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Losing Track of Lipids in Children and Adolescents with Type 1 Diabetes: Towards Individualized Patient Care

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ABSTRACT

Aim To assess 1) the prevalence of children and adolescents with type 1 diabetes (T1D) changing from low-risk into borderline-high-risk lipid levels or from borderline-high-risk into high-risk lipid levels ('lose track of lipids') and 2) the power of a risk score including the determinants HbA1c, body mass index (BMI), gender, age, diabetes duration and ethnicity in predicting which patients lose track of lipids.

Methods 651 children and adolescents with T1D were included in this longitudinal retrospective cohort study. Lipid dynamics and the impact of the risk score on losing track of lipids were evaluated. Kaplan-Meier analysis was used to estimate screening intervals.

Results 31–43 % percent of the patients had lost track of one or more lipids at the next lipid measurement. This happened more frequently in patients with a low-risk lipid level at start. Depending on the lipid parameter, 5 % of patients with low-risk lipid levels lost track of lipids after 13–23 months. The risk score based on concomitant information on the determinants was moderately able to predict which patients would lose track of lipids on the short term.

Conclusions A considerable number of children and adolescents with T1D loses track of lipids and does so within a 2-year screening interval. The predictive power of a risk score including age, BMI, gender, HbA1c, diabetes duration and ethnicity is only moderate. Future research should focus on another approach to the determinants used in this study or other determinants predictive of losing track of lipids on the short term.

Introduction

Patients with type 1 diabetes (T1D) have an increased risk for premature cardiovascular disease (CVD) and cardiovascular mortality [1, 2]. Dyslipidemia, an abnormal level of the lipids low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol (non-HDL-C), total cholesterol (TC) and/or triglycerides (TG), is considered to be one of the risk factors [3–6]. At present, an abnormal LDL-C is seen as the primary modifiable risk factor [5] whereby treatment is especially effective when started early [3]. Consequently, timely detection of lipid abnormalities by regular screening of lipids is warranted. Maahs showed that intervention could have been considered in a quite large number of children and adolescents with T1D since sustained lipid abnormalities were found during a mean follow up period of 2.9 years [7]. In addition, this study and the studies of Reh and Edge showed patients to change lipid trajectories frequently and showed also that a considerable number of patients changed from low-risk or borderline-high-risk levels to more unfavourable lipid levels (los-

ing track of lipids) [7–9]. This losing track of lipids is especially seen in patients with an increased glycated hemoglobin (HbA1c), longer diabetes duration, female gender and an increased body mass index (BMI) [7–12]. A diagnostic algorithm, such as suggested by Schwab [13], includes most of these determinants and was used by Schwab to develop group-specific reference curves for the several lipid parameters for children and adolescents with T1D [13]. To the best of our knowledge, a risk score derived from the determinants of this diagnostic algorithm to identify individual patients at risk for losing track of lipids on the short term, has not yet been studied before in another cohort, nor has the impact of using this algorithm on the lipid screening interval. If applicable, this index will facilitate individualized patient care.

Our study has 3 aims: 1) to determine how many children and adolescents with T1D change from low-risk into borderline-high-risk or high-risk lipid levels or from borderline-high-risk to high-risk levels ('lose track of lipids'), 2) to study if the determinants of the diagnostic algorithm of Schwab [13] enriched with the determinants ethnicity and diabetes duration are applicable for individual patient care and, based on this information, 3) to provide insight into when to screen for lipid abnormalities for the individual patient, allowing optimization of the individual lipid screening interval.

Methods

Study design; patient selection

This study was a longitudinal, retrospective cohort study of children and adolescents with T1D that were visiting the outpatient clinic of Diabeter, a large center for focused T1D care and research in Rotterdam, The Netherlands, between March 1989 and January 2013. Included were all children and adolescents with proven T1D until the age of 25.0 years. Excluded were 472 patients (39.8 %), of which 420 (89.0 %) were excluded for not having at least two LDL values [7, 12], and 43 (9.1 %) for having celiac disease. Patients receiving lipid-lowering medication at the start of this longitudinal study as well as patients starting this medication in the course of the study, were excluded. Also we did not include patients with other dyslipidemia-related conditions. Furthermore, we did not use laboratory values of included patients if (A) HbA1c and lipid measurements were performed within 3 months after diagnosis of T1D, and/or if (B) lipid measurements were done when TSH was ≥ 10 mU/l.

