Metabolic dysfunction in late-puberty adolescent girls with type 1 diabetes: Relationship to physical activity and dietary intakes


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Abstract

Aims. – At puberty, type 1 diabetes (T1D) among young girls can lead to excess body weight, insulin resistance, deterioration of glycaemic control and dyslipidaemia. Although biological factors contribute largely to such metabolic dysfunction, little is known of the role of behavioural factors such as physical activity and diet.

Methods. – This study investigated the association between metabolic dysfunction measured after a 12-h overnight fast and behavioural factors, including diet (4-day diary) and physical activity (validated questionnaire), in 19 postmenarchal adolescent girls with T1D compared with 19 healthy girls.

Results. – T1D girls displayed higher levels of fat mass, insulin resistance (higher plasma glucose, serum leptin and waist-to-hip ratios) and dyslipidaemia (higher LDL-C and apolipoprotein B levels, lower HDL-C and apolipoprotein A-1 levels). Also, contrary to what is usually observed in T1D adults, serum adiponectin, an important vessel protector, was not raised in T1D adolescent girls compared with healthy controls. Quantity and quality of dietary macronutrient intakes as well as physical activity levels were comparable in both groups, although the T1D girls with the poorest metabolic profiles reported having the healthiest diets (fewer total calories, more protein and less carbohydrates). However, in T1D girls, less physical activity and more time spent watching television were associated with poorer metabolic profiles (higher waist-to-hip ratios, fat mass and leptin levels, and lower adiponectin, HDL-C and apolipoprotein A-1 levels).

Conclusion. – Collectively, these data suggest that physical inactivity is linked to metabolic dysfunction to a greater extent than unhealthy dietary habits in postmenarchal T1D adolescent girls.

Keywords: Adolescence; Diet; Metabolism; Exercise; Type 1 diabetes

Résumé

Dysfonctions métaboliques chez des adolescentes diabétiques de type 1 en fin de puberté : quelles relations avec le niveau d’activité physique et les apports alimentaires?

Objectifs. – Au moment de la puberté chez la femme, le diabète de type 1 (DT1) peut conduire à des dysfonctions métaboliques (surcharge pondérale, insulinorésistance, déséquilibre glycémique, dyslipidémie). Si de nombreux travaux explorent les mécanismes de ces dysfonctions métaboliques, le rôle des comportements liés à l’alimentation et l’activité physique reste à préciser.

Méthodes. – Les relations entre le profil métabolique à jeun et les facteurs comportementaux incluant l’alimentation (questionnaire sur quatre jours) et l’activité physique (questionnaire validé) ont été étudiées chez 19 adolescentes DT1 menstruées en comparaison de 19 adolescentes non diabétiques.

Résultats. – Les adolescentes DT1 présentaient un excès de masse grasse, des marqueurs et des facteurs de risques d’insulinorésistance (glucose, leptine et rapport taille/hanche supérieurs), et une dyslipidémie (LDL-C et apolipoprotéine-B plus élevés ; HDL-C et apolipoprotéine-A plus...
faibles). De plus, à la différence de ce qui est rapporté chez les adultes DT1, l’adiponectine, protecteur vasculaire majeur, n’était pas élevée chez les adolescentes DT1 en comparaison des témoins. L’apport en macronutriments (quantité et qualité) ainsi que les niveaux d’activité physique étaient comparables dans les deux groupes. Les adolescentes DT1 qui présentaient le profil métabolique le plus altéré rapportaient avoir une alimentation plus saine (moins de calories et de glucides ; davantage de protéines). Néanmoins, chez ces adolescentes DT1, les dysfonctions métaboliques (rapport taille/hanche, masse grasse, leptine plus élevés ; adiponectine, HDL-C, apolipoprotéine-A plus faibles) étaient associées à un investissement moindre dans l’activité physique et à des comportements plus sédentaires. **Conclusion**

L’altération du profil métabolique des adolescentes DT1 en fin de puberté semble davantage liée au manque d’activité physique qu’au déséquilibre de l’alimentation.

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**Mots clés** : Adolescence ; Alimentation ; Diabète de Type 1 ; Exercice ; Métabolisme

1. **Introduction**

At puberty, and especially during the stages of late-puberty, type 1 diabetes (T1D) and female gender can often lead to excess body weight, insulin resistance, deterioration of glycaemic control and dyslipidaemia [1–3], all of which are important risk factors for cardiovascular diseases and long-term cardiovascular complications. Although biological factors, including hormonal changes associated with puberty in girls, and intensified insulin therapy contribute largely to metabolic dysfunction in T1D adolescent girls, little is known of the role of behavioural factors, such as physical activity and diet.

Studies published to date on the relationship between either of these behavioural factors and the metabolic profile of T1D adolescents [4–11] have included few metabolic profile markers, such as body mass index (BMI), glycated haemoglobin (HbA1c), glycaemia, high-density lipoprotein cholesterol (HDLC) and low-density lipoprotein cholesterol (LDLC).

Although overweight occurs from the time of menarche in girls with T1D [12], the data are scanty for strictly selected late-puberty adolescent girls. Sarnblä et al. [13] studied the link between physical activity and diet with HbA1c and BMI in Tanner stages 4/5 T1D girls compared with healthy controls. However, their examinations were conducted over two seasons. Moreover, saturated and unsaturated fatty acids were not distinguished in their dietary intake, and the BMI does not reflect body composition accurately. Schweiger et al. [10] found that the postmenarchal girls with T1D who had lower HbA1c and BMI levels were also younger and less physically active. However, it was difficult to distinguish between the effects of age and physical activity in that study.

For this reason, the present study examined, in a well-characterized population of late-puberty T1D adolescent girls compared with healthy controls, the relationship of both physical activity and dietary composition with body composition, and markers of lipid and apolipoprotein profiles and insulin resistance.

2. **Patients and methods**

Nineteen Caucasian postmenarchal adolescent girls (aged <18.5 years) at Tanner’s pubic-hair stages 4/5 with T1D for at least 1 year (mean duration: 7.4 ± 4.5 [SD] years) were recruited from the regional Unit of Paediatric Endocrinology (Brittany, France). All were receiving multiple insulin injection regimens consisting of both rapid-acting (Novorapid® or Humalog®, 40.9 ± 2.0 U.day⁻¹) and long-acting (Lantus®, 27.4 ± 1.4 U.day⁻¹) insulin analogues, and all were free of microvascular diseases and had negative microalbuminuria screening and normal ophthalmoscopy tests. A control group of 19 healthy Caucasian girls was recruited from among the friends and classmates of the T1D girls. They were selected specifically to closely match the T1D group in terms of age and puberty development ( Tanner’s pubic-hair stages 4/5). All subjects were tested in November. Our study was approved by the ethics committee of Rennes (France), and written informed consent was obtained from all participants and their parents.

2.1. **Metabolic profiles**

These were investigated after a 12-h overnight fast and, in the case of T1D patients, before their morning insulin injections. Height and weight were measured, and subscapular and tricipital skinfolds from the right side were obtained in triplicate by one investigator, and the percentage of body fat mass calculated [14]. Waist and hip circumferences were measured in triplicate by the same investigator, measuring the waist at the level of the umbilicus and the hip at its widest point. The waist-to-hip ratio, an index of insulin sensitivity in T1D [15], was then calculated.

Blood samples were collected in 7-mL heparinized containers (plasma) and 7-mL additive-free containers (serum) from an antecubital vein and centrifuged. Plasma was analyzed for glucose (automated hexokinase method, Beckman Coulter, Brea, CA, USA), total cholesterol and triglycerides (enzyme kits, Beckman Coulter, Roissy, France) and HDLC (polyethylene glycol (PEG)-modified enzymes and dextran sulphate, Roche HDL-Cholesterol Plus, Roche Diagnostics Corporation, Indianapolis, IN, USