RESEARCH LETTER

An increase in high-density lipoprotein cholesterol concentration after initiation of insulin treatment is dose-dependent in newly diagnosed type 1 diabetes

The results of the InLipoDiab1 study

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Introduction Type 1 diabetes (T1D) is a chronic autoimmune disease that affects both children and adults.[1] It is extremely important to adequately treat diabetes from the onset of the disease, due to the metabolic memory phenomenon revealed in the Epidemiology of Diabetes Intervention and Complications Study.[2] The study showed that patients treated from the beginning with intensive insulin therapy derived greater benefits in the follow-up.[2] The management of diabetes includes also the assessment of lipid profile. Lipid abnormalities are common in patients with T1D and depend on metabolic control.[3] Dyslipidemia has an indisputable effect on the development of diabetic complications, including cardiovascular disease.[4] High-density lipoprotein cholesterol (HDL-C) seems to play a protective role in the development of long-term complications of T1D; however, this phenomenon is still unclear because the available data are conflicting.[5] It has been shown that the initiation of insulin therapy may modify the lipid profile, including HDL-C levels. However, this trend has not been fully evaluated in patients with T1D.[6] It is necessary to investigate whether an increase in HDL-C levels depends on an insulin dose and glycation process in the course of hyperglycemia.

The aims of the study were a prospective assessment of changes in the lipid profile after initiation of insulin therapy in newly diagnosed T1D and analysis of biomarkers associated with the therapy.

Patients and methods **Patients** The preliminary analysis included 78 patients with newly diagnosed T1D (28 women and 50 men; mean age, 25.7 years [range, 21.6–30.0 years]), who participated in the Insulin Therapy and Lipoproteins Profile in Type 1 Diabetes Study (InLipoDiab1, NCT02306005). All patients were treated with intensive insulin therapy from the onset of the disease. The inclusion criteria for the study were as follows: age between 18 and 35 years, newly diagnosed T1D and initiation of insulin therapy, as well as consent for participation in the study. Patients were assessed at the time of diagnosis (the samples collected before administration of insulin) and then at a follow-up visit in an outpatient clinic after 3 months of insulin treatment. The diagnosis of T1D was confirmed by the measurement of disease-specific autoantibodies.

Measurements Anthropometric data including body mass index and body weight were assessed. The daily dose of insulin (DDI) was defined as the requirement for insulin per kilogram body weight per day. This amount of insulin was calculated as the sum of units of long- and short-acting insulin. The final DDI at the time of diagnosis (baseline DDI) was established on the last day of hospitalization when glucose levels reached the treatment target and the patient could be discharged home. The DDI after 3 months was calculated at the follow-up visit based on data derived from patients' self-monitoring logs from the last month. The average dose of insulin that has been used by patients over the last 30 days was calculated. The lipid profile including the levels of total cholesterol, HDL-C, and triglycerides was measured with a Cobas 6000 biochemistry analyzer

TABLE 1 Differences between the study groups according to daily dose of insulin at baseline

Variable	Baseline DDI		*P* value
	≥0.13 (U/kg body weight) n = 39	<0.13 (U/kg body weight) n = 39	
Baseline (before administration of insulin)			
Body mass, kg	68.3 (56.9–74.1)	69.0 (54.5–78.3)	0.58
BMI, kg/m^2	21.7 (19.5–23.6)	21.3 (19.6–25.4)	0.48
HbA_{1c}, %	11.9 (11.2–12.7)	10.2 (8.3–11.6)	<0.0001
HbA_{1c}, mmol/mol	106.5 (98.9–115.3)	88.0 (66.1–103.3)	<0.0001
TC, mmol/l	4.2 (3.6–5.0)	4.2 (3.8–4.9)	0.89
HDL-C, mmol/l	1.0 (0.8–1.2)	1.3 (1.1–1.5)	<0.0001
LDL-C, mmol/l	2.5 (1.9–2.9)	2.4 (1.8–3.1)	0.76
Triglycerides, mmol/l	1.3 (0.9–1.8)	1.2 (0.9–1.5)	0.54
MFG, mmol/l	8.0 (7.3–9.2)	7.1 (6.2–7.7)	0.001
MPG, mmol/l	10.1 (9.2–11.0)	9.2 (8.0–9.7)	0.004
At 3 months			
Body mass, kg	70.0 (58.0–77.2)	68.2 (56.9–78.0)	0.89
BMI, kg/m^2	21.6 (19.6–24.4)	22.1 (20.5–24.7)	0.7
HbA_{1c}, %	6.4 (5.9–7.4)	6.2 (5.8–7.1)	0.20
HbA_{1c}, mmol/mol	46.4 (41.0–57.4)	46.4 (41.0–57.4)	0.20
TC, mmol/l	4.5 (4.0–5.1)	4.5 (4.0–5.0)	0.79
HDL-C, mmol/l	1.7 (1.4–2.0)	1.7 (1.4–2.1)	0.21
LDL-C, mmol/l	2.4 (1.9–2.9)	2.4 (1.6–3.0)	0.43
Triglycerides, mmol/l	0.7 (0.6–1.2)	0.8 (0.5–1.1)	0.62
MFG, mmol/l	7.2 (6.4–9.0)	6.7 (6.4–7.5)	0.32
MPG, mmol/l	7.1 (6.3–8.1)	6.9 (6.2–8.2)	0.65

The results are presented as median and interquartile range.

