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RESEARCH

Frequency and characteristics of diabetes in lipodystrophies and insulin receptoropathies compared with type 1 and type 2: results from the multicenter DPV registry

Clemens Kamrath[1], **Alexander Eckert**[2,3], **Birgit Rami-Merhar**[4], **Sebastian Kummer**[5], **Martin Wabitsch**[6], **Katharina Laubner**[7], **Florian Kopp**[8], **Silvia Müther**[9], **Steffen Mühldorfer**[10] and **Reinhard W Holl**[2,3]

[1]Center of Child and Adolescent Medicine, Justus Liebig University, Giessen, Germany
[2]German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany
[3]Institute of Epidemiology and Medical Biometry, ZIBMT, Ulm University, Ulm, Germany
[4]Department of Pediatrics and Adolescent Medicine, Medical University Vienna, Vienna, Austria
[5]Department of General Pediatrics, Neonatology and Pediatric Cardiology, Heinrich Heine University, Medical Faculty, Duesseldorf, Germany
[6]Center for Rare Endocrine Diseases, Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, Ulm University Medical Centre, Ulm, Germany
[7]Division of Endocrinology and Diabetology, Department of Medicine II, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg im Breisgau, Germany
[8]Forth Clinical Department of Medicine, Academic Teaching Hospital Augsburg, Augsburg, Germany
[9]Center for Pediatric Diabetology, DRK-Kliniken-Berlin Westend, Berlin, Germany
[10]Department for Gastroenterology, Endocrinology and Metabolic Diseases, Bayreuth University Hospital, Friedrich-Alexander University Erlangen-Nuremberg, Bayreuth, Germany

Correspondence should be addressed to C Kamrath: clemens.kamrath@paediat.med.uni-giessen.de

Abstract

Objective: To investigate the frequency, treatment, and outcome of patients with diabetes due to severe insulin resistance syndromes (SIRS).

Research Design and Methods: Based on data from the multicenter prospective Diabetes Registry DPV, we analyzed diagnosis, treatment, and outcome of 636,777 patients with diabetes from 1995 to 2022.

Results: Diabetes due to SIRS was documented in 67 cases (62.7% females), 25 (37%) had lipodystrophies (LD) and 42 (63%) had congenital defects of insulin signaling. The relative frequency compared to type 1 diabetes (T1D) was about 1:2300. Median age at diabetes diagnosis in patients with SIRS was 14.8 years (interquartile range (IQR) 12.8–33.8).

A total of 38 patients with SIRS (57%) received insulin and 34 (51%) other antidiabetics, mostly metformin. As high as 16% of patients with LD were treated with fibrates. Three out of eight patients with generalized LD (37.5%) were treated with metreleptin and one patient with Rabson–Mendenhall syndrome was treated with recombinant insulin-like growth factor 1.

The median glycated hemoglobin level at follow-up was 7.1% (54 mmol/mol). Patients with LD had higher triglycerides than patients with T1D and T2D ($P < 0.001$ and $P = 0.022$, respectively), and also significantly higher liver enzymes and lower high-density lipoprotein cholesterol than patients with T1D ($P < 0.001$).

Patients with insulin receptor disorders were significantly less likely to be treated with antihypertensive medication than patients with T2D ($P = 0.042$), despite having similar levels of hypertension.

Conclusions: Diabetes due to SIRS is rarely diagnosed and should be suspected in lean children or young adults without classical T1D. Awareness of cardiovascular risk factors in these patients should be raised.

Key Words

- diabetes
- rare diseases/syndromes

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Introduction

Diabetes mellitus due to insulin resistance is among the most prevalent endocrine disorders. It is commonly associated with obesity and lifestyle factors but may also occur in a very rare and severe form in patients with defects in adipose tissue development or function (lipodystrophy (LD)) or primary disorders of insulin signaling (1, 2, 3).

LDs are rare heterogeneous disorders characterized by selective loss of body fat and can be divided into congenital and acquired as well as generalized and partial forms (Table 1) (4, 5). This results in the four main categories congenital generalized lipodystrophy (CGL (Berardinelli–Seip syndrome)) and acquired generalized lipodystrophy (AGL), which are phenotypically characterized by near-total lack of body fat and prominent muscularity, familial partial lipodystrophy (FPL), which is phenotypically characterized by loss of s.c. fat from the extremities, and acquired partial lipodystrophy (APL), which is phenotypically characterized by a loss of fat in the upper body and increased fat in the buttocks, hips, and thighs. Other types of LD include progeroid syndromes or the SHORT syndrome.

