

Perspective

Lipid Profile in a Cohort of Patients Aged between 3 and 18 with Type 1 Diabetes. Correlation with Homologous Age Range of the General Population

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Introduction

Type 1 diabetes mellitus (T1D) accounts for approximately 5-10% of all diagnosed cases of diabetes. Diagnosis generally occurs in subjects under 30 years of age and of normal weight. The International Diabetes Federation (IDF) estimates that there are 600,900 children under the age of 15 years living with T1D worldwide [1]. The cause of T1D remains unknown. There is clear evidence of a genetic predisposition and strong, but circumstantial, evidence for environmental factors triggering an autoimmune destruction of the beta cells leading to absolute dependence on insulin treatment. Acute complications are the leading cause of death in people with T1D under the age of 30 [2]. Chronic complications in the pediatric setting are not frequent; however latent structural or functional alterations may be present as early as a few years after the onset of the disease [3]. Childhood and adolescence therefore represent a period of time during which intense education and careful monitoring are able to prevent or delay the onset and progression of complications. The ESC-EASD 2019 guidelines emphasize that in general T1D confers an excess of risk of out-come of CV events (coronary heart disease, ischemic stroke and vascular death) that is twice as high [4]. As part of the prevention of medium and long-term cardiovascular risk, it is essential to perform the complete lipid profile in young diabetics, at least annually, with intensification of checks in the event of unsatisfactory results. The goals of this study were to compare lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride) of a group of pediatric patients with T1D, aged between 3-18 years, treated at the Day Hospital of Endocrinology of the Complex Structure of Pediatrics and Neonatology Asl 2, center of Savona, San Paolo Hospital, with as many aged patients 3-18 years who have been hospitalized in the same Structure.

Research Design and Methods

The monocentric study is conducted on a sample of patients with T1D, aged between 3 and 18 years, treated at the DH of Endocrinology of the Complex Structure of Pediatrics and Neonatology Asl 2, Savona center, San Paolo Hospital. The indices acquired both for the pediatric patients affected by T1D and for the control group were:

- Stature (cm)
- Weight (Kg)

- BMI (Kg/m²)
- Triglycerides (TG)
- Total Cholesterol (TC)
- High Density Cholesterol (HDL-C)
- Low Density Cholesterol (LDL-C)

The guidelines provided by NCEP were used as a reference to assess the levels of TC, LDL-C, HDL-C, TG [5].

For the group of diabetic patients, the glycated hemoglobin value (HbA1c) was also taken into consideration. The result is expressed as a percentage (%).

Inclusion criteria

- Pediatric subjects suffering from T1D, aged between 3 and 18 years, under treatment at the Day Hospital of Endocrinology of the Complex Structure of Pediatrics and Neonatology Asl2 of the Savona San Paolo Hospital.
- Non-diabetic pediatric subjects, aged between 3 and 18 years, who were hospitalized at the Complex Structure of Pediatrics and Neonatology Asl2 of the Savona San Paolo Hospital (control group).

Exclusion criteria

- Subjects affected by T1D, under treatment at the Endocrinology Day Hospital of the Complex Structure of Pediatrics and Neonatology Asl2, of younger age 3 years old or over 18 years old.
- For the control group, subjects not suffering from T1D but suffering from celiac disease, autoimmune thyroid disease, and severe obesity and from diseases / treatments that could affect liver function.

Data was collected using FileMaker and One.sys databases.

Results

Eighty-nine pediatric patients affected by T1D were recruited (mean age 12.22 ± 3.4 years, range 3-18 years). The group of patients with T1D consists of 52 male patients (58.5%) and 37 female patients (41.6%). The control group consisted of 89 pediatric subjects unaffected by T1D (mean age 9.40 ± 3.4 years, range

3-18 years). In the control group, 49 subjects were male (55.1%) and 40 of female sex (44.9%).

It was calculated, thanks to the measurement of weight (kg) and height (cm), the BMI (Kg/m²) of each subject. The mean BMI of diabetic patients is 19.2 (±3.4), while in the control the mean BMI is 16.4 (±2.5). The BMI-for-age percentile is used in order to interpret the numerical value of the BMI; cut-off value equal to the 85th centile

Table 1: Mean values of HbA1c based on the duration of the disease.

Duration of disease (years)	Number of patients	HbA1c % (\pm SD)
0-1.9	31	7.9 (\pm 1.1)
2-5.9	29	8.5 (\pm 1.4)
6+	29	8.3 (\pm 1.1)

Table 2: Comparison between T1D patients and the control group.

	T1D patients	Control group	p
N subjects	89	89	
M/F	52/37	49/40	
Age	12.2 (\pm 3.4)	9.4 (\pm 3.4)	0.341
BMI (Kg/m ²)	19.2 (\pm 3.4)	16.4 (\pm 2.5)	0.0004
TC (mg/dL)	175.0 (\pm 33.6)	171.0 (\pm 27.5)	0.992
LDL-C (mg/dL)	101.0 (\pm 30.2)	100.0 (\pm 23.1)	0.489
HDL-C (mg/dL)	62.1 (\pm 13.2)	57.6 (\pm 12.6)	0.741
TG (mg/dL)	61.2 (\pm 21.9)	64.8 (\pm 32.9)	0.075

Table 3: Levels of TC, LDL-C and HDL-C in the T1D patient group and control group.

		T1D patients	Control group
N Subjects		89	89
TC	Acceptable: <170mg/dL	42 (47.2%)	46 (51.7%)
	Borderline: 170-199 mg/dL	30 (33.7%)	24 (27.0%)
	High: \geq 200mg/dL	17 (19.1%)	19 (21.3%)
LDL-C	Acceptable: <110mg/dL	60 (66.3%)	65 (73.0%)
	Borderline: 110-129 mg/dL	18 (20.2%)	17 (19.1%)
	High: \geq 130mg/dL	12 (13.5%)	7 (7.9%)
HDL-C	Low: <40mg/dL	3 (3.4%)	4 (4.5%)
	Borderline: 40-45 mg/dL	3 (3.4%)	8 (9.0%)
	Acceptable: >45mg/dL	84 (93.2%)	77 (86.5%)

is evaluated as overweight while higher than the 95th centile is an indication of obesity [6]. Percentile membership was assessed for each subject, both in the T1D patients group and in the control group, using BMI/age percentile growth curves based on gender. In the study group of subjects with T1D, 12 patients (13.50%) have a BMI/ age base on sex >85th percentile. For the control group, 2 subjects (2.20%) have a BMI/age based on sex between the 85th and 95th percentile. No patient has a BMI/age based on gender above the 95th percentile, as already decided in the study design phase. For the group of patients with T1D, the HbA1c (%) value was taken into consideration. The mean recorded HbA1c value in the T1D patient group is 8.2% (\pm 1.3). The minimum value of HbA1c found in the group of patients with T1D is 5.8% while the maximum value is 11.5%. Values of HbA1c \leq 7% were recorded in 42 subjects (47.2%), while values \geq 8% were found in 47 patients (52.8%). According to the duration of the disease, the 89 patients were divided and the mean values of HbA1c were recorded (Table 1).

Subsequently, the comparison between the two groups in relation to the levels of TC was taken into consideration.

TC values are considered acceptable if <170mg/dL, borderline values if included 170-199mg/dL, while high values if \geq 200mg / dL.

Table 4: TG levels (3-9 years) in the T1D patient group and control group.

		T1D patients	Control group
N Subjects		24	45
TG 3-9 years	Acceptable: <75mg/dL	20 (83.3%)	35 (77.8%)
	Borderline: 75-99 mg/dL	4 (16.7%)	3 (6.6%)
	High: \geq 100mg/dL	0 (0%)	7 (15.6%)

Table 5: TG levels (10-18 years) in the T1D patient group and control group.

		T1D patients	Control group
N Subjects		65	44
TG 10-18 years	Acceptable: <90mg/dL	58 (89.3%)	36 (81.8%)
	Borderline: 90-129 mg/dL	6 (9.2%)	4 (9.1%)
	High: \geq 130mg/dL	1 (1.5%)	4 (9.1%)

Diabetic patients and control subjects were categorized based on their TC levels.

In the group of T1D patients, the mean TC value found was 175 (\pm 33.6) mg/dL.

Acceptable TC values (<170mg/dL) in diabetic patients were recorded in 42 subjects (47.2%); borderline values (170-199 mg/dL) were found in 30 subjects (33.7%), while elevated values (\geq 200mg/dL) in 17 patients (19.1%).

In the control group, on the other hand, the mean recorded TC value was 171 (\pm 27.6) mg/dL.

Acceptable values were recorded in 46 patients (51.7%), borderline values in 24 subjects (27.0%) and finally elevated values were found in 19 subjects (21.3%).

Subsequently, the level of LDL-C was assessed for the group of patients with T1D and for the control group. According to the NCEP guidelines [5], LDL-C values are considered acceptable if <110mg/dL, borderline values if between 110-129 mg/dL while high values if \geq 130mg/dL. In diabetic patients, the mean recorded LDL-C level was 101 (\pm 30.2) mg/dL. Acceptable LDL-C values were found in 60 patients (66.3%), borderline values in 18 subjects (20.2%), while elevated values in 17 subjects (13.5%). However, for patients with T1D with moderate CV risk, the ESC-EAS guidelines [7] recommend improving LDL-C levels below 100mg/dL.