Anthropometric and laboratory data

Data on duration of diabetes, gender, ethnicity, body mass index (BMI), blood pressure, HbA1c and non-fasting LDL-C, HDL-C, TG, non-HDL-C [14] and TC was retrieved from electronic patient charts. In line with previous studies [11, 15, 16] and Dutch data of pubertal development [17, 18], patients were divided in 3 age groups, reflecting 3 pubertal stages: age < 11 years, reflecting childhood/pre-puberty; age ≥ 11 years and < 18 years, reflecting puberty/adolescence; and age ≥ 18 years, reflecting post-puberty/adulthood. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were expressed in percentiles [19]. BMI was expressed as age and gender-adjusted categories 'normal', 'overweight', 'obesity grade 1', 'obesity grade 2', 'obesity grade 3' for age > 2 years old. This means that the category 'overweight' corresponds to an adult BMI of 25 mg/m^2, and the obesity categories correspond to adult BMI values of 30 mg/m^2 (obesity grade 1), 35 mg/m^2 (obesity grade 2) and 40 mg/m^2 (obesity grade 3) respectively [20, 21]. HbA1c was measured at every clinic visit by immunochemical assay (Vantage System, Siemens Medical Solutions Diagnostics, Tarrytown, NY). The assay had intra- and inter-assay coefficients of variation (CV) of < 3.7 % and < 4.3 %, respectively. HbA1c was categorized into optimal HbA1c (< 7.5 %; < 58 mmol/mol), suboptimal HbA1c (7.5 % - ≤ 9.0 %; 58- ≤ 75 mmol/mol) and high risk HbA1c (> 9.0 %; > 75 mmol/mol)[22]. Non-fasting LDL-C, HDL-C, TC and TG were measured every 2 years according to the local protocol. When abnormal lipid values were found, lipids were measured more frequently. Lipids were measured by enzymatic colorimetric assay on a Hitachi Cobas C501 analyser (Roche Diagnostics; Mannheim, Germany). The intra-assay CVs were: 0.90 % for LDL-C, 0.70 % for HDL-C, 1.10 % for TC and 1.10 % for TG. The inter-assay CVs were: 2.10 % for LDL-C, 0.90 % for HDL-C, 1.60 % for TC and 1.90 % for TG. Non-HDL-C was calculated by subtracting HDL-C from TC levels [14]. LDL-C was obtained by using the Friedewald formula until 2006; hereafter, a direct measurement for LDL-C was used. Low-risk, borderline-high-risk and high-risk levels of LDL-C, HDL-C, non-HDL-C, TC and TG were defined according to the recommended cut-offs displayed by the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (▶ **Supplemental Table 1S**) [23]. 'Losing track' was defined as change from low-risk to borderline-high-risk or high-risk lipid levels or from borderline-high-risk to high-risk lipid levels.

Statistical analysis

Data were summarized with conventional statistical measures: mean and standard deviation (SD) for continuous variables with normal distributions, median and interquartile range (IQR) for continuous variables with skewed distributions, and n (%) for categorical variables. For each lipid parameter, multiple binary logistic regression analysis was used to study the impact of an index including potential risk factors on the likelihood of 'losing track' of that lipid parameter. Determinants included were age, gender, ethnic background, duration of diabetes, and HbA1c. Goodness of fit was expressed as the proportion of correct predictions and the area under the receiver operating characteristic (ROC) curve (or c statistic). It was defined as moderate between 60–70 % and acceptable above 70 %. Screening intervals for lipid parameters were estimated using Kaplan-Meier analysis. 'Event' was defined as losing track of lipids in the patients with a low-risk lipid level at start. Time to event was defined as the follow-up time that passed between the date of losing track of lipids and the date of study entry. The 5 % cumulative incidence of losing track of lipids in the patients with a low-risk lipid level at start was used as cut-off. P-values were determined using the log-rank test.

