidica [5.11 years (2.08–8.83); $P = 0.014$]. Necrobiosis lipoidica is predominantly observed in girls and women (67.1%). In comparison, 47.4% of all patients with Type 1 diabetes are female ($P < 0.0001$). The following results are adjusted for the confounding factors age, diabetes duration, treatment year and sex. BMI standard deviation scores were not significantly different between patients with Type 1 diabetes with or without necrobiosis lipoidica (+0.30 vs. +0.28; $P = 0.7353$). Metabolic control, measured by HbA1c, was worse in the group with necrobiosis lipoidica (72 vs. 67 mmol/mol, 8.7% vs. 8.3%; $P = 0.0065$). Smoking was significantly associated with necrobiosis lipoidica. In the Type 1 diabetes plus necrobiosis lipoidica group, 22.5% were smokers compared with 11.0% in the Type 1 diabetes without necrobiosis lipoidica group ($P < 0.0001$). Furthermore, 6.1% of patients in the group Type 1 diabetes plus necrobiosis lipoidica are regular smokers (smoking > 15 cigarettes per day), whereas 2.8% of patients with Type 1 diabetes but without necrobiosis lipoidica are regular smokers (data not adjusted for confounders). It should be noted that reliable information about how long regular smokers had been smoking was not available.

**Insulin therapy**

Differences in the use of short- and long-acting insulin analogues and differences in the total insulin dosage per kg body weight between patients with Type 1 diabetes with or without necrobiosis lipoidica are shown in Table 2. Short-acting insulin analogues are used more often in patients with Type 1 diabetes who do not have necrobiosis lipoidica. However, after adjusting for confounding factors, such as

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**Table 1** Clinical data of people with Type 1 diabetes with or without necrobiosis lipoidica

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Type 1 diabetes</th>
<th>n</th>
<th>Type 1 diabetes and necrobiosis lipoidica</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, n</td>
<td>63 972</td>
<td>52.6/47.4</td>
<td>161</td>
<td>32.9/67.1</td>
<td>$&lt; 0.0001</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>63 972</td>
<td>15.59 (11.89–17.67)</td>
<td>161</td>
<td>15.80 (12.92–17.54)</td>
<td>0.62</td>
</tr>
<tr>
<td>Age, years</td>
<td>63 972</td>
<td>5.11 (2.08–8.83)</td>
<td>161</td>
<td>6.24 (3.28–9.97)</td>
<td>0.014</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>41 322</td>
<td>11.0</td>
<td>114</td>
<td>22.5</td>
<td>$&lt; 0.0001</td>
</tr>
</tbody>
</table>

Data are shown as the median (lower–upper quartile) or percentage. n, number of all patients with available results in the database.

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age, diabetes duration, treatment year and sex, 65.0% of patients with necrobiosis lipoidica use short-acting insulin analogues, whereas 61.5% of patients without necrobiosis lipoidica use short-acting insulin analogues ($P = 0.398$; not significant). Concerning the use of long-acting insulin analogues, there was no difference between the two groups after adjustment for demographic parameters. Of the patients with Type 1 diabetes and necrobiosis lipoidica, 40.2% use long-acting insulin analogues vs. 38.7% of those with Type 1 diabetes without necrobiosis lipoidica ($P = 0.738$; not significant). Patients with Type 1 diabetes and necrobiosis lipoidica require higher insulin doses per kg of body weight than patients with Type 1 diabetes without necrobiosis lipoidica. After adjustment for demographic confounders, the results remained significant: the insulin dosage was 1.02 U/kg/day in the group with necrobiosis lipoidica and 0.92 U/kg/day in the group without necrobiosis lipoidica ($P < 0.0001$).

**Thyroid antibodies**

The percentages of positive thyroid antibodies for patients with Type 1 diabetes with or without necrobiosis lipoidica are provided in Table 2. The following results are adjusted for confounding factors, including age, diabetes duration, treatment year and sex. There was an association between necrobiosis lipoidica and thyroid antibodies. Of the patients in the Type 1 diabetes plus necrobiosis lipoidica group, 24.8% tested thyroid antibody-positive, whereas thyroid antibodies were detected in 17.5% of the general Type 1 diabetes population ($P = 0.051$; not significant).