In our sample of T1D patients only 40 patients (44.9%) manage to reach the target recommended by the ESC-EASD guidelines [7], while 49 patients (55.1%) have values \geq 100mg/dL.

In the control group, on the other hand, the average LDL-C value recorded was 100 (\pm 23.1) mg/dL. In this group, in particular, 73% of subjects manage to reach the target, while in 27% there are no acceptable values.

Subsequently, for both diabetic patients and the control group, the level of HDL-C was considered.

According to the NCEP guidelines [5], the values are considered acceptable if \geq 45mg/dL; values between 40-45 mg/dL are considered borderline, while values >40mg/dL are low.

The mean recorded HDL-C value in T1D patients is 62.1mg/dL

(± 13.2).

In the group of diabetic patients, 84 people (93.2%) have acceptable values, while 58 in 3 subjects (3.4%) borderline values are found, and in as many (3.4%) low values.

The mean recorded HDL-C value in the control group is 57.6 (± 12.6) mg/dL.

In the control group, 77 subjects (86.5%) have acceptable values, 8 subjects (9%) borderline values and the remaining 4 subjects (4.5%) values considered low.

The last parameter taken into consideration was the TG value.

In the group of T1D patients the mean TG recorded was 61.2 (± 21.9) mg/dL, while for the control group it was 64.8 (± 32.9) mg/dL.

According to the NCEP guidelines [5], the pediatric population is divided into two age groups 3-9 years and 10-18 years.

TG values in the first age group (3-9 years) are considered acceptable if <75 mg/dL, borderline when between 75-99 mg/dL, while elevated when ≥ 100 mg/dL.

In the group of diabetic patients in the age group 3-9 there are 24 subjects, acceptable values were recorded in 20 subjects (83.3%), borderline values in 4 patients (16.7%) while in no case high values were found.

In the control group, 45 subjects are present in the age group 3-9 years. In this group, acceptable values are recorded in 35 subjects (77.80%), borderline values in 3 subjects (6.60%) and high values in 7 patients (15.5%).

According to the NCEP guidelines [5], in the age group 10-18 years, TG values are considered acceptable if <90 mg/dL, borderline if between 90-129 mg/dL, while high if ≥ 130 mg/dL.

In the group of T1D patients, 65 subjects are aged between 10-18 years. Acceptable values in patients with T1D were found in 58 subjects (89.3%), borderline values in 6 patients (9.2%) and in only one patient (1.5%) the recorded values were elevated. In the control group, 36 (81.8%) subjects showed acceptable values, 4 (9.1%) borderline values and as many (9.1%) high values.

Overall, if we consider the entire age group 3-18 years, in T1D patients, 87.6% of subjects have acceptable TG values, while in the control group, acceptable values are found in 79.8% of subjects (Table 2-5).

Discussion

Before the discovery of insulin, survival after the diagnosis of T1 was extremely short: about half of the patients died within the first 20 months of diagnosis and less than 10% survived to 5 years.

Thanks to the introduction of insulin therapy, mortality and morbidity have been significantly reduced in diabetic patients and today this therapy remains the irreplaceable cure for patients with type 1 diabetes.

If it is true that the cornerstone of therapy remains insulin, with different modes of action and administration, it is equally true that over the years the awareness of the importance of motor activity,

nutrition and above all self-control has grown while the ideal values of HbA1c and glycemic range for a metabolic control to be considered satisfactory over the years have become tighter.

All this in order to make the long-term life prospect better and reduce the possible complications related to the disease and poor control of it.

As part of the prevention of medium and long-term cardiovascular risk, it is essential to carry out the complete lipid profile in young diabetics, at least annually, with intensification of checks in the event of unsatisfactory results.

In our group of pediatric T1D patients, only less than half (47.2%) of the sample managed to reach the recommended TC target (<170 mg/dL), while 19.1% of the sample had elevated values (≥ 200 mg/dL).

Dyslipidemia, especially LDL-C, seems to be the main cause of the extent and severity of atherosclerosis in children and adolescents and therefore its prevention must become a target for all diabetics.

The NCEP guidelines [5] recommend maintaining LDL-C levels below 110mg/dL in children and adolescents; however, in the case of patients with T1D the recent ESC-EASD guidelines [7] focus attention on the CV risk of diabetic patients.

In the case of subjects with T1D and age <35 years, with T1D of duration <10 years, without other risk factors, it is recommended to further reduce LDL-C levels below 100mg/dL.

In our sample of young diabetic patients only 44.9% succeeds in reaching this target, while in the remaining 55.1% values ≥ 100 mg/dL are recorded.

A US study evaluated the daily calorie intake of young patients with T1D [8]. It has been observed that total fat intake, especially saturated fat, is higher than the recommended levels for young people with T1D. The lower percentage of total energy coming from carbohydrates seems to be compensated by a greater consumption of saturated fats which, as known, do not cause an immediate rise in blood sugar. Parents of young diabetic patients report that their children demonstrate a preference for foods from the food industry and provided for labels, such as processed and prepackaged foods, which allow them to calculate more precisely the amount of carbohydrates introduced and consequently the insulin dose [9].