Results

Patients and follow-up

There were 1187 patients with proven T1D with at least 3 months follow-up. Excluded were 536 patients (45.2 %). Of the 651 included patients, 52.7 % were male, 55.9 % were of Dutch/Western ori-

gin, 15.7 % of non-western origin and in 28.4 % the origin was not further specified in the patient chart. The mean age of the patients was 12.63 years (SD 4.62); 36.4 % were < 11 y, 51.3 % were 11- < 18 y, and 12.3 % ≥ 18 y. SBP and DBP values were normal in > 95 % of patients. Thirty-two (4.9 %) of included patients had mildly elevated TSH levels (5.0- < 10.0 mU/l) and were users of levothyroxine.

Patients' trajectories over time

▶ **Table 1** shows the lipid-related and other parameters at the onset of a patient's trajectory (first observation) and at the end of a patient's trajectory (last observation). Median follow-up was 3.24 years (IQR 1.93–4.79 years). Over time, included patients aged with gradually/slightly increasing values of BMI and lipid parameters.

Dynamics and losing track of lipids per lipid parameter

Of the patients, 42 % changed their LDL-C level to a less favourable lipid level at the next lipid measurement: 35 % lost track of their HDL-C level and 31, 38 and 43 % lost track of their non-HDL-C, TC and TG level respectively. ▶ **Fig. 1** and ▶ **Supplemental Table 2S** show, for each lipid parameter, the prevalence at study entry in three categories: low-risk, borderline-high-risk and high-risk lipid levels, and their dynamics between categories. For example, in case of LDL-C (▶ **Fig. 1a**), 520 of 651 included patients (79.9 %) had low-risk LDL-C levels at study entry, whereas 78 (12.0 %) had borderline-high-risk LDL-C levels and 53 (8.1 %) had high-risk LDL-C levels. In total 202 of 651 patients (31.0 %) switched to another category later in their LDL-C profile, with the switch rate differing considerably by LDL-C category at onset. The switch rate was 20.8 % in the low-risk LDL-C level subgroup, 80.8 % in the borderline-high-risk LDL-C level subgroup, and 58.8 % in the high-risk LDL-C level subgroup. In summary, the switch rate is considerably higher in the categories with lowest prevalence, being the borderline-high-risk and high-risk categories. ▶ **Fig. 1a** shows that switches to unfavourable categories occurred more frequently in patients with low-risk LDL-C levels at study entry/onset compared with patients with a borderline-high-risk LDL-C level at study entry (69.4 % vs. 15.9 %).

The patterns of HDL-C, TC and non-HDL-C are more or less comparable to the pattern seen in LDL-C, except for TG. Compared with the other parameters, TG levels at study onset were low-risk less frequently (46.7 %) and high-risk more frequently (29.6 %).

