CLINICAL STUDY

Subclinical hypothyroidism and dyslipidemia in children and adolescents with type 1 diabetes mellitus

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Abstract

Objective: Recent epidemiological evidence suggests that subclinical hypothyroidism (SCH), defined as elevated TSH concentrations with normal circulating levels of triiodothyronine (T₃) and thyroxine (T₄), is associated with dyslipidemia and cardiovascular disease in adult populations. As currently no data are available on the prevalence of SCH and its potential association with lipoprotein profile in children and adolescents with type 1 diabetes (T1DM), we investigated the prevalence of SCH and associated lipid levels in young diabetic patients.

Design and methods: Cross-sectional analysis of 22 747 children, adolescents, and young adults (age <25 years) with T1DM with normal T₃ and T₄ and either normal TSH (≥ 0.5 to <4.0 mIU/l, euthyroid group) or elevated TSH (≥ 4.0 to <25.0 mIU/l, SCH group) and simultaneous measurement of serum lipid and lipoprotein status.

Results: The prevalence rate of SCH in the study population was 7.2%. Adjusted for age, gender, diabetes duration, current insulin dose, HbA1c, and BMI z-score, patients with SCH had significantly higher levels of total cholesterol (178.7 vs 175.3 mg/dl, $P < 0.001$) and LDL-cholesterol (97.0 vs 93.7 mg/dl, $P < 0.001$) compared with euthyroid patients.

Conclusions: SCH is a common finding in children, adolescents, and young adults with T1DM. SCH is associated with increased levels of total cholesterol, and LDL-cholesterol adjusted for potential confounders. SCH-associated increases in lipid and lipoprotein levels may therefore add to an increased long-term cardiovascular risk in young patients with T1DM.

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Introduction

Subclinical hypothyroidism (SCH), defined as elevated TSH concentrations with normal circulating levels of triiodothyronine (T₃) and thyroxine (T₄), is a prevalent finding in adult populations with reported prevalence rates of up to 10% (reviewed in (1)). Epidemiological data on the prevalence of SCH in childhood and adolescence comes, however, mostly from smaller cohort studies in obese subjects. Reported prevalence rates of SCH in obese children range from 10 to 23%, whereas in healthy, nonobese control populations, the prevalence of SCH is below 1% (reviewed in (2)). Currently, there are no data available on the prevalence of SCH in young patients with type 1 diabetes (T1DM). Over the past years, there has been considerable controversy on the potential impact of SCH on the development of atherosclerosis and cardiovascular disease (reviewed in (1, 3)). Very recently, a meta-analysis from

the Thyroid Studies Collaboration provided unequivocal epidemiological evidence that SCH is associated with an increased risk of coronary heart disease and mortality (4). This increase in risk may be mediated by adverse changes in traditional (e.g. lipid profile) and emerging nontraditional cardiovascular risk factors (e.g., CRP and coagulation parameters) associated with SCH (1, 3, 5). As T1DM is associated with a sharply increased risk for cardiovascular disease in adulthood and high prevalence rates of cardiovascular risk factors have been demonstrated already in childhood and adolescence (6), early detection of potentially modifiable cardiovascular risk factors is essential for effective prevention of premature morbidity and mortality. The aim of this study was therefore to describe the prevalence rate of SCH in a large population of children, adolescents, and young adults with T1DM and to investigate the potential association of SCH with an adverse lipid profile.

Materials and methods

Study population

Cross-sectional analysis examining the association of TSH serum level with serum lipids was performed in a large cohort of children, adolescents, and young adults with T1DM. Patients' data were extracted from the diabetes data acquisition system for prospective surveillance (DPV, Diabetessoftwaressystem zur prospektiven Verlaufsdokumentation) database. The electronic DPV system has been described in detail elsewhere (7, 8). In brief, since 1995, the DPV surveillance database continuously records demographic, anthropometric, and metabolic data obtained from patients treated for diabetes in participating centers from Germany and Austria. Anonymized longitudinal patient data are transmitted for central analysis twice yearly. Consistency of the data is reviewed in a standardized process, and inconsistent data are verified or corrected at the centers. For the present analysis, data from 45 557 patients with T1DM for more than 3 months and a maximum age of 25 years were available. To be eligible for inclusion in the final study sample, the following criteria had to be fulfilled:

- simultaneous measurement of TSH and lipid status;
- TSH ≥ 0.5 and < 25.0 mIU/l;
- normal values for total T_4 (TT $_4$, 76–152 nmol/l) or free T_4 (FT $_4$, 11.0–28.0 pmol/l), otherwise if not available normal values for total T_3 (TT $_3$, 1.3–3.3 nmol/l), or free T_3 (FT $_3$, 5.1–10.0 pmol/l) (simultaneous measurement with TSH mandatory in the SCH group (TSH ≥ 4.0 mIU/l));
- no ketoacidosis at the time of laboratory measurements (pH > 7.35);
- no replacement therapy with L-T $_4$ or iodine;
- no medication affecting thyroid function (glucocorticoids, propranolol, amiodarone, salicylates, phenytoin, phenobarbital, carbamazepine); and
- no lipid-lowering drugs.

In order to exclude patients with overt disorders of lipid metabolism (e.g. familiar hypercholesterolemia), the following cutoff levels for serum lipids were defined:

- total cholesterol < 300 mg/dl
- LDL-cholesterol < 200 mg/dl
- HDL-cholesterol > 20 mg/dl.

Applying the described criteria to the available data set in March 2011 resulted in a final sample of 22 747 patients with T1DM from 272 institutions (for a complete list of contributing centers, see Acknowledgements section). If more than one observation was available for a single patient, only the most recent observation was included in the analysis. A number of available observations for each investigated variable are given in Table 1. The most important reason for the exclusion of study subjects was a missing laboratory measurement of TSH and lipid status at the same time point. Other main reasons for exclusion were: use of L-T $_4$, iodine, and statins; age; and diabetes duration. Characteristics of the total population compared with the selected study population are detailed in Supplementary Table 1, see section on supplementary data given at the end of this article. Thyroid function was defined as euthyroid if TSH was ≥ 0.5 and < 4.0 mIU/l, and conversely, SCH was assumed if serum TSH was ≥ 4.0 and < 25.0 mIU/l.

Laboratory parameters

Measurements of TSH, peripheral thyroid hormones, and thyroid autoantibodies to thyroperoxidase (anti-TPO) and thyroglobulin (anti-TG) were performed locally at the participating centers using commercially available assays. Centers were advised to measure plasma concentrations of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides after a 12-h fasting period. As previously described, fasting periods were not sufficiently met in all registered patients (6). Determination of total cholesterol, LDL-cholesterol, and HDL-cholesterol has been

Table 1 Anthropometric and laboratory characteristics of $n=22\,747$ patients with type 1 diabetes.

	<i>n</i>	Mean	s.d.	Median	Interquartile range
Age (years)	22 747	13.71	4.25	14.27	6.02
Duration of diabetes (years)	22 747	5.72	3.92	4.96	5.57
BMI z-score	22 350	0.54	0.93	0.54	1.22
HbA1c (%)	22 353	8.06	1.66	7.77	1.85
TSH (mIU/l)	22 747	2.24	1.45	1.94	1.34
FT $_4$ (pmol/l)	12 796	15.01	2.36	14.80	3.61
TT $_4$ (nmol/l)	2412	101.63	17.48	97.91	24.46
FT $_3$ (pmol/l)	2228	5.98	0.61	5.85	0.77
TT $_3$ (nmol/l)	2952	1.89	0.58	1.70	0.75
Cholesterol (mg/dl)	22 416	175.30	33.12	172.0	42.0
LDL-cholesterol (mg/dl)	16 827	92.78	28.45	90.0	37.0
HDL-cholesterol (mg/dl)	18 132	62.15	15.61	61.0	19.0

FT $_3$, free triiodothyronine; FT $_4$, free thyroxine; TT $_3$, total triiodothyronine; TT $_4$, total thyroxine.

demonstrated to be only marginally influenced by food intake (9). As available data on triglyceride levels from the DPV database may not represent fasting levels and may be biased by food intake (10), triglycerides were excluded from the analysis. Total cholesterol was measured enzymatically, LDL-cholesterol was either calculated using Friedewald's formula or directly measured using a homogenous photometric procedure, and HDL-cholesterol was determined after dextran sulfate–magnesium precipitation. Values of locally determined HbA1c as a measure of long-term metabolic control were standardized to the Diabetes Control and Complications Trial (DCCT) reference range (11).