**Coeliac disease**

The percentages of histologically proven coeliac disease for patients with Type 1 diabetes with or without necrobiosis lipoidica are provided in Table 2. The following results are adjusted for confounding factors, including age, diabetes duration, treatment year and sex. Moreover, 3.4% of patients with Type 1 diabetes and necrobiosis lipoidica have coeliac disease (proven by histological examination), whereas coeliac disease is documented in 1.0% of patients with Type 1 diabetes who do not have necrobiosis lipoidica ($P = 0.0035$).

**Retinopathy and microalbuminuria**

There is a trend for developing microalbuminuria or retinopathy more often if necrobiosis lipoidica is present, but the data were not significant. The following results were adjusted for confounding factors, including age, diabetes duration, treatment year and sex.

In 2.0% of patients with Type 1 diabetes, there was a coincidence of retinopathy and necrobiosis lipoidica, but only 1.1% of patients with Type 1 diabetes who did not have necrobiosis lipoidica were diagnosed with retinopathy ($P = 0.092$; not significant). Mydriatic ophthalmoscopy was the method of choice to detect diabetic retinopathy during the period of data collection. However, more widespread implementation of fundus photography may lead to a more frequent detection of early retinopathy.

The prevalence of microalbuminuria also did not differ between patients with Type 1 diabetes with and without necrobiosis lipoidica (11.7% vs. 9.6%; $P = 0.526$, not significant). The number of patients available for the analyses is in Table 2.

**Discussion**

This multicentre study presents data obtained from 64 133 patients (0–25 years old) with Type 1 diabetes, 161 of whom
were documented with necrobiosis lipoidica. This is the largest number of patients with Type 1 diabetes and necrobiosis lipoidica in the literature. Several studies with a relatively small number of participants have demonstrated no significant difference in HbA1c levels between groups with and without necrobiosis lipoidica [14–17]. In their review, Reid et al. [5] concluded that glucose control does not affect the presence or progression of necrobiosis lipoidica. By contrast, Cohen et al. [13] postulated an association between necrobiosis lipoidica and poor glucose control after an intensive literature review.

In this survey, the median HbA1c level was 63 mmol/mol (7.9%) for all patients with Type 1 diabetes. In patients with Type 1 diabetes plus necrobiosis lipoidica, the median HbA1c level was 72 mmol/mol (8.7%). After adjustment for demographic confounders, the difference in metabolic control between the two groups was still significant. Patients with Type 1 diabetes and necrobiosis lipoidica have a longer diabetes duration than those without necrobiosis lipoidica (6.24 vs. 5.11 years), and have an earlier onset of diabetes than patients without necrobiosis lipoidica (8.16 vs. 8.85 years). We, therefore, propose that metabolic consequences of hyperglycaemia may play a role in necrobiosis lipoidica pathogenesis. However, microvascular complications of diabetes were not associated with necrobiosis lipoidica in our study, which differs from the results obtained in two studies examining a small number of patients with diabetes. Verrotti et al. [14] compared 18 children and adolescents with Type 1 diabetes and necrobiosis lipoidica with 40 children and adolescents with Type 1 diabetes without necrobiosis lipoidica. They found a significantly higher frequency of persistent microalbuminuria and retinopathy in the group of children and adolescents with Type 1 diabetes plus necrobiosis lipoidica. A study performed by Kelly et al. [15] supported this result, but the number of participants was similarly small.

Numerous mechanisms may cause microangiopathy, the most important being excess sorbitol formation, oxidative damage, an increase in glycation end products and protein kinase C overactivity. Additional stressors, such as infections, trauma or immunological processes can accentuate vascular damage, thereby promoting the clinical signs of microangiopathy [3]. In our study with patients younger than 26 years, there was no significant correlation between necrobiosis lipoidica and microalbuminuria and retinopathy. Thus, we assumed that additional pathogenetic mechanisms, apart from hyperglycaemia, must be involved in the development of necrobiosis lipoidica.

Smoking is a well-known additional risk factor for microvascular comorbidity, and it was confirmed to be strongly associated with necrobiosis lipoidica in our study (22.5% of those in the Type 1 diabetes plus necrobiosis lipoidica group were smokers compared with 11.0% in the Type 1 diabetes group; results adjusted for demographic confounders).

We confirmed previous data demonstrating the predominance of necrobiosis lipoidica in women. In our study, sex distribution was 67.1% female vs. 32.9% male in the group with Type 1 diabetes with necrobiosis lipoidica, whereas the sex distribution for patients with Type 1 diabetes was almost equal. The importance of oestrogen in the development of necrobiosis lipoidica skin lesions has been previously postulated, although the precise mechanism remains unclear. Oestrogen has been described to have a positive effect on skin vascularization and enhances the collagen content and quality of the skin [27].

A surprising result in our study was the significantly higher frequency of conventional diabetes therapy in patients with Type 1 diabetes plus necrobiosis lipoidica in contrast to patients without necrobiosis lipoidica (14.4% vs. 8.0%; adjusted for demographic confounders). Conventional diabetes therapy was defined as one to three injections per day, and is usually the first line of treatment for necrobiosis lipoidica. Erfurt-Berge et al. [4] described a higher prevalence of thyroid disorders in patients with necrobiosis lipoidica, but no data exist regarding the frequency of thyroid or other antibodies. Of the 40 819 patients with Type 1 diabetes who were tested for thyroid antibodies in our study, 18.5% were antibody-positive, whereas 32% of the 97 patients with Type 1 diabetes plus necrobiosis lipoidica were positive for thyroid antibodies. However, this difference was not significant after correction for confounders.

Ours is the first study to demonstrate an association between necrobiosis lipoidica and coeliac disease in patients with Type 1 diabetes. The prevalence of histologically proven coeliac disease in patients with Type 1 diabetes was 1.0% compared with 3.4% if necrobiosis lipoidica is present (numbers adjusted for demographic confounders). This finding may be interpreted as an indicator of immunological alterations, resulting in both necrobiosis lipoidica and coeliac disease.

A surprising result in our study was the significantly higher insulin requirement in relation to body weight in patients with Type 1 diabetes and necrobiosis lipoidica compared with patients without necrobiosis lipoidica. This difference remains significant after correcting for demographic confounders. One potential explanation for this finding might be the higher frequency of conventional diabetes therapy in patients with necrobiosis lipoidica in contrast to patients without necrobiosis lipoidica (14.4% vs. 8.0%; adjusted for demographic confounders). Conventional diabetes therapy was defined as one to three injections per day, and is usually associated with a higher insulin dosage and worse glycaemic control than intensive insulin therapy and insulin pump therapy. However, the difference in insulin dosage per kg of body weight between the two groups was confirmed after adjustment for different treatment modalities ($P < 0.0001$).

Insulin dosage is used as a measurement for insulin resistance in children and adolescents. Several studies have suggested that insulin resistance is involved in the
development of microvascular complications in Type 2 diabetes and other diseases [29]. Until recently, insulin resistance and endothelial dysfunction have not been described as potential pathogenic factors for the development of necrobiosis lipoidica. The strength of this study is the large number of participants from many diabetes centres. The study’s retrospective nature is a limitation. However, necrobiosis lipoidica is a rare disease, and sufficient power for statistical analysis is extremely difficult to achieve with a prospective study design. Another limitation is that we had to rely on each centre in the diagnosis of necrobiosis lipoidica. However, the involvement of a dermatologist is recommended and is most likely performed by most centres.

In conclusion, the results of our multicentre analysis indicate a strong correlation between metabolic control as well as diabetes duration and necrobiosis lipoidica development in patients with Type 1 diabetes. Smoking, female sex and a higher insulin dosage per body weight are also associated with necrobiosis lipoidica. In our study, the prevalence of coeliac disease is significantly higher in patients with Type 1 diabetes and necrobiosis lipoidica, which indicates that immunological alterations may play a role in the aetiology of necrobiosis lipoidica.

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Competing interests
None.

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Author contributions
E.H. collected the data and wrote the manuscript. E.L., S.E.H., S.S., E.B. and R.W.H. collected the data, contributed to the discussion and reviewed/edited the manuscript. R.W.H. is the guarantor of this work; he had full access to the data and takes responsibility for the integrity and accuracy of the data and analyses.

References


Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Participating diabetes centres in Germany and Austria.