Lipid screening intervals

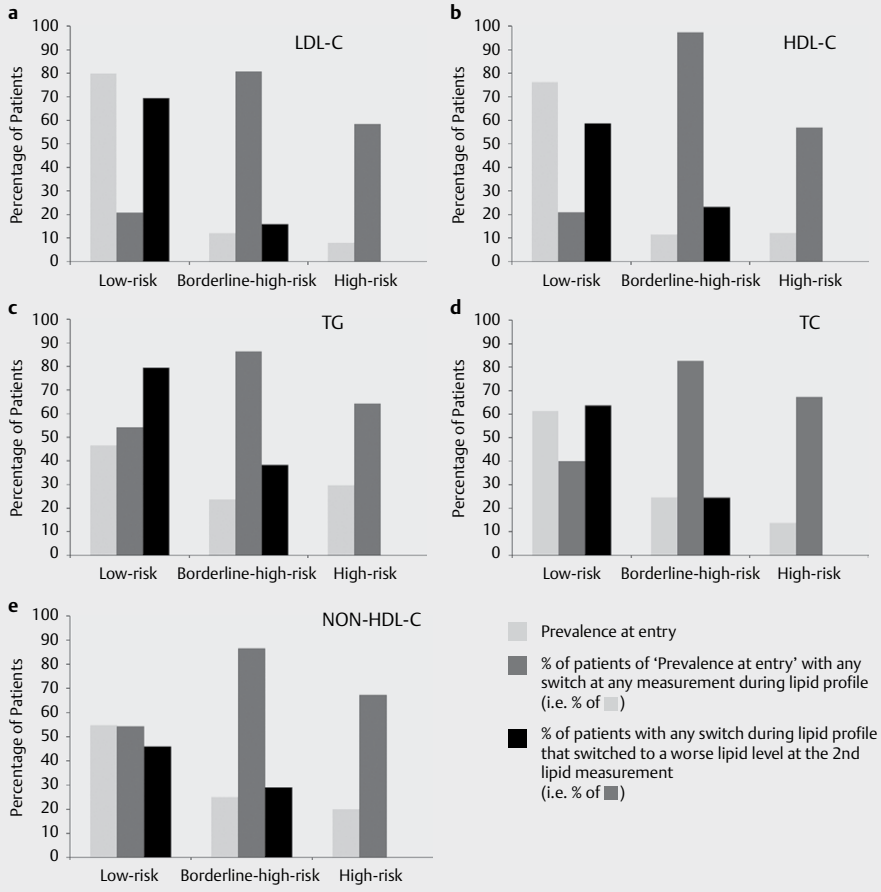
Many risk factors had a significant impact on the likelihood of losing track of lipids in the multiple logistic regression analysis (▶ **Table 2**). Higher age was associated with a higher risk for losing track of LDL-C and lower risk for losing track of HDL-C and TG. Being male was associated with a higher risk for losing track for HDL-C and lower risk for losing track of TC, LDL-C and non-HDL-C. When compared with Dutch patients, those with a non-Dutch Western background showed a higher risk of losing track of all lipids. With respect to BMI, being overweight showed an increased risk of losing track of only LDL-C. Longer duration of diabetes showed a higher risk of losing track of TC, HDL-C and TG. All assessed risk factors analyzed together had significant impact on the likelihood of losing track of lipids of at least one of the lipid parameters , although predictive power was moderate.

Kaplan-Meier analysis showed that 5 % of patients lost track of: LDL-C levels within 22 months; HDL-C levels within 20 months; non-HDL-C levels within 16.5 months; TC levels within 13.5 months; and TG levels within 13 months (▶ **Fig. 2**).

▶ **Table 1** Profile of lipid-related and other parameters over time (n = 651 patients, unless stated otherwise).

Parameter	At start of profile	At end of profile	Length of Follow-up interval (y)[a]	No of observations in follow-up interval
TG (mmol/l)	1.00 (0.80–1.40)	1.10 (0.80–1.60)	3.34 (1.92–5.02)	1 984
HDL-C (mmol/l)	1.42 (1.17–1.68)	1.44 (1.20–1.70)	3.33 (1.90–5.04)	1 997
LDL-C (mmol/l)	2.30 (1.90–2.70)	2.50 (2.10–2.90)	3.24 (1.93–4.79)	1 852
Non-HDL-C (mmol/l)	2.78 (2.36–3.26)	2.94 (2.50–3.54)	3.07 (1.82–4.79)	1 813
HbA1c (%)	7.70 (7.00–8.60)	8.10 (7.50–8.90)	5.17 (3.76–6.54)	16 077
HbA1c (mmol/mol)	61 (53–70)	65 (58–74)		
TC (mmol/l)	4.21 (3.80–4.80)	4.40 (3.90–5.00)	3.53 (2.08–5.06)	2 341
BMI (category) n = 649	18.66 (16.81–21.69)	22.28 (19.53–25.04)	5.16 (3.73–6.48)	12 640
Duration of diabetes[b] (y)	4.05 (2.08–7.15)	8.04 (5.22–11.93)	3.24 (1.93–4.79)	n. a.
BMI class, age- and gender-adjusted[c]			5.16 (3.73–6.48) n = 649	12 603 n = 649
0: normal	490 (76.3 %)	437 (67.9 %)		
1: overweight	123 (19.2 %)	170 (26.4 %)		
2: obesity grade 1	23 (3.6 %)	32 (5.0 %)		
3: obesity grade 2 or 3	6 (0.9 %)	5 (0.8 %)		
	n = 642	n = 644		

At start/end of profile displays the number of patients (n), and median + IQR of parameter values. N.a.: not available. [a] between the start and end of LDL-C profile: [b] at start of profile of LDL-C values [c] missing in 7 patients with age < 2.0 y for which reference data are unavailable: BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.