Anthropometric measurements

Body weight and height were determined to the nearest 0.1 kg and 0.1 cm respectively using calibrated scales. Z-scores for height and BMI were calculated using the LMS method (12) based on German references (13). Duration of diabetes was calculated as the time difference between age at examination and the documented age at diabetes onset.

Statistical analysis

Statistical analysis was performed using the SAS software package version 9.2 (SAS Institute, Cary, NC,

USA). Data are presented as mean, s.d., median, and interquartile range. For analytical purposes, the study population was stratified into quartiles of TSH. Median differences of investigated parameters within TSH quartiles were assessed using the nonparametric Wilcoxon signed rank test and the Holm–Bonferroni method for multiple comparisons. Hierarchical linear modeling was used to perform multilevel analysis of predictors of serum lipid status (14). Denominator degrees of freedom were calculated according to Kenward–Roger, parameters were estimated using restricted partial likelihood, and iterations were optimized according to Newton–Raphson. Each model included the following set of predictor variables: SCH (categorical; TSH ≥ 0.5 to < 4.0 mIU/l, TSH ≥ 4.0 to < 25.0 mIU/l), gender (categorical), age group (categorical; ≤ 5 years, > 5 to ≤ 10 years, > 10 to ≤ 15 years, > 15 to ≤ 20 years, > 20 to ≤ 25 years), diabetes duration (categorical; ≤ 2 years, > 2 to ≤ 5 years, > 5 to ≤ 10 years, > 10 years), BMI z-score (linear), current insulin dose (linear; IU/kg body weight), current HbA1c (linear), and diabetes center as random factor (random intercept model, covariance-structure Cholesky). Based on these models, differences in adjusted levels of the respective serum lipid concentrations between the euthyroid and the SCH group were assessed calculating least square means and two-tailed *t*-tests. *P* values < 0.05 were considered statistically significant (15).

Table 2 Mean and median values of TSH, cholesterol, LDL-cholesterol, HDL-cholesterol, and BMI z-score in the study population stratified into quartiles of TSH (q1–q4). *P* values for median differences of investigated parameters within TSH quartiles calculated with Wilcoxon tests and the Holm–Bonferroni method for multiple comparisons.

TSH q1–q4	<i>n</i>	Mean	s.d.	Median	Interquartile range	<i>P</i> Holm–Bonferroni
TSH (mIU/l)						
q1	5723	1.04	0.22	1.06	0.34	
q2	5652	1.66	0.16	1.67	0.28	
q3	5701	2.30	0.23	2.29	0.40	
q4	5671	3.96	1.87	3.45	1.14	
Cholesterol (mg/dl)						
q1	5601	173.69	33.62	170.00	42.19	<0.001
q2	5581	174.08	33.21	171.00	42.00	
q3	5615	175.57	32.55	173.00	40.00	
q4	5619	177.85	32.94	175.00	42.00	
LDL-cholesterol (mg/dl)						
q1	4073	91.70	28.69	89.00	36.28	<0.001
q2	4168	91.43	28.47	89.00	37.00	
q3	4279	93.00	28.04	90.10	36.74	
q4	4307	94.89	28.49	92.00	37.00	
HDL-cholesterol (mg/dl)						
q1	4433	61.62	15.24	60.00	19.00	0.04
q2	4528	62.10	15.51	61.00	19.35	
q3	4573	62.30	15.48	61.00	19.00	
q4	4598	62.56	16.16	61.00	19.00	
BMI z-score						
q1	5584	0.51	0.93	0.52	1.22	0.04
q2	5568	0.52	0.92	0.52	1.18	
q3	5608	0.55	0.93	0.55	1.21	
q4	5590	0.57	0.96	0.57	1.26	

Results

Data sets from a total of 22 747 children and adolescents (12 055 boys) were available for analysis. Anthropometric and metabolic characteristics of the study population are given in Table 1. For a subset of 18 431 subjects, data on thyroid autoantibody status were available, which was positive for either anti-TPO or anti-TG in 3562 children and adolescents (19.3%). A total of 1638 children and adolescents with T1DM had SCH according to the definition applied, yielding a prevalence rate of 7.2%.

Regrouping the study population by quartiles specific for TSH revealed stepwise increases in total cholesterol levels from TSH quartiles 1–4 and of LDL-cholesterol levels from TSH quartiles 2–4 respectively (Table 2). There was a trend for marginally higher HDL-cholesterol levels in the upper TSH quartiles, and mean BMI z-score also increased with increasing TSH level.

As described in the Materials and methods section, hierarchical linear modeling was performed to investigate differences in serum lipid and lipoprotein status between both groups accounting for potential confounders. Adjusted for the potentially confounding variables of age, gender, diabetes duration, diabetes center, insulin dose, HbA1c, and BMI z-score, patients with elevated TSH had significantly higher total cholesterol and LDL-cholesterol (both $P<0.001$) (Table 3). Furthermore, mean BMI z-score was higher in the SCH group ($P<0.001$), whereas there was no difference in mean height z-scores between the groups.

Discussion

This study provides evidence for an association of SCH with increased levels of serum lipids in a large population of children, adolescents, and young adults with T1DM. Of note, the reported associations of elevated TSH with total cholesterol and LDL-cholesterol remained after adjusting for confounding variables

including BMI z-score, age, gender, diabetes duration, current insulin dose, HbA1c, and treating diabetes center. For the first time, our study reports the prevalence of SCH in a young population of patients with T1DM. The finding of a prevalence rate of 7.2% is in line with published prevalence rates of SCH in samples of nondiabetic adult populations (1). Of note, the here reported prevalence rate of SCH markedly exceeds the prevalence rate of 4.3% in the comparatively young and healthy NHANES III study population (16), which suggests that SCH represents a rather common disorder in children and adolescents with T1DM. The finding of an increased prevalence of SCH in our study population should be qualified by noting that given the epidemiological scale of the DPV database, which is covering >80% of all patients with T1DM below the age of 25 years living in Germany and Austria (17), we decided to follow the proceedings of epidemiological reference studies reporting on prevalence rates of SCH and the potential association of SCH with dyslipidemia (16, 18, 19, 20) and rely on a single measurement of TSH and peripheral thyroid hormones for the diagnosis of SCH. Defined inclusion criteria aimed at excluding subjects with transient or secondary hyperthyrotropinemia (most importantly acute and chronic use of medication); however, only a timely second measurement of thyroid hormones could have safely excluded subjects with transient hyperthyrotropinemia (21).

T1DM is associated with increased cardiovascular disease risk factors already during childhood and adolescence (6). Besides poor glycemic control and hypertension, dyslipidemia and more specifically even mildly elevated levels of LDL-cholesterol may contribute significantly to the increased risk for premature cardiovascular disease and cardiovascular mortality in adult patients with T1DM (22).

Available data on the risk of cardiovascular disease in SCH remain in part controversial (reviewed in (1)), although published meta-analyses concluded that SCH

Table 3 Anthropometric measures and laboratory data of euthyroid patients and patients with SCH adjusted for age, gender, diabetes duration, current insulin dose, HbA1c, BMI z-score, and treating diabetes center by hierarchical linear modeling. Presented figures are adjusted least square means, S.E.M.s, and *P* values of *t*-tests for comparison between groups.

	Euthyroid		SCH		<i>P</i>
	TSH 0.5–4 mIU/l		TSH 4–25 mIU/l		
	Mean	S.E.M.	Mean	S.E.M.	
Cholesterol (mg/dl)	175.3	0.41	178.7	0.86	<0.001
LDL-cholesterol (mg/dl)	93.7	0.66	97.0	0.99	<0.001
HDL-cholesterol (mg/dl)	62.2	0.24	62.6	0.46	0.428
BMI z-score	0.53	0.01	0.59	0.02	<0.001
Height z-score	0.00	0.01	−0.03	0.03	0.186

SCH, subclinical hypothyroidism.

may be at least associated with a modestly increased risk for cardiovascular disease and mortality (4, 23, 24). More recently, data from the population-based HUNT study (25) and reanalysis of the Wickham Survey cohort (26) revealed further support for the concept of a direct association of SCH with an increased incidence of ischemic coronary heart disease and mortality.

Thyroid hormone status has major effects on the cardiovascular system, and overt hypothyroidism leads to substantial alterations of traditional risk factors for cardiovascular disease including increased systemic vascular resistance and diastolic hypertension, decreased cardiac preload and impaired cardiac performance, increased coagulability, and as a hallmark feature elevated levels of total cholesterol and LDL-cholesterol (1, 27). Therefore, the potential adverse effects of SCH on cardiovascular disease risk may well be mediated by alterations in traditional cardiovascular risk factors, of which increased total cholesterol and LDL-cholesterol levels have been most frequently reported to be associated with SCH across different study populations (3).

This study reports for the first time a positive association of SCH with increased total cholesterol and LDL-cholesterol in a very large at-risk population for cardiovascular disease of young patients with T1DM. Importantly, levels of serum lipids and lipoproteins in childhood and adolescence are related to age, gender, stage of pubertal development, and ethnicity of the subjects studied (28). Moreover, the association of SCH with dyslipidemia may be modified by insulin sensitivity (29). Therefore, we applied hierarchical linear modeling to account for the effects of potentially confounding variables including BMI z-score, gender, age group, diabetes duration, current insulin dose, and HbA1c.

The magnitude of the observed differences in mean levels of serum lipids between the euthyroid and the SCH group of our study population is well in line with previous observations in middle- or older age non-diabetic populations, although reported differences in lipid patterns vary considerably according to applied definitions of SCH and demographic characteristics (1). The concept of mild thyroid failure represented by rising TSH levels as a risk factor for adverse serum lipid levels is further supported by our observation of increasing cholesterol and LDL-cholesterol levels with TSH quartiles and significantly highest levels of cholesterol and LDL-cholesterol in the highest TSH quartile.

Reference values for total cholesterol levels in children and adolescents are available from NCEP guidelines (30) and from the Lipid Research Clinic Pediatric Prevalence Study (31), which have been recommended by the American Academy of Pediatrics in a recent policy statement on 'Lipid screening and cardiovascular health in childhood' (28). Applying these references, mean total cholesterol in the SCH group ranges in the mid to upper limit of 'borderline'

cholesterol levels, whereas total cholesterol in the euthyroid group is closer to the lower limit of the definition of 'borderline' cholesterol. Of note, mean cholesterol levels in both groups fall in the range of 'borderline' cholesterol.

The strength of this study is the large sample size of children, adolescents, and young adults with T1DM, representing a significant proportion of all T1DM patients in this age range living in Germany and Austria. Furthermore, the DPV database system provides detailed information on patients' characteristics allowing for careful correction of potential confounding factors in the analysis.

On the other hand, the cross-sectional design of our study does not allow any conclusions to be drawn about a causal relationship between elevated TSH and lipid levels, although small intervention studies with T_4 supplementation support causality (32). Even more importantly, the impact of the observed differences in lipids in the SCH and the euthyroid group on prospective cardiovascular morbidity cannot be assessed directly from the study results. Furthermore, variations in applied assays for the determination of thyroid hormones and differences in fasting periods of study participants before blood sampling may have affected study results. In order to account for potentially confounding effects of methodical proceedings, treating diabetes center was included as a random factor in the analysis.

Currently, there are no data available on the association of SCH and cardiovascular disease from studies spanning the life period from childhood or adolescence into adulthood. Nonetheless, today it is well established that the process of developing atherosclerosis begins in childhood and the extent of atherosclerotic lesions in adulthood is associated with levels of traditional cardiovascular risk factors such as dyslipidemia and hypertension in early life (33, 34, 35). Evidence from the DCCT/EDIC study demonstrates that progression of carotid intima media thickness is associated with serum lipoprotein status in patients with T1DM (36).

Conclusion

In conclusion, this study's findings of borderline elevated levels of total cholesterol and LDL-cholesterol associated with SCH in children and adolescents with T1DM make it reasonable to suggest an additional increase of cardiovascular risk for affected patients. As SCH may especially affect cardiovascular morbidity and mortality in young adulthood (37), and elevated lipoprotein levels represent potentially modifiable risk factors, the reported high prevalence of SCH should warrant careful screening for thyroid dysfunction and associated mild dyslipidemia in an at-risk population of young patients with T1DM.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-12-0703>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Financial Disclosure: the authors have no financial relationships relevant to this article to disclose.

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Author contribution statement

C Denzer: Dr Denzer conceptualized the study, drafted the initial manuscript, and approved the final manuscript as submitted. B Karges: Dr Karges contributed to the study conception, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. A Näke: Dr Näke critically reviewed and revised the manuscript and approved the final manuscript as submitted. J Rosenbauer: Dr Rosenbauer contributed to the statistical analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. E Schober: Dr Schober critically reviewed and revised the manuscript and approved the final manuscript as submitted. K Schwab: Dr Schwab contributed to the study conception, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. R W Holl: Dr Holl supervised data collection, carried out statistical analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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