LDs lead to insulin resistance and further complications such as diabetes mellitus, hypertriglyceridemia, nonalcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome, and acanthosis nigricans. The prevalence of generalized lipodystrophy, which includes both AGL and CGL, was reported as less than one case per million in Europe (4, 5). Differentiating LD from uncontrolled diabetes mellitus can be difficult because extreme hypertriglyceridemia and loss of body fat can occur in both.

Primary defects in insulin signaling due to impaired insulin receptors or abnormal signal transduction are very rare disorders leading to diabetes with severe insulin resistance. The spectrum of clinical severity is related to the degree of residual insulin receptor activity and ranges from infants with Donohue syndrome and young children with Rabson–Mendenhall syndrome (RMS) to adolescents or adults with type A insulin resistance (Table 1) (1, 2). Most patients develop diabetes as endogenous insulin secretion does not compensate for the degree of insulin resistance (1, 2, 3).

Treatment of these very rare severe insulin resistance syndrome (SIRS) is not well defined and is largely based on individual case reports or small case series.

The aim of this study was to evaluate frequency, diabetes care, and outcome of patients with LD and insulin receptoropathies in the large multicenter DPV Registry.

Patients and methods

Data source and study population

The current study is based on data from the German/Austrian/Swiss/Luxembourgian Prospective Diabetes Follow-up (DPV) Registry (Diabetes-Patienten-Verlaufsdokumentation), comprising 514 diabetes centers (hospitals and practices), including 283 pediatric health care facilities and 25 centers caring for both pediatric and adult patients, and 636,776 patients with diabetes mellitus from 1995 to March 2022. Twice a year, locally collected pseudonymized longitudinal data are transmitted for central plausibility checks and analyses to Ulm University, Ulm, Germany. Inconsistent data are reported back to participating centers for validation and/or correction. The data are then anonymized for benchmarking and patient-centered analyses. Verbal or

Table 1 Classification for syndromes of severe insulin resistance.

Phenotype	Subtype	Inheritance
Lipodystrophies		
Generalized	CGL (Berardinelli–Seip syndrome) (subtypes CGL1–4)	Autosomal recessive
	AGL (Lawrence syndrome)	Acquired
Partial	FPL (Kobberling/Dunningham)	Autosomal dominant
	APL	Acquired
Other	SHORT syndrome, Progeria syndromes	
	Nonclassified LD forms	
Insulin receptoropathies (primary insulin-signaling defects)		
Severe	Donohue syndrome or Rabson–Mendenhall syndrome (RMS)	Autosomal recessive
Mild	Type A insulin resistance syndrome	Autosomal recessive or dominant

AGL, acquired generalized lipodystrophy; APL, acquired partial lipodystrophy; CGL, congenital generalized lipodystrophy; FPL, familial partial lipodystrophy.

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written informed consent for participation in the DPV registry was obtained from patients or their guardians. The ethics committee of Ulm University approved the analysis of anonymized data from the DPV registry and local review boards approved data collection (6).

Study population

The aim of this study was to characterize patients with SIRS due to LD or congenital defects of insulin signaling and compare them with patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). A total of 636,777 patients of all ages with the diagnosis of T1D, T2D, and diabetes due to LD and congenital defects of insulin signaling (insulin receptoropathies) between 1995 and March 2022 were included in the study. Patients with LD were further clinically categorized into CGL (Berardinelli–Seip syndrome), AGL (Lawrence syndrome), APL, FPL (Kobberling/Dunningham), and other rare or unclassified forms. Patients with severe congenital insulin resistance syndromes were further categorized into RMS and type A insulin resistance syndrome (Table 1).

Diabetes subtype classification was based on documentation by the local treating diabetologist. We restricted the inclusion of patients with insulin receptoropathies to cases that were defined by the local clinicians as genetically confirmed.

If available, we additionally revalidated sequence information in the database. All classified patients with a diagnosis of SIRS were reviewed for plausibility according to guidelines (1, 2, 3, 4), and only those patients whose diagnosis stood up to scrutiny were included in the analysis.

We had to rely on what was entered into the DPV database by the local clinicians for the genetic results. Unfortunately, only a few diabetes centers have documented genetic data, mostly for reasons of data protection and laws in Germany (Human Genetic Examination Act (Genetic Diagnosis Act – GenDG) (7)). Therefore, the exact genotype with documentation of the disease-causing mutation was unfortunately only available in seven patients with LD and in one patient with RMS in the DPV registry. However, for reasons of data protection and in accordance with the ethical vote from the DPV registry, we are only allowed to publish aggregated data from at least five patients, which do not allow any conclusions to be drawn about the individual patient. Therefore, we are not allowed to share individual genetic data.

Variables

Demographic data included age at diabetes onset, age at follow-up, sex, duration of diabetes, and year of diabetes diagnosis.

Anthropometric data included height (in centimeters) and body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). Height and BMI values were transformed to standard deviation scores (SDS) based on German reference values by applying the Box-Cox transformation method (8).

Clinical and metabolic outcome parameters were also evaluated at the time of diabetes diagnosis and at the most recent documented follow-up visit and included daily dose of insulin (units per kilogram body weight), glycated hemoglobin levels (HbA_{1c}, % (mmol/mol)), cardiovascular risk factors such as lipids (triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low- density lipoprotein cholesterol (all in mg/dL)), systolic blood pressure (mmHg; SDS), and diastolic blood pressure (mmHg; SDS), as well as the liver enzymes (all in U/L) aspartate aminotransferase, alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) as indicators for NAFLD. Systolic and diastolic blood pressure SDS values were calculated according to German references (9).

In order to adjust for different laboratory methods, local HbA_{1c} values were mathematically standardized to the DCCT (Diabetes Control and Complications Trial) reference range (4.05–6.05%) using the 'multiple of the mean' transformation method (10).

Statistical analyses

All data were aggregated for each patient at two time points; diabetes manifestation (±6 weeks of the date of diagnosis) and at last follow-up defined as the most recent treatment year. Unadjusted outcomes were presented as median with interquartile range (IQR) or as percentage (%). Patient data were compared between different types of diabetes via Wilcoxon's rank sum test for continuous outcomes or $-\chi^2$ test for dichotomous outcomes. Corresponding *P*-values were adjusted for multiple testing using the Bonferroni-Holm method.

A two-sided *P*-value ≤ 0.05 was considered statistically significant. All analyses were performed with SAS 9.4

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(TS1M7, AS Institute, Cary, NC, USA) on a Windows Server 2019 mainframe.

Results

Study cohort

Among 636,777 patients with diabetes documented between 1995 and March 2022 in the DPV database, 155,287 patients were classified as T1D (24.4%) and 439,977 patients as T2D (69.1%). Diabetes due to SIRS was documented in 67 cases (1: 2317 cases with T1D, and 1: 6567 cases with T2D) from 53 out of 514 diabetes centers participating in the DPV registry.

Of these 67 patients, 25 (37%) were classified as LD and 42 (63%) as congenital defects of insulin signaling. Of those with LD, seven patients (28%) had CGL, five patients (20%) had FPL, three patients (12%) had APL, one patient (4%) had AGL, and nine patients had other or unclassified forms of LD. Of those with insulin receptoropathies, 2 patients were documented as RMS, while the remaining 40 patients were documented as genetic SIRS or type A insulin resistance syndrome.

Demographic characteristics of patients with LD and congenital defects of insulin signaling

The median age at diabetes diagnosis was 16.1 years (IQR 13.9–30.1) in patients with LD and 14.4 years (10.7–33.8) in patients with congenital insulin receptoropathies (Table 2). Among the LD cohort, the median age at diabetes diagnosis was 14.7 years (IQR 12.9–16.0) in patients with generalized LDs ($n=8$) and 26.5 years (18.3–40.3) in patients with partial LDs ($n=8$). In contrast, the median age at diagnosis was 11.7 years (7.0–20.8) in patients with T1D and 58.3 years (48.6–67.8) in patients with T2D. Age at diagnosis of diabetes differed significantly between patients with LD and either T1D ($P=0.006$) or T2D ($P<0.001$), as well as between patients with congenital defects of insulin signaling and T2D ($P<0.001$; Table 2).

In contrast to patients with T1D or T2D, patients with SIRS had a clear sexual dimorphism with a higher proportion of females. In the LD group, female dominance was mainly due to the group of patients with CGL, where all seven patients were female. Table 2 shows the demographic data of the study cohort.

Anthropometry in patients with LD and congenital defects of insulin signaling

The median age at the last documented visit was 21.0 and 21.1 years in patients with LD and congenital defects of insulin signaling, respectively (Table 2). Median height–SDS and BMI–SDS at last follow-up were –1.59 and –0.56 in LD patients, and –0.77 and 0.41 in patients with congenital insulin receptoropathies, respectively (Table 2).

Height–SDS was significantly lower in patients with congenital defects of insulin signaling than in T1D patients ($P=0.007$). Furthermore, patients with LD had significantly lower BMI–SDS than patients with T2D ($P=0.005$).

Treatment and outcome in patients with LD and congenital defects of insulin signaling

The median diabetes duration at the last follow-up was 4.4 years (IQR 1.7–10.7) in patients with LD and 4.7 years (IQR 0.5–8.2) in patients with insulin receptoropathies. Table 3 shows the results of the laboratory analysis at the last follow-up visit. Patients with LD and congenital defects of insulin signaling had elevated median HbA_{1c} values at the most recent documented visit (7.2% (55 mmol/mol) and 6.9% (52 mmol/mol), respectively) that did not differ from patients with T1D or T2D (Table 3). At the last follow-up, 14 (56%) patients with LD and 24 (57%) patients with defects in insulin signaling were treated with insulin. This was similar to patients with T2D, 51.6% of whom were treated with insulin. Of those patients treated with insulin, the median (IQR) daily insulin dose was 0.89 IU/kg (0.61–1.32) in patients with LD, 0.56 IU/kg (0.37–0.88) in patients with congenital defects in insulin signaling, 0.48 IU/kg (0.28–0.74) in patients with T2D, and 0.77 IU/kg (0.57–0.99) in patients with T1D. Patients with LD had significantly higher daily insulin dose than patients with T2D ($P=0.018$).

Other antidiabetic drugs were taken by 15 (60%) patients with LD and 19 (45%) patients with congenital defects of insulin signaling. Table 4 gives an overview of non-insulin treatments in patients with T1D, T2D, LD and patients with insulin receptoropathies.

Metformin was the most used drug in patients with T2D, LD, and congenital defects of insulin signaling (Table 4). After that, however, there were clear differences in the choice of antidiabetic drug. While gliptins were used

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Table 2 Demographic data of the study cohort.

Variable (median (IQR))	Type 1 diabetes (n = 155,288)	Type 2 diabetes (n = 439,977)	Lipodystrophies (n = 25)	Congenital insulin receptoropathies (n = 42)	Adjusted P-values (T1D vs LD)	Adjusted P-values (T2D vs LD)	Adjusted P-values (T1D vs insulin receptoropathies)	Adjusted P-values (T2D vs insulin receptoropathies)
Age at diagnosis (years)	11.7 (7.0; 20.8)	58.3 (48.6; 67.8)	16.1 (13.9; 30.1)	14.4 (10.7; 33.8)	0.006	<0.001	ns	<0.001
Female (%)	46.7	46.4	64.0	61.9	ns	ns	ns	ns
Age at last visit (years)	18.4 (15.4; 39.1)	70.1 (60.0; 78.1)	21.0 (17.9; 49.5)	21.1 (15.7; 44.1)	ns	<0.001	ns	<0.001
Diabetes duration at last visit (years)	7.3 (2.8; 14.1)	8.5 (2.8; 15.4)	4.4 (1.7; 10.7)	4.7 (0.5; 8.2)	ns	ns	ns	ns
Height at last visit (cm) (SDS)	169 (160; 177) (−0.18 (−0.90; 0.52))	169 (163; 176) (−0.83 (−1.56; −0.10))	163 (155; 171) (−1.59 (−2.84; 0.28))	165 (154; 171) (−0.77 (−1.81; −0.12))	ns[a]	ns[a]	0.007[a]	ns[a]
BMI at last visit (kg/m^2) (SDS)	22.9 (20.0; 26.2) (0.27 (−0.53; 1.03))	29.8 (26.2; 34.4) (0.55 (−0.38; 1.49))	19.6 (17.7; 26.3) (−0.56 (−3.17; 0.14))	24.0 (20.9; 30.3) (0.41 (−0.27; 1.17))	ns[a]	<0.001[a]	ns[a]	ns[a]
Systolic blood pressure at last visit (mmHg) (SDS)	122 (114; 132) (0.71 (−0.08; 1.58))	132 (120; 145) (1.48 (0.50; 2.61))	125 (118; 132) (1.15 (0.52; 1.55))	130 (115; 135) (1.62 (0.46; 2.14))	ns[a]	ns[a]	ns[a]	ns[a]
Diastolic blood pressure at last visit (mmHg) (SDS)	73 (67; 80) (0.53 (−0.25; 1.24))	80 (70; 82) (0.98 (−0.18; 1.41))	74 (69; 80) (0.85 (−0.27; 1.40))	75 (66; 81) (0.69 (−0.19; 1.39))	ns[a]	ns[a]	ns[a]	ns[a]

[a]Statistical analyses were performed using the SDS values.
ns, not significant; SDS, standard deviation score.

most frequently after metformin in patients with T2D, patients with LD were often treated with GLP-1 receptor agonists and patients with insulin receptor defects were often treated with SGLT2 inhibitors (Table 4).

Patients with congenital defects of insulin signaling had elevated systolic blood pressure (median systolic blood pressure 1.62 SDS), which corresponds to almost the 95th percentile for gender and age and means that almost half of the patients were hypertensive (Table 2). Nevertheless, patients with insulin receptoropathies were significantly less likely to be treated with antihypertensive medication than patients with T2D (P = 0.042, Table 4). ACE (angiotensin converting enzyme) inhibitors were used most often (9 out of 11 patients).

Of those patients with T1D and T2D who received antihypertensive drugs, hypertension had been previously documented in 66.2 and 58.4%, respectively, whereas microalbuminuria had been documented in 40.2 and 33.6%, respectively. In contrast, microalbuminuria had been documented in the majority of patients with LD or congenital defects of insulin signaling, namely in 8 out of 15 patients (53%) receiving antihypertensive drugs. In four patients with SIRS, no information on the presence or absence of microalbuminuria were available. Hypertension was documented in 8 out of 19 patients (42%) with SIRS receiving antihypertensive treatment.

Although patients with LD were more often treated with fibrates than patients with T1D or T2D (P < 0.001 each, Table 4), patients with LD had markedly elevated triglyceride levels, which were significantly higher compared to T1D or T2D patients (P < 0.001 and P = 0.022, respectively, Table 3). Moreover, patients with LD also had significantly lower HDL-cholesterol than patients with T1D (P < 0.001, Table 3).

Furthermore, patients with LD had higher ALT and GGT concentrations than T1D patients (P = 0.006 and P < 0.001, respectively, Table 3).

Table 5 shows treatments of the different subtypes of patients with LD. Three out of eight patients with generalized LD (38%) were treated with metreleptin, a human analog of leptin, but none of the other 17 patients with the other LD types (Table 4). One patient documented with RMS was treated with recombinant human insulin-like growth factor 1 (rhIGF1).

Discussion

This study found that diabetes due to SIRS is extremely rare, with about 1 case per 10,000 diabetes cases in the

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Table 3 Results of laboratory analysis at the last follow-up visit.

Variable (median (IQR))	Type 1 diabetes	Type 2 diabetes	Lipodystrophies	Congenital insulin receptoropathies	Adjusted *P*-values (T1D vs LD)	Adjusted *P*-values (T2D vs LD)	Adjusted *P*-values (T1D vs insulin receptoropathies)	Adjusted *P*-values (T2D vs insulin receptoropathies)
HbA_{1c} (%) (mmol/mol)	7.8 (7.0; 9.0) (62 (53; 75)) (n = 147,039)	7.2 (6.3; 8.5) (55 (45; 69)) (n = 395,474)	7.2 (6.7; 7.8) (55 (49; 62)) (n = 20)	6.9 (5.7; 8.8) (52 (38; 73)) (n = 42)	ns	ns	ns	ns
Total cholesterol (mg/dL)	178 (154; 206) (n = 105,188)	183 (151; 217) (n = 278,527)	180 (158; 209) (n = 18)	177 (151; 207) (n = 24)	ns	ns	ns	ns
HDL-cholesterol (mg/dL)	58 (48; 70) (n = 95,180)	43 (35; 53) (n = 246,810)	31 (26; 42) (n = 15)	47 (37; 66) (n = 25)	<0.001	ns	ns	ns
LDL-cholesterol (mg/dL)	99 (78; 123) (n = 94,131)	106 (79; 136) (n = 250,190)	108 (62; 133) (n = 15)	96 (88; 123) (n = 25)	ns	ns	ns	ns
Triglycerides (mg/dL)	100 (70; 151) (n = 101,360)	155 (110; 225) (n = 269,726)	317 (180; 524) (n = 16)	97 (82; 275) (n = 21)	<0.001	0.022	ns	ns
AST (U/L)	21 (17; 27) (n = 48,839)	25 (19; 34) (n = 80,331)	39 (19; 66) (n = 11)	25 (19; 38) (n = 12)	ns	ns	ns	ns
ALT (U/L)	18 (14; 24) (n = 55,205)	24 (17; 37) (n = 99,035)	36 (27; 72) (n = 12)	21 (15; 41) (n = 12)	0.006	ns	ns	ns
GGT (U/L)	15 (11; 23) (n = 46,476)	38 (23; 75) (n = 102,122)	54 (35; 123) (n = 11)	15 (13; 36) (n = 10)	<0.001	ns	ns	ns

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant.

DPV registry and a relative frequency compared to T1D of about 1:2300. Congenital defects in insulin signaling account for about two-thirds of cases with SIRS and one-third with LD. Considering that the prevalence of T1D in Germany is about 500 per 100,000 people (11), the prevalence of diabetes due to SIRS can be estimated to be about 2 cases per 1 million people. This is in agreement with the literature data on the prevalence of SIRS (1, 2, 3, 4, 5). However, it can be assumed that there is a high number of unreported or misclassified cases. This is underlined by two reasons. First, the female predominance in this as well as in other cohorts is probably not due to actual female predominance, but rather to the fact that the phenotype of LD, including hyperandrogenism and more muscular appearance in the absence of s.c. fat, is much more obvious in women and therefore more likely to be diagnosed than in men (12). Secondly, in a recent analysis of large clinical cohorts, the clinical prevalence of LD was estimated to be considerably higher, at approximately 1:20,000 individuals (12). Furthermore, the difficulty in diagnosing SIRS and distinguishing it from more common forms of diabetes may be due to the rarity of these forms of diabetes. Nevertheless, patients with SIRS can be clinically distinguished from patients with T1D or T2D. Compared to patients with T2D, they were significantly younger and slimmer, and compared to patients with T1D, they were islet autoantibody negative and had no insulin deficiency (13). In addition, patients with SIRS were often characterized by short stature.

Another characteristic laboratory feature of patients with LD was the often markedly elevated triglyceride concentrations along with low HDL cholesterol concentrations and elevated liver enzymes indicative of NAFLD (14, 15). The presence of significant dyslipidemia and hepatic steatosis has been considered a sensitive indicator of underlying LD (3). However, specificity is low as patients with T1D and T2D also frequently develop NAFLD (16).

Our study showed remarkably high systolic blood pressure levels after several years of medical care, especially in patients with defects in insulin signaling. Although an association between insulin resistance and hypertension has been frequently described, this association mainly relates to patients with metabolic syndrome, obesity, or T2D (17). Hypertension has not been specifically mentioned in patients with congenital insulin receptor disorders (1, 2, 3). Our study suggests that this may be an under-recognized clinical feature in these patients. In combination with existing diabetes and dyslipidemia, hypertension is an important cardiovascular risk factor (18, 19, 20, 21).

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Table 4 Overview of treatments at the last follow-up visit.

Treatment (%)	Type 1 diabetes (n = 155,288)	Type 2 diabetes (n = 439,977)	Lipodystrophies (n = 25)	Congenital insulin receptoropathies (n = 42)	Adjusted *P*-values (T1D vs LD)	Adjusted *P*-values (T2D vs LD)	Adjusted *P*-values (T1D vs insulin receptoropathies)	Adjusted *P*-values (T2D vs insulin receptoropathies)
Other antidiabetic drugs	3.0	51.2	60.0	45.2	<0.001	ns	<0.001	ns
Metformin	2.4	37.7	52.0	35.7	<0.001	ns	<0.001	ns
Glinides	0.1	2.8	4.0	2.4	<0.001	ns	<0.001	ns
Sulfonylureas	0.4	9.6	4.0	2.4	ns	ns	ns	ns
GLP-1 analogs	0.1	3.9	12.0	2.4	<0.001	ns	0.005	ns
DPP4 inhibitors	0.4	17.0	4.0	4.8	ns	ns	0.002	ns
SGLT2 inhibitors	0.3	4.5	4.0	7.1	ns	ns	<0.001	ns
Lipid-lowering drugs	6.9	28.3	28.0	19.1	0.001	ns	ns	ns
Statins	6.4	26.4	8.0	16.7	ns	ns	ns	ns
Fibrates	0.1	0.8	16.0	0.0	<0.001	<0.001	ns	ns
Antihypertensive drugs	12.7	51.8	32.0	26.2	ns	ns	ns	0.042
ACE inhibitors	6.8	26.2	20.0	21.4	ns	ns	0.008	ns

ACE, angiotensin converting enzyme; DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; ns, not significant; SGLT2, sodium glucose linked transporter 2.

Antihypertensive treatment, however, was less frequently documented in these patients compared with patients with T2D although blood pressure SDSs were comparable between the two groups. One reason for this may be that patients with congenital insulin receptor defects were younger and leaner, and therefore, there may be less awareness of cardiovascular risk factors in these patients. Interestingly, those patients with SIRS who were receiving antihypertensive drugs, mainly ACE inhibitors, had documented microalbuminuria in more than half of the cases. This highlights the high cardiovascular morbidity of these patients.

In patients with LD, HbA_{1c}, triglycerides, and liver enzymes were significantly above the normal range and HDL cholesterol concentrations were significantly decreased at the last documented follow-up, despite a high proportion of patients being treated with insulin and fibrates. HbA_{1c}, triglycerides, and low HDL-cholesterol concentrations are known risk factors for later cardiovascular events (18, 19, 20, 21). In addition, hypertriglyceridemia is associated with an increased risk of acute pancreatitis in patients with LD, and NAFLD may progress to cirrhosis (14, 15). Acute pancreatitis, liver disease (liver failure, gastrointestinal bleeding, hepatocellular carcinoma), and heart disease (cardiomyopathy, heart failure, myocardial infarction, arrhythmias) are major causes of mortality in patients with SIRS (1, 2, 3, 4, 5, 14, 15).

Leptin replacement therapy with metreleptin is associated with improvements in metabolic disturbances in patients with LD, and since 2018, it has been approved by the European Medicines Agency in the European Union in addition to diet to treat the consequences of leptin deficiency in adults and children over 2 years of age with generalized LD (CGL or AGL), and in adults and children over 12 years of age with partial LD, when standard treatments have failed to achieve adequate metabolic control (22, 23, 24). Our analysis showed that only three out of eight patients with generalized LD and none with partial LD were treated with metreleptin. However, the main reason for the apparent infrequent use of metreleptin in LD patients in our cohort is that only four patients with generalized or partial LD had their last documented visit after 2018 when metreleptin was approved.

In contrast to other types of diabetes, a significant number of patients with inborn defects of insulin signaling have been treated with SGLT2 inhibitors. This approach has been described in several case reports as a successful therapeutic approach in this disorder, as the glucosuric effect leads to an insulin receptor-independent lowering of

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Table 5 Overview of treatments in patients with lipodystrophy (*n* = 25).

Treatment (%)	**Generalized** (CGL, AGL) (*n* = 8)	**Partial** (APL, FPL) (*n* = 8)	**Others** (*n* = 9)
Insulin treatment	37.5	75.0	55.6
Oral antidiabetic drugs	75.0	50.0	55.6
Biguanides	75.0	25.0	55.6
Glinides	0.0	12.5	0.0
Sulfonylureas	0.0	12.5	0.0
GLP-1 analogs	0.0	12.5	22.2
DPP4 inhibitors	0.0	12.5	0.0
SGLT2 inhibitors	0.0	12.5	0.0
Lipid-lowering drugs	37.5	50.0	0.0
Statins	37.5	50.0	0.0
Fibrates	25.0	25.0	0.0
Antihypertensive drugs	50.0	50.0	0.0
ACE inhibitors	25.0	37.5	0.0
Other specific drugs			
Leptin analog (metreleptin)	37.5	0.0	0.0
rhIGF-1 (mecasermine)	0.0	0.0	0.0

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; rhIGF-1, recombinant human insulin-like growth factor-1; SGLT2, sodium glucose linked transporter 2.

blood glucose (25, 26, 27, 28). In addition, SGLT2 inhibitors may be beneficial in this indication due to their positive effect on blood pressure (29, 30). However, these potential benefits must be weighed against the increased risk of ketoacidosis in patients treated with SGLT2 inhibitors (31). Moreover, of two patients with the most severe defects in the insulin receptor, one received treatment with rhIGF-1, a treatment option described as successful in several case reports or case series (32, 33, 34, 35, 36).