Abbreviations: BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MFG, mean fasting glucose; MPG, mean postprandial glucose; TC, total cholesterol

(Roche Diagnostics, Basel, Switzerland), using enzymatic colorimetric methods. Low-density lipoprotein levels were calculated by the Friedewald formula.[7] ΔHDL was defined as the difference between the value of HDL-C at onset and at follow-up. Glycated hemoglobin A_{1c} (HbA_{1c}) levels were measured twice: at baseline and at 3 months. HbA_{1c} levels were assessed by a turbidimetric inhibition immunoassay using Cobas 6000. All measurements were performed in serum.

Statistical analysis The statistical analysis was performed using the STATISTICA 12.0 program (StatSoft, TIBCO Software Inc., Palo Alto, California, United States). All data were expressed as median values and interquartile ranges (IQRs) and as a number (percentage) of patients. First, the data at onset and at follow-up were compared. Then, patients were divided into 2 groups according to the median ΔHDL value (0.48 mmol/l) and baseline DDI (0.13 U/kg body weight). The Mann–Whitney and Wilcoxon tests were used for continuous variables, and the Fisher test or the χ^2 test for categorical variables was used to assess differences between the groups. Looking for factors that may influence an increase in HDL-C levels, the impact of baseline DDI was investigated in the multiple regression model adjusted for sex, HbA_{1c}, and triglycerides. The differences with a probability value of less than 0.05 were considered significant.

Results The median HbA_{1c} level at baseline was 11.3% (IQR, 9.8–12.3); 16 patients (20.5%) were smokers. At 3 months, the HDL-C level significantly increased (median [IQR], 1.2 mmol/l [0.9–1.4] vs 1.7 mmol/l [1.4–2.0]; P <0.0001), whereas the triglyceride level significantly decreased (median [IQR], 1.2 mmol/l [0.9–1.6] vs 0.7 mmol/l [0.6–1.1]; P <0.0001). DDI did not change significantly during the follow-up. The groups with higher and lower baseline DDI are compared in **TABLE 1**. A multiple regression analysis revealed that the DDI at baseline was related to a higher ΔHDL value (r = 0.29; P = 0.02) after adjustment for sex, HbA_{1c} value, and triglyceride levels.

Discussion To the best of our knowledge, there has been no prospective study addressing and explaining how the initiation of insulin therapy affects HDL-C levels in newly diagnosed T1D. Our results confirm that the initiation of insulin treatment increases HDL-C levels in T1D. Moreover, this is the first study to show that an increase in HDL-C levels is dependent on an insulin dose, independently from the HbA_{1c} level.

Our results are in line with other studies.[6,8] Sinha et al[6] examined the effects of insulin on the lipid profile in patients with newly diagnosed T1D and in those with type 2 diabetes unsuccessfully treated with oral agents, requiring initiation of insulin therapy. The authors showed that initiation of insulin therapy improved all components of the lipid profile only in patients with T1D. The limitation of the cited study was a small number of patients (n = 9) with newly diagnosed T1D and the follow-up duration of only 6 months. In our study, we observed changes in the lipid profile over a shorter time of insulin treatment—already after 3 months.

We would like to emphasize that during our prospective observation, not only changes in the lipid profile were observed. One of our aims was to investigate whether these changes were dependent on DDI and HbA_{1c}. It has been shown that HDL-C protects against diabetes complications.[9] Still, the life expectancy of patients with T1D, despite the increased levels of HDL-C, is shorter than that of the general population.[10] Interestingly, Costacou and Evans[11] showed that both low and very high levels of HDL-C are associated with an increased incidence of coronary artery disease. The authors revealed a U-shaped curve for the risk of coronary artery disease in women with HDL-C concentrations below 47 mg/dl and above 80 mg/dl. Thus, it seems important to further investigate this issue. It was reported that the increase in HDL-C levels in patients with T1D may

be dependent on the DDI. Guy et al[8] showed that patients with higher insulin requirement presented higher levels of HDL-C compared with patients with lower insulin requirement. These data show that the increase in HDL-C levels is closely related to the dose of insulin, similarly to our observations. However, the study by Guy et al[8] was performed on a group of youth and it was not a prospective follow-up.

One of the objectives of our study was the evaluation of the relationship between the increase in HDL-C and HbA_{1c} levels. Guy et al[8] showed differences in the lipid profile and insulin requirement between the groups divided according to HbA_{1c} levels. The authors proved that patients with poor glycemic control have an atherogenic lipid pattern, including a decrease in HDL-C levels. In our study, the group with low and high ΔHDL value and low and high DDI did not differ in the level of HbA_{1c} at follow-up. Manjunatha et al[12] suggested that simple laboratory measurements of HbA_{1c} and HDL-C concentrations may be insufficient to determine cardiovascular risk in patients with T1D. They showed that despite normal HDL-C levels, its function (determined by cholesterol efflux and antioxidant capacity) is reduced in patients with long-term T1D, irrespective of glycemic control, compared with healthy controls. The authors explained this phenomenon by irreversible posttranslational modifications of the HDL-C proteins. It follows that the quality, and not the quantity, of HDL-C determines its function. In our future studies, we are planning to assess the HDL-C function in patients with newly diagnosed T1D.

The prospective analysis confirmed the association between the initiation of insulin therapy and changes in lipid profile in patients with newly diagnosed T1D. An increase in HDL-C levels was related to baseline DDI. The higher the baseline DDI, the higher the increase of HDL-C levels in adults with newly diagnosed T1D. From a clinical point of view, it is surprising that we demonstrated the relationship between insulin dose and HDL-C level in a prospective study. Due to the evidence that HDL-C may have a protective effect on diabetic complications, we should consider how to maintain normal HDL-C levels in these patients. Our findings suggest that intensive insulin therapy contributes to an increase in HDL-C levels, so it is important to investigate the mechanism of this phenomenon and its clinical implications in patients with T1D.

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