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Polycystic ovary syndrome (PCOS) in juvenile and adult type 1 diabetes in a German/Austrian cohort

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Abstract

Context: While an association between PCOS and type 2 diabetes is well established, to date there have been few data on clinical care of type 1 diabetes (T1D) patients with PCOS.

Objective: The aim of our study was to characterize T1D patients with the comorbidity of PCOS within the DPV cohort with regard to diabetes phenotype, therapy and metabolic control.

Design and Setting: Clinical data from the prospective German/Austrian DPV cohort on patients with T1D and documented PCOS (n=76) were compared to female T1D controls (n=32,566) in reproductive age.

Results: The age at T1D manifestation in PCOS patients was later than in the control group (14.9 ± 8.2 vs. 11.8 ± 7.0 years, p <0.001). PCOS patients had higher BMI-SDS (0.92 ± 0.11 vs. 0.38 ± 0.01, p <0.001), metformin and oral contraceptives were used more frequently (p<0.001). A1c levels were significantly lower (7.92 +/- 0.23% vs. 8.43 ± 0.01%, p <0.05) despite of lower insulin requirements (0.76 ± 0.04 IU/kg/d vs. 0.84 ± 0.00 IU/kg/d, p <0.05). In the PCOS group, higher rates of dyslipidemia (63.4 vs. 48.7 %, p =0.032) and thyroid disorders (42.2 % vs. 21.2 %, p <0.001) were present.

Discussion: While patients with T1D and comorbid PCOS showed features of a “type 1.5 diabetes” phenotype, insulin requirements per kg body weight were not higher and metabolic control was better, which could be explained only partially by additional metformin therapy. A more precise genetic and metabolic characterisation of these patients is needed to answer open questions on the underlying autoimmune process and residual ß-cell function.

Keywords

Diabetes < Autoimmunity

Polycystic ovary syndrome < Hormones

Obesity

Introduction

The polycystic ovary syndrome (PCOS) is one of the most important reasons for female infertility and a common metabolic disorder [1]. According to several cross-sectional studies, 6-15 % of the female population of childbearing age worldwide suffer from PCOS [2], while an unknown percentage is still undiagnosed. Prevalence depends on the genetic and socioeconomic background as well as the criteria used for diagnosis The common definitions (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop 2004 [3]) share hyperandrogenism as a central feature, besides oligo-/anovulation and a polycystic morphology of the ovaries on ultrasound examination, with two out of three criteria required in adults. Adolescents in particular should exhibit clinical or laboratory androgen excess, as anovulation and polycystic ovaries may physiologically occur in puberty, and the latter do not belong to the diagnostic criteria [4]. Other causes of androgen excess or related disorders such as non-classic adrenal 21-hydroxylase deficiency, hyperprolactinemia, or androgen secreting neoplasm have to be ruled out before making the diagnosis [5]. More than 40 % of PCOS patients are insulin resistant, measured by patch clamp, OGTT or HOMA-index [6]. While an association of PCOS with the spectrum of impaired glucose tolerance to type 2 diabetes (T2D) is well established [7] the scope of this study is to investigate the clinical presentation of combined insulin dependent type 1 diabetes (T1D) and PCOS. A recent meta-analysis of nine studies showed a higher prevalence of PCOS in patients with T1D compared to the general population and a cumulative incidence of up to 24 % [8]. Although in T1D increased androgen levels, menstrual abnormalities and delayed puberty are common, it is assumed that currently many PCOS cases in T1D are undiagnosed. The consequences of the comorbidity for the diabetes disease are unknown and a general or selective screening for PCOS is not yet implemented in T1D clinical practice guidelines.

Objective

To date there have been few data on clinical care of T1D patients with PCOS. Aim of the study was to analyse within the DPV database diabetes phenotype, therapy and metabolic control of female patients with T1D in reproductive age with or without documented PCOS.

Research design, methods

Research design

We performed an observational cross sectional multicentre analysis of patients with T1D and PCOS between age 12 and 40 years and compared data to female T1D subjects without PCOS registered in the German/Austrian DPV database (Diabetes Patienten Verlaufsdokumentation). DPV is a nationwide prospective population-based registry of 437.289 patients (June 2016) with any type of diabetes in 446 centres in Germany, Luxemburg, Switzerland and Austria. Data are collected during routine care, anonymized and updated twice a year at a central administrative unit at the University of Ulm, Germany. The DPV has the ethical approval at the University of Ulm plus local data safety approval.

Patients

Within the study population 76 female patients with the documented diagnosis of both T1D and PCOS were identified. This cohort was compared to 32,566 female patients with T1D, but without the documented diagnosis of PCOS in the same age group (12-40 years). Diabetes duration was at least 6 months in all patients.

Calculations/definitions

Body mass index (BMI) values in these female patients were adjusted for age. Sex-specific standard deviation scores for BMI were calculated with national reference data from the German Health Interview and Examination Survey for Children and Adolescents and the German National Nutrition Survey for Adults [9; 10]. Glycated hemoglobin (A1c) was tested by the local laboratories and results were adjusted to the Diabetes Control and Complication Trial (DCCT) reference range (20-42 mmol/mol [4.05-6.05 %]) for comparability [11]. The total daily insulin dose was calculated as units per body weight (kg) per day. Dyslipidemia was defined by total cholesterol levels >200 mg/dl, HDL <35 mg/dl, LDL >130 mg/dl or triglycerides >150 mg/dl. Thyroid disease was defined by clinical diagnosis of thyroid disease or laboratory diagnosis of autoimmune thyroid disease (TPO, TG or TRAK antibodies). The clinical diagnosis of PCOS was made by the treating physicians in the individual centres and documented in the DPV registry.

Statistics

Analyses were performed with the SAS 9.4 statistical software package (SAS Institute Inc., Cary, USA). Unadjusted data are presented as mean +/- SD or percentage. *P*-values for continuous data were determined by

Wilcoxon, *p*-values for categorical variables by chi-square test, and *p* was corrected for multiple comparisons (false discovery rate). $p < 0.05$ was considered as statistically significant in a two-sided test. Additionally, linear and logistic regression models were used to adjust comparisons for age (12-<20, 20-<40 years) and diabetes duration (<5, >=5 years). Adjusted data were presented as mean +/- SEM or percentage.

Results

Age at diabetes manifestation

Patients in the PCOS group had a significantly and clinically relevant later onset of diabetes at a mean age of 14.9 instead of 11.5 years (p <0,001). For 85.3 % of all patients, positive ß-cell specific autoantibodies were documented, with no significant difference between the two groups.

Weight

Obesity was more common in T1D patients with PCOS. In PCOS BMI and BMI-SDS were significantly higher compared to control T1D patients. Body weight differed between the groups, PCOS patients weighing about 6 kg more, while height was similar (PCOS 164.1 vs. controls 165.0 cm, n.s.).

Hypertension and late complications

The prevalence of arterial hypertension did not differ among groups. We saw no significant difference in the incidence of albuminuria or retinopathy (no documented case in PCOS vs. 6.4 % in controls, n.s.) as markers of current microvascular disease.

Dyslipidemia

Patients with PCOS exhibited a significantly higher rate of dyslipidemia or taking lipid lowering drugs. Dyslipidemia rates did not differ significantly between PCOS patients using metformin therapy and those without (table 2).

Associated disease

More than 4 in 10 patients with PCOS showed thyroid disorders, about twice as much as T1D controls, defined by the diagnosis of thyroid disease, and/or positive autoantibodies. While the frequency of thyroid autoantibodies

was not significantly higher, medication with levothyroxine or iodine was significantly more common in the PCOS group (table 1, p= 0.006). TSH levels were similar and in the normal range in both groups (PCOS 2.2 +/- 0.9 and 2.4 +/- 0.04 µU/ml without PCOS, n.s.). The prevalence of other autoimmune diseases such as rheumatoid arthritis, chronic inflammatory bowel disease, multiple sclerosis, pernicious anemia or adrenal autoantibodies in our cohort was too low to make sensible comparisons. We did not observe any patient with celiac disease within the PCOS group.

Treatment

Hormonal contraceptives were used by one in three PCOS patients, three times more often than in patients without PCOS (table 1). Although BMI and BMI-SDS were higher in the PCOS group, the total daily amount of insulin was similar. PCOS patients did not show higher insulin doses per kg bodyweight than controls (table 1). Metformin was more extensively used in the PCOS group. While 21 % of PCOS patients were using metformin, only 1.2 % of all female T1D patients were on biguanid therapy (table 1, p<0.001). Within the PCOS group those patients with metformin use had a higher body weight and a significantly higher BMI-SDS. Patients on metformin used conventional insulin therapy (CT) more often and had a lower daily insulin dose for body weight, however not quite significant. PCOS patients without metformin had similar insulin requirements as controls (table 2).

Metabolic control

Overall metabolic control was only partially sufficient, with A1c above target of 7-7.5% in both groups. A1c levels were significantly better in the PCOS group (table 1), where both patients with and without metformin had a significantly better A1c than controls (table 2).

Discussion

The aim of our study was to characterize T1D patients with the comorbid PCOS within the DPV database with regard to diabetes phenotype, therapy and metabolic control. Therefore, we identified females with both diagnoses in the DPV registry and compared their data to T1D patients without PCOS. As expected, patients with T1D and PCOS were more overweight and showed a higher rate of dyslipidemia. More patients in the PCOS group were taking oral contraceptives, possibly mainly because of the antiandrogenic effects.

Pathophysiology

The age of diabetes onset in the PCOS group was delayed by more than three years. This was an unexpected finding, and in contrast to previous data [14; 15]. A possible explanation is that the pathogenesis of T1D is different in those patients with PCOS. There might be a different genetic background with respect to the underlying autoimmune process. We saw a similar frequency of beta-cell autoimmunity and autoimmune thyroid disorders, but no celiac disease in our T1D-PCOS cohort. This supports the hypothesis of a lower prevalence of T1D or celiac disease specific high risk HLA-alleles (HLA-DR3/4-DQ2/8) in the PCOS group. Patients with PCOS might be more prone for a different kind of autoimmunity compared to the T1D cohort in general. Only genotyping of PCOS patients for HLA-alleles and other T1D associated genes could finally clarify these questions on the genetic background.

It is unclear to date, whether patients develop (subclinical) PCOS or T1D first. Considering pathophysiology, insulin resistance associated with PCOS might be a driving factor for development of T1D comparable to the "accelerator hypothesis" [12; 13]. The surprisingly high percentage of patients on conventional insulin therapy (CT) fits a T2D-like phenotype.

On the other hand, PCOS might also be a secondary phenomenon to diabetes, triggered by high doses of insulin, administered subcutaneously in a non-physiological fashion surpassing the hepatic first pass mechanism [14; 15]. Insulin exerts a trophic action on ovary cells [16; 17] and drives the vicious circle of PCOS. Moreover, girls with T1D onset in puberty show rapid weight gain [18] which may lead to obesity related complications and comorbidities like PCOS. Regardless of what comes first, the T1D-PCOS cohort shows features of type 1.5 diabetes, with both autoimmunity and traits of a T2D phenotype [19; 20].

Implications for treatment

Patch clamp studies were able to show that PCOS women have significant insulin resistance which is independent of adiposity [21]. Surprisingly, our clinical practice data do not show higher insulin requirements in T1D patients with PCOS. Although PCOS patients were overweight in our cohort, metabolic control was even better than in T1D controls with similar insulin requirements. This could be explained by a less aggressive autoimmune disease and a persisting beta-cell-function. Unfortunately, we do not have sufficient data available

on C-peptide in the cohort. PCOS patients with and without metformin had a better A1c than controls, so favourable metabolic control can only be explained in part by metformin therapy (table 2). While T1D patients in total did not show a significant benefit from metformin therapy [22-25] our subgroup of PCOS patients seemed to benefit in terms metabolic control and experiences an insulin sparing effect, compensating for otherwise higher insulin requirements in a disease commonly associated with insulin resistance. Notably metformin treatment was more commonly initiated in obese patients, so our data cannot provide information on whether lean T1D women with PCOS will equally benefit with regard to metabolic control. There might be a benefit in fertility treatment, where metformin can be added to clomiphene or used alone [26; 27] and therefore a subgroup of the women in our cohort will use metformin not only for improvement of metabolic control but also to induce pregnancy. All women were in reproductive age, and those who desire to have children may be more disciplined in terms of treatment, eating habits and lifestyle and this might have influenced metabolic control in addition to a direct effect of metformin.

Of note, we saw a high rate of thyroid disorders in PCOS patients. While a high prevalence of autoimmune thyroid disorders in PCOS patients was described previously [28], many women might however be treated with levothyroxine for fertility treatment or for obesity-associated hyperthyrotropinemia. Still, not only in diabetes but also in PCOS in general a screening for autoimmune thyroiditis or hypothyroidism should be considered

Screening

Escobar-Morreale et al. warn that PCOS is the most commonly missed comorbidity in T1D patients as screening is not yet implemented, while incidence is high [8]. In his meta-analysis of nine studies, 24% (CI 15-34) of T1D patients were diagnosed with PCOS. Our prevalence was much lower, reflecting a certain degree of underdiagnosis or underreportation, although it has to be taken into account that prevalence depends on the ethnic background and patients were young, while diagnosis is often delayed. Despite clinical practice guidelines recommendations to screen PCOS patients for diabetes, neither T1D nor T2D patients are currently screened for PCOS [29; 30].

PCOS belongs to the most common comorbidities, and even without general screening diabetologists should include evaluation of menstrual abnormalities or clinical hyperandrogenism (hirsutism, acne) in their routine examinations as already practised for other comorbidities as hypertension, dyslipidemia, celiac and thyroid

disorders to gain a better understanding of this patient group. While some patients have no metabolic comorbidities, especially those 50-70% PCOS patients at risk, who exhibit obesity, dyslipidemia, hypertension and insulin resistance, have an elevated risk for cardiovascular diseases. The higher rate oral contraceptive use may add up to the elevated risk for cardiovascular diseases in women with diabetes. It is currently unknown whether an added cardiovascular risk arises from PCOS diagnosis in normal weight women with type 1 diabetes who have no other cardiovascular risk factors [8].

Limitations

This study has some limitations. First, due to potential underreporting of secondary diagnoses, the true prevalence of PCOS in T1D patients in the DPV registry may be higher. We deliberately decided not to include patients without the documented diagnosis of PCOS but isolated findings such as anovulation, hirsutism, infertility etc., though this would have yielded a higher patient number. Also, the database does not allow to conclude whether PCOS or T1D developed first.

A second limitation is that we have no information about body composition (body fat, waist circumference) or regularity of menses available and miss laboratory data on steroid hormones. The data available in the registry are the diabetes-specific clinical parameters on which this study has focused.

Conclusion

Patients diagnosed with PCOS and T1D presented with diabetes later in life, showed lower insulin requirements and a better metabolic control compared to T1D patients without PCOS. They demonstrated features of type 1.5 diabetes. Screening for PCOS should be implemented in the clinical care of female adolescents and adults with T1D, as this comorbidity is common, and the early diagnosis may have implications for evaluating the cardiovascular risk and deciding on additional metformin treatment, which appears to be beneficial in these patients. In terms of pathogenesis of the PCOS in female patients with T1D our data raises open questions concerning the underlying autoimmune process and the residual beta-cell function. A deeper genetic and metabolic characterisation of these patients is needed for a better understanding.

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	T1D and PCOS	T1D only	adjusted p-value
All patients [n]	76	32.566	
Age [years]	24.6 ± 7.6	20.0 ±7.2	<0.001*
Age at diabetes onset [years]	14.9 ± 8.2	11.5 ± 7.0	<0.001*
Duration of diabetes [years]	9.7 ± 7.4	8.5 ± 6.6	n.s. (0.44)*
Weight [kg]	72.9 ±1.6	65.1 ± 0.1	<0.001
BMI [kg/m²]	26.78 ± 0.52	23.83 ± 0.02	<0.001
BMI-SDS	0.92 ±0.11	0.38 ± 0.01	<0.001
A1c [%]	7.93 ±0.23	8.43 ± 0.01	0.031
Insulin dosage [IU/kg body weight/d]	0.77 ± 0.04	0.84 ± 0.002	n.s. (0.11)
Absolute insulin dosage [IU/d]	54.53 ± 2.77	53.56 ± 0.13	n.s. (0.73)
Thyroid disease [%]	42.2 ± 5.8	21.2 ± 0.2	<0.001
Thyroid antibodies [%]	19.9 +/- 6.8	28.7 +/- 0.4	n.s. (0.26)
Thyroid medication [%]	26.9 ± 5.4	14.7 ± 0.2	0.006
Dyslipidemia/ lipid lowering medication [%]	63.4 ± 6.5	48.7 ± 0.3	0.032
Hypertension/ antihypertensive medication [%]	17.2 ± 4.3	13.4 ± 0.2	n.s. (0.33)
Oral contraceptives [%]	35.6 ± 5.7	11.2 ± 0.2	<0.001
Metformin [%]	21.0 ± 4.5	1.2 ± 0.0	<0.001
Microalbuminuria [%]	15.6 ± 5.1	13.2 ± 0.2	n.s. (0.61)

Table 1: Comparison of female patients with T1D and documented PCOS versus T1D only. Data are shown as mean ± SD/SEM or percentage (*=unadjusted data, other comparisons are adjusted for age and T1D-duration)

	PCOS and metformin (n=19)	PCOS/no metformin (n=57)	adjusted p-value
Weight [kg]	79.4 ± 3.4	73.4 ± 2.1	n.s. (0.13)
BMI [kg/m²]	29.4 ± 1.1	26.6 ± 0.7	0.043
BMI-SDS	1.20 ± 0.21	0.75 ± 0.13	n.s. (0.08)
A1c [%]	8.00 ± 0.41	7.76 ± 0.23	n.s. (0.62)
Insulin dosage [IU/kg body weight/d]	0.58 ± 0.07	0.75 ± 0.05	n.s. (0.051)
Absolute insulin dosage [IU/d]	44.7 ± 5.4	53.7 ± 3.4	n.s. (0.16)
Conventional therapy/CT [%]	25.5 ± 11.1	2.1 ± 2.3	0.031
Oral contraceptives [%]	14.2 ± 8.0	35.1 ± 6.8	n.s. (0.10)
Dyslipidemia/ lipid lowering medication [%]	61.6 ± 15.1	65.0 ± 7.2	n.s. (0.84)
Hypertension/ antihypertensive medication [%]	25.5 ± 10.1	16.4 ± 5.1	n.s. (0.39)

Table 2: Comparison of female patients with T1D and PCOS with and without metformin therapy. Data are shown as mean ± SEM or percentage

Collaborating DPV centers

Augsburg Kinderklinik Zentralklinikum, Aachen - Uni-Kinderklinik RWTH, Ahlen St. Franziskus Kinderklinik, Aue Helios Kinderklink, Aurich Kinderklinik, Wien Uni-Kinderklinik, Weingarten Kinderarztpraxis, Berlin Lichtenberg - Kinderklinik, Berlin Virchow-Kinderklinik, Berlin Vivantes Hellersdorf Innere, Berlin Klinik St. Hedwig Innere, Berlin Schlosspark-Klinik Innere, Bad Aibling Internist. Praxis, Bremerhaven Kinderklinik, Bielefeld Kinderklinik Gilead, Bonn Uni-Kinderklinik, Braunfels-Wetzlar Innere, Hinrichsegen-Bruckmühl Diabetikerjugendhaus, Bottrop Kinderklinik, Bottrop Knappschaftskrankenhaus Innere, Celle Klinik für Kinder- und Jugendmedizin, Chemnitz Kinderklinik, Coesfeld Kinderklinik, Düsseldorf Uni-Kinderklinik, Darmstadt Kinderklinik Prinz. Margaret, Deggendorf Pädiatrie-Praxis, Deggendorf Medizinische Klinik II, Bad Driburg / Bad Hermannsborn Innere, Düren-Birkesdorf Kinderklinik, Delmenhorst Kinderklinik, Deggendorf Kinderklinik, Detmold Kinderklinik, Dortmund Kinderklinik, Dortmund-St. Josefshospital Innere, Dresden Uni-Kinderklinik, Datteln Vestische Kinderklinik, Essen Uni-Kinderklinik, Erlangen Uni-Kinderklinik, Erfurt Kinderklinik, Esslingen Klinik für Kinder und Jugendliche, Eutin St.-Elisabeth Innere, Eutin Kinderklinik, Frankfurt Uni-Kinderklinik, Offenbach/Main Kinderklinik, Freiburg Uni-Kinderklinik, Friedberg Innere Klinik, Friedrichshafen Kinderklinik, Fürth Kinderklinik, Fulda Kinderklinik, Gaissach Fachklinik der Deutschen Rentenversicherung, Bayern Süd, Garmisch-Partenkirchen Kinderklinik, Gießen Uni-Kinderklinik, Göppingen Kinderklinik am Eichert, Gelsenkirchen Kinderklinik Marienhospital, Göttingen Uni-Kinderklinik, Görlitz Städtische Kinderklinik, Hannover Kinderklinik MHH, Hannover Kinderklinik auf der Bult, Hannover Henriettenstift - Innere, Halle Uni-Kinderklinik, Halle-Dölau Städtische Kinderklinik, Hachenburg Kinderpraxis, Hamm Kinderklinik, Bremen Zentralkrankenhaus Kinderklinik, Bremen - Kinderklinik Nord, Heilbronn Innere Klinik, Heidelberg Uni-Kinderklinik, Heidenheim Kinderklinik, Herford Klinikum Kinder & Jugendliche, Bad Hersfeld Kinderklinik, Herzberg Kreiskrankenhaus Innere, Hermeskeil Kinderpraxis, Hagen Kinderklinik, Hamburg Altonaer Kinderklinik, Hamburg Kinderklinik Wilhelmstift, Hamburg-Nord Kinder-MVZ, Hildesheim Kinderklinik, Hildesheim Kinderarztpraxis, Liste der in diese Auswertung eingehenden Zentren, Lübeck Uni-Kinderklinik, Lübeck Uni-Klinik Innere Medizin, Homburg Uni-Kinderklinik Saarland, Hanau Kinderklinik, Itzehoe Kinderklinik, Jena Uni-Kinderklinik, Köln Uni-Kinderklinik, Karlsruhe Städtische Kinderklinik, Kaiserslautern-Westpfalzklinikum Kinderklinik, Karlsburg Klinik für Diabetes & Stoffwechsel, Kempen Heilig Geist - Innere, Kiel Städtische Kinderklinik, Konstanz Innere Klinik, Koblenz Kinderklinik Kemperhof, Koblenz Kemperhof . 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Hietzing Innere, Leoben LKH Kinderklinik, Duisburg-Huckingen, Münster Herz Jesu Innere, Marktredwitz Innere Medizin, Krefeld-Uerdingen St. Josef Innere, Wien Wilhelminenspital. Med. Abteilung, Wien SMZ Ost Donauspital, Wien Rudolfstiftung, Villingen-Schwenningen SPP, Worms - Weierhof, Dornbirn Innere Medizin, Linz Landes-Kinderklinik, Wels Klinikum Pädiatrie, Duisburg Sana Kinderklinik, Villingen-Schwenningen Schwarzwald Baar Klinikum, Kinderklinik, Kamen Klinikum Westfalen Hellmig Krankenhaus, Freiburg St. Josef Kinderklinik, Feldkirch Kinderklinik, Lappersdorf Kinderarztpraxis, Ludwigshafen diabetol. SPP, Oberhausen St.Clemens Hospitale Sterkrade, Dortmund-Hombruch Marienhospital, Dessau Kinderklinik, Murnau am Staffelsee - diabetol. 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