▶ **Fig. 1** Prevalence of low-risk, borderline-high-risk and high-risk levels of five lipid parameters at study entry, percentage of switchers during profile, and percentage of patients that have switched to a worse level at the next measurement (i. e., from low-risk to borderline-high-risk, from low-risk to high-risk, or from borderline-high-risk to high-risk; N = 651). HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Discussion

Our study showed that a considerable number of patients changed their lipid trajectory. Of these, 31–43 % lost track of lipids at the next measurement, depending on the lipid parameter. Most patients had low-risk levels at study entry, but changed frequently to a borderline-high-risk or high-risk level at the next lipid measurement. Notably, power to predict this change, using a risk score including age, gender, BMI, HbA1c, diabetes duration and ethnicity, appeared moderate. To identify patients losing track of lipids, lipid screening intervals would range from 13 months (TG) to 22 months (LDL-C), depending on the lipid measured, which is considerably shorter than the interval recommended in the international guidelines [5, 24].

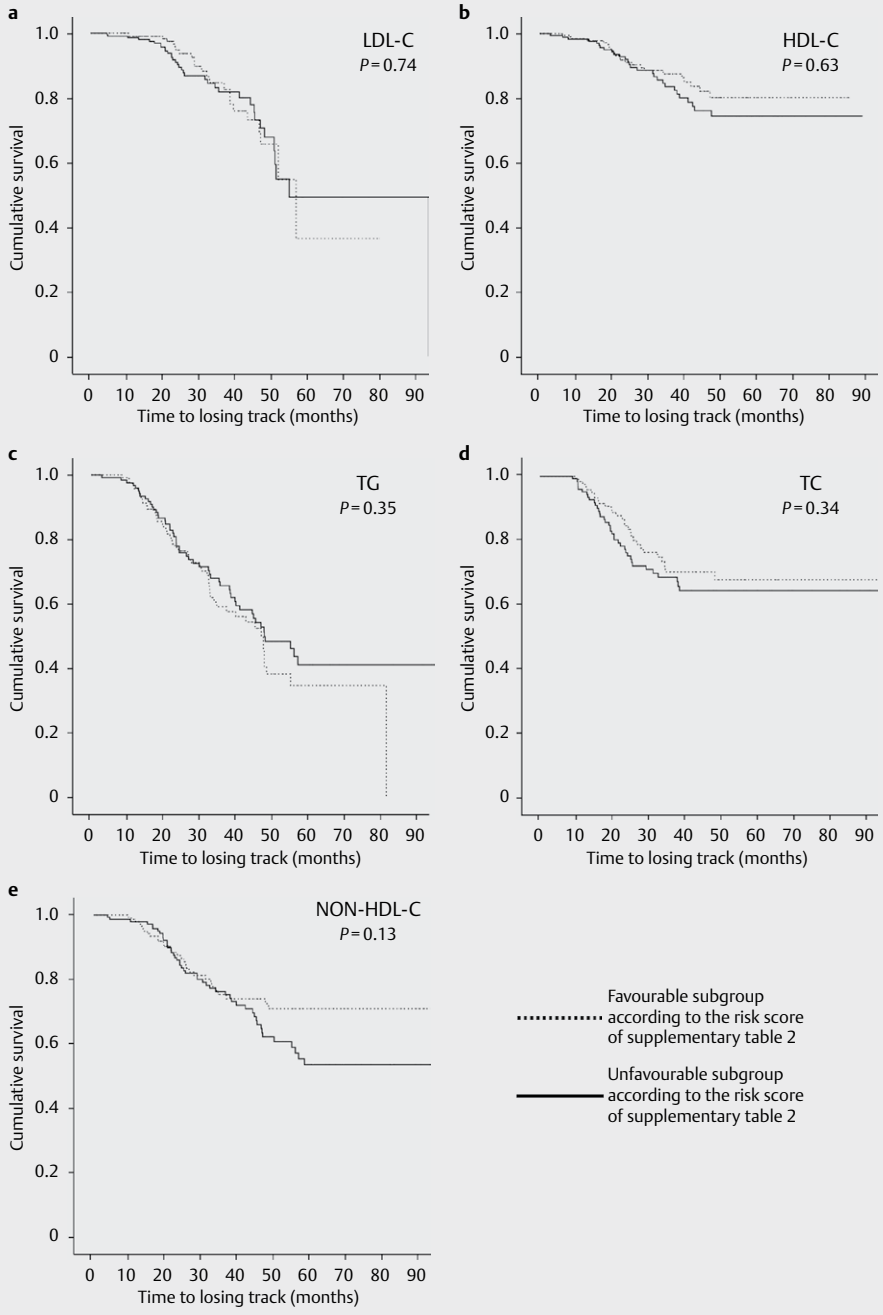
Interestingly, the dynamics of the lipids LDL-C, HDL-C, non-HDL-C, TC and TG in children and adolescents with T1D [7–9, 25] appear different in healthy peers who have more stable lipids [16, 26]. The exact pathophysiology of this increased prevalence and heterogeneous pattern of losing track of lipids in the children and adolescents with T1D [7–9, 25] compared with healthy controls remains to be elucidated. We hypothesized on a role of