The strengths of the present study include the large sample size of a population-based cohort of more than 600,000 patients with diabetes, with stringent prospective data collection. The DPV register covers about 80–90% of pediatric patients with diabetes in Germany and Austria, with coverage likely to be even higher for young children with diabetes. This allowed us to access a relatively large number of cases and identify a large number of patients with SIRS. This study, which involved 25 patients who had documented LD and 44 who had documented genetic defects in the insulin signaling pathway, is one of the largest series of data on these two very rare forms of diabetes in young patients. Unlike other studies, the DPV registry collects clinical and laboratory data, as well as details of diabetes therapy, allowing us to provide a comprehensive characterization of these rare forms of diabetes. Moreover, the results reported in this study are based on registry data from patients receiving usual care in different clinical settings and reflect current advances in clinical practice. This study provides real-world long-term outcomes data from patients with SIRS with a median disease duration of approximately four and a half years.

Limitations of our study include the lack of individual genotype information. Our analysis was based on documented genotype information from the treatment center and we did not have direct access to the original laboratory reports. However, all clinicians contributing data are qualified according to national/international standards. In addition, all cases with SIRS were checked by us for plausibility according to guidelines (1, 2, 3, 4, 37). As we did not collect information on the specific pathogenic variants of each case, a correlation between genotype and phenotype was not possible. Furthermore, conclusions must be drawn with caution, as the rarity of the disease and the associated small number of cases allowed only case description and limited the possibility of statistical evaluation.

Another limitation of our study is that the effect of individual diet could not be taken into account. We also analyzed a large time series from 1995 to 2022. During this time, knowledge and treatment options for these rare diseases have improved, so some of the reported patients with SIRS would be treated differently today than they were a few years ago. For example, during this period, metreleptin was introduced as a leptin replacement therapy for patients with LD. Unfortunately, more recent documented data are missing for some patients, which may be due to the fact that patients have been transferred over time to other care facilities that do not actively participate in the DPV register.

Another limitation is that the DPV registry is mainly diabetes-centered, so very important other aspects of the disease, such as hyperandrogenism or the incidence of complications such as pancreatitis, are prone to under-reporting and cannot be reliably assessed from the data reported to the DPV. Moreover, the relatively high number of patients with T1D and their young age at the last follow-up, as well as the high proportion of almost 60% of facilities caring for pediatric patients with diabetes, reflects the lower completeness of coverage in the DPV register for adult patients with diabetes compared to pediatric patients. Ratios of the different types of diabetes are therefore not representative of the general population. In particular, the ratios of patients with SIRS compared to T1D and T2D are therefore unlikely to reflect the true ratios in the population. However, as the DPV

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register covers about 90% of pediatric patients with T1D, it seems to us that the case ratios of SIRS to T1D and the estimated prevalence of SIRS derived from the prevalence of T1D are reasonably representative. In addition, 53% of diabetes centers that documented patients with SIRS carried for children, a proportion comparable to the overall DPV registry.

In conclusion, diabetes due to SIRS is an extremely rare and underdiagnosed condition. It is therefore important to inform about the diagnosis and management of these rare disorders, as treatment is still inadequate and affected patients have significant risk factors for subsequent cardiovascular and non-cardiovascular sequelae. Therefore, patients with SIRS should be managed by or in collaboration with specialized centers, e.g. using the framework of the European Reference Network on Rare Endocrine Conditions (Endo-ERN) for genetic disorders of glucose and insulin homeostasis, to ensure that patients receive the best possible care (38).

Declaration of interest

CK and MW received honoraria for lectures and an advisory board from Aegerion Pharmaceuticals and Amryt Pharma. BRM has received honoraria for lectures and advisory boards (last 3 years) from: Abbott, Medtronic, Sanofi, Eli Lilly, Insulet. KL has received in the last 3 years honoraria for lectures from Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Novartis. All other authors have nothing to declare.

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Data availability

AJE and RWH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Access to the data is possible by remote data processing upon request.

Author contributor statement

Prof Kamrath conceptualized the study, interpreted the analyses, wrote the initial manuscript, and reviewed and revised the manuscript. Alexander J Eckert, MSc, analyzed the data and designed the analyses, contributed to the interpretation of results, and reviewed and revised the manuscript. Prof Holl conceptualized the study, coordinated and supervised data collection, acquired funding for the study, and critically reviewed the manuscript for important intellectual content. All other authors collected data, contributed intellectually to the research topics of the DPV initiative, and critically reviewed the scientific content of the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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