However, the most common processed foods are known to be higher in saturated fat than unprocessed foods.

When LDL-C values are higher than 100 mg / dL it is therefore necessary to intervene with the support of nutrition specialists, in order to encourage the adoption of correct eating habits, also recommending the patient to exercise more.

Also, in the control group there is a situation of dyslipidemia that absolutely should not be underestimated.

A study conducted by 69 pediatricians in the provinces of Milan and Bergamo examined the lipid profile of 1910 children not suffering from chronic or acute diseases, concluding that 4.5% of the subjects had hypercholesterolemia, that is TC level $s >200$ mg/dL; 3.3% of the sample had low HDL-C levels (<40 mg/dL) and 23.5% high triglyceride

levels (≥ 100 mg/dL under 10 years of age, or ≥ 130 mg/dL in patients over 10 years) [10]. Comparing this data with those of our control group of 89 subjects, we find in our experience higher percentages of hypercholesterolemia (21.3%) and low levels of HDL-C (4.5%) while in a lower percentage values of triglycerides above the control range (12.5%).

To our knowledge, few other Italian studies have measured plasma lipid concentrations in the general pediatric population.

A US study, conducted on children and adolescents aged between 6 and 19 years, in which the same cut-offs were used for the definition of high levels of TC and low levels of HDL-C, found hypercholesterolemia and HDL-C levels < 40 mg/dL in 7.4% and 13.4% of the sample, respectively [11].

We can therefore affirm that the prevalence of dyslipidemia in our group of control patients is considerable if compared with the available experiences and this data confirms the importance of nutrition education as a fundamental preventive activity by pediatrics, given the increasingly frequent trend in population pediatric in general to an unbalanced diet and less and less regular physical activity.

There are obvious differences in the management of the disease between children, adolescents and adults.

As already mentioned, diabetic patients treated at the Complex Structure of Pediatrics and Neonatology, San Paolo Hospital in Savona, are followed in their path of disease management by a multidisciplinary team in order to prevent complications and allow better management of the disease. Acceptance of the disease can be difficult for the young diabetic patient as it tends to focus on the limitations that it undoubtedly imposes on a social and educational level.

It is essential to set up and personalize, with the figure of the dietician or nutritionist, a diet based on the preferences of the child without forgetting the basic pathology and age recommendations.

In the last 20 years, the incidence of overweight and obese children and adolescents with T1D has increased, so the importance of assessing the BMI at each check-up and reporting it in the reference centiles for age and sex is emphasized.

In fact, excess weight further prevents the achievement of therapeutic goals.

At the same time as the lipid control, the HbA1c value was measured in diabetic patients. The American Diabetes Association (ADA) confirms that for young patients with diabetes, regardless of age group, HbA1c values $< 7\%$ represent an indication of good glycemic control over time [12].

In our study, the percentage of pediatric subjects in which HbA1c $\geq 8\%$ was recorded was 52.8%, while the remaining 47.2% had HbA1c $\leq 7\%$.

The mean HbA1c value in the group of 89 diabetic subjects was 8.2 ± 1.3 with a mean duration of the disease of 4.5 years.

In 2005, a survey conducted by the National Pediatric Diabetes Centers (MCDC) showed that the average of HbA1c in the Italian pediatric population stood at around 8.8% [13].

An international multicenter study, conducted on a series of about 142,000 T1D patients from 13 countries, including Italy, showed that well over 26% of patients had HbA1c values $> 9\%$ [14].

It is essential, during the year, to check the HbA1c value on a regular basis.

Diabetic patients, treated at the Day Hospital of the San Paolo Hospital in Savona, go to the Department about every 3 months to perform the HbA1c dosage and when values $\geq 8\%$ are recorded, it is necessary to intervene in a timely manner to try to reach the therapeutic goal again.

It is important to emphasize the individualization of glycemic goals: successful management of diabetes in the pediatric age needs to set realistic targets, which take into account the age, stage of pubertal development and the emotional impact of the disease as there are significant differences in the management of the disease between children, adolescents and adults.

An overall evaluation of the data in our possession can lead to the conclusion that probably the diet of diabetic patients in follow-up at the Day Hospital of the San Paolo Hospital in Savona is not optimal, even when compared to literature data and this confirms the importance of a multidisciplinary team. Coordinated in which the role of the dietician / nutritionist is fundamental, the carbohydrate count as a necessary but not sufficient prevention weapon.

Unfortunately, the data from the control group are not very comforting in relation to the lipid structure and are an alarm bell that should not be underestimated by Pediatrics as a whole.

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