some factors. First, the lack of information on pubertal stages may have influenced our results. Although Eissa et al. showed that lipid levels correspond better with pubertal stage than age [16], we faced the same problem (i. e., pubertal stage not being assessed during routine clinical care) as previous studies in children and adolescents with type 1 diabetes and healthy children and adolescents [7, 8, 12, 27, 28]. Second, the puberty-related factors insulin resistance and resistance to the growth hormone-insulin-like-growth-1 (GH-IGF-1) axis appear to have an impact on lipid dynamics. Both factors have been shown to be worse in patients with T1D when compared with healthy peers [29–32]. Third, HbA1c itself appears to have an impact on lipid dynamics [8, 12, 25], although this does not support any specific pathophysiological mechanism. Fourth, the probable increased prevalence of non-alcoholic fatty liver disease (NAFLD) in patients with T1D [33–36] may be associated with losing track of lipids. NAFLD may disadvantage lipid processing [37], is suggested to be an entity as risk factor for premature CVD, separately from dyslipidemia [33, 34], and development of NAFLD may be enhanced by factors that are related to puberty and/or T1D such as glycaemic control, insulin resistance and increase of BMI [12, 30, 38, 39].

Unfortunately the determinants used in the diagnostic algorithm of Schwab [13], enriched by us with the determinants ethnicity and

▶ **Table 2** Predictors of the switch (to a less favourable state) of TC, LDL-C, HDL-C, non-HDL-C and TG parameters. Estimated ORs (95 % CIs) obtained with multiple logistic regression analysis.

Parameter	TC		LDL-C		HDL-C		Non-HDL-C		TG	
	OR (95 %CI)	P	OR (95 %CI)	P	OR (95 %CI)	P	OR (95 %CI)	P	OR (95 %CI)	P
Age (ref: < 11y)										
11 to < 18 y	0.82 (0.62–1.09)	0.107	1.47 (1.07–2.02)	**0.018**	0.70 (0.53–0.93)	**0.013**	1.32 (0.98–1.78)	0.073	0.64 (0.47–0.87)	**0.004**
≥ 18 y	0.70 (0.48–1.00)	0.052	1.55 (1.05–2.31)	**0.029**	0.72 (0.50–1.04)	0.080	1.20 (0.81–1.77)	0.360	0.43 (0.29–0.64)	**< 0.001**
Gender (ref: Female)										
Male	0.59 (0.48–0.74)	**< 0.001**	0.64 (0.51–0.80)	**< 0.001**	1.62 (1.30–2.02)	**< 0.001**	0.64 (0.51–0.81)	**< 0.001**	1.19 (0.93–1.50)	0.160
Ethnic background (ref: Dutch)										
Western non-Dutch	1.91 (1.47–2.47)	**< 0.001**	1.40 (1.05–1.85)	**0.020**	1.58 (1.21–2.06)	**0.001**	1.43 (1.08–1.88)	**0.011**	2.08 (1.59–2.74)	**< 0.001**
Non-western	1.12 (0.79–1.58)	0.520	1.21 (0.83–1.77)	0.320	0.83 (0.57–1.19)	0.300	1.75 (1.18–2.58)	**0.005**	1.21 (0.84–1.73)	0.310
BMI (ref: normal)										
overweight	1.15 (0.88–1.49)	0.300	1.45 (1.12–1.89)	**0.006**	1.21 (0.93–1.56)	0.150	1.11 (0.84–1.48)	0.460	1.08 (0.81–1.43)	0.600
obesity grade 1 +	1.06 (0.66–1.72)	0.810	1.04 (0.63–1.74)	0.870	1.83 (1.14–2.93)	0.120	1.12 (0.66–1.92)	0.680	0.62 (0.38–1.02)	0.062
Duration of diabetes (y)	1.04 (1.00–1.07)	**0.025**	1.02 (0.99–1.06)	0.140	1.06 (1.03–1.10)	**< 0.001**	1.02 (0.99–1.06)	0.150	1.07 (1.04–1.11)	**< 0.001**
HbA1c (ref: < 7.5 %; 58 mmol/mol)										
7.5 (58) to ≤ 9.0 (75)	1.03 (0.80–1.33)	0.790	1.22 (0.93–1.62)	0.150	1.44 (1.11–1.87)	**0.006**	1.18 (0.90–1.55)	0.220	1.27 (0.97–1.67)	0.082
> 9.0 (75)	1.50 (1.07–2.09)	**0.018**	1.92 (1.36–2.71)	**< 0.001**	1.99 (1.43–2.77)	**< 0.001**	1.35 (0.93–1.94)	0.110	1.79 (1.24–2.57)	**0.002**
C coefficient/AUROC *	0.63 (0.60–0.66)	**< 0.001**	0.64 (0.61–0.67)	**< 0.001**	0.64 (0.61–0.67)	**< 0.001**	0.61 (0.58–0.64)	**< 0.001**	0.65 (0.61–0.68)	**< 0.001**
Proportion of correct predictions	61.5 %		67.8 %		63.3 %		69.0 %		71.1 %	

* AUROC, Area under the ROC-curve; p-value is significance test compared to null hypothesis AUROC = 0.5: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.



▶**Fig. 2** Time losing track for 5 lipid parameters. The survival curve represents losing track at the second measurement for the subgroup of patients who had a low-risk lipid level at baseline. HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

diabetes duration, were not very sensitive in identifying patients that lost track of lipids on the short term. Herein, looking at patients with appropriate HbA1c and BMI in the current study population may have attenuated the strength of abovementioned determinants [7, 11–13]. Consequently, other determinants influencing lipid dynamics such as the abovementioned determinants insulin resistance, resistance of the GH-IGF-1 axis and NAFLD, but also determinants such as social economic status (SES), physical activity, smoking, and familial dyslipidemia may be considered. Indeed, lower SES has been related to unfavourable lipid profiles in children and adolescents [40, 41], physical activity and smoking have been found to associate to a more favourable lipid profile in adults with T1D [42], and abnormal maternal and paternal lipid levels have been shown to associate mildly with an abnormal lipid profile in children and adolescents with T1D [43]. However, SES comprises more than parental income and education and the accumulation of family income and family stability have been

shown to be important SES related factors as well [44, 45]. The favourable effect of physical activity on lipid levels was shown to be small in (healthy) children [46] or indirect [41]. Besides, gathering information about physical behaviour by questionnaires was shown to be only partly reliable and valid [47]. Assessing smoking status is difficult since it may change throughout puberty and may be subject to under-reporting in this age-group. Finally, the exact influence of a positive family history for premature CVD on lipids has still to be determined [48]. Thus, because of several caveats on the applicability of these determinants on lipid dynamics, more research is needed before they can be used in an adapted diagnostic algorithm of Schwab [13].

The current study shows that even with a 2-year lipid screening interval, 5–10 % of patients lose track with regard to their LDL-C and HDL-C and 25–30 % for the other parameters. Although early identification of dyslipidemia and consequently the opportunity to intervene is important [3, 43], we feel this percentage to be quite acceptable, taking into account the current lack of tools for earlier intervention for these other lipid parameters.

A screening interval of 2 years (or less) is at odds with the current ADA/ISPAD guidelines in which a 5-year lipid screening interval is recommended [5, 24]. The reasons behind this discrepancy remain to be elucidated.

After Edge's study in 2008, our study is the first one that has longitudinally studied the lipid dynamics of European children and adolescents with T1D [9]. Supplemental to Edge's study, we were able to include anthropometric parameters and ethnicity [9]. Another strength of our study is that we used an individualized approach based on a patient's profile of risk factors and used a risk score including determinants of the diagnostic algorithm of Schwab to evaluate its applicability for more individualized patient care instead of determination of reference curves.

Possible limitations of the current study are: a considerable number of patients had a quite short follow up duration; the screening intervals were variable; and thus the time point of lipid change was less accurate. Moreover, although the study did include non-HDL [6], inclusion of more atherogenic information, such as determination of apolipoprotein B, may have improved risk stratification [49–51]. Another limitation may be that information about smoking status and lipid-lowering diets was not included (both were not consistently recorded in our study group). However, improvement of such a diet on LDL-C levels has been shown to be small [52, 53] and adherence to a recommended diet is found to be insufficient in youth with type 1 diabetes [54, 55]. Finally, the studied lipids were measured in a non-fasting state. We do not think that measuring fasting levels would have altered the findings of this study as previous studies showed only a slight, clinically irrelevant, difference in fasting versus non-fasting LDL-C, HDL-C, TC, and TG levels [11, 56]. The apparent relationship of TG levels with the non-fasting state and the assumed increased fat-containing meals during puberty was refuted by previous reports [57, 58].

In conclusion, the current longitudinal study in children and adolescents with T1D shows that a considerable number of patients change their lipid levels from low-risk into borderline-high-risk or high-risk levels or from borderline-high-risk to high-risk levels (lose track of lipids), mainly in patients having a low-risk lipid level at start. A screening interval of 2 years allows timely detection of losing track of LDL-C and HDL-C in 5–10 % of the patients. Research on determinants predictive of which patients will lose track of lipids on the short term is important. This should include the determinants age, BMI, gender, HbA1c, diabetes duration and ethnicity (which are only moderately predictive in our model when analysed together), but also other determinants. All these efforts aim to early identify children and adolescents with T1D at high risk for macrovascular complications, so that early intervention, targeted at improving this lifetime perspective of macrovascular complications, can be initiated.

Ethics Approval and Consent to Participate

For the retrospective data analysis, written informed consent was obtained from all patients for anonymized use of their medical record data for research purposes. The study was performed in accordance with the Code of Conduct for the Use of Data in Health Research and the Dutch Act on the Protection of Personal Data. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from a medical research ethics committee in the Netherlands.

Author Contributions

J.C.v.d.H. was responsible for the medical care of the patients, researched data, contributed to the study design and wrote the manuscript. E.B. contributed to the study design, helped to interpret the results, and performed the statistical analyses. S.B. was responsible for the medical care of the patients and helped to interpret the results. P.D. helped to interpret the results and worked on draft revisions of the manuscript. H.J.V. was responsible for the medical care of the patients and the data collection. D.M. helped with interpreting the results and edited the manuscript. H.J.A. was responsible for the medical care of the patients, contributed to the study design and the interpretation of the results, and edited the manuscript. All authors reviewed the manuscript.

Conflict of Interest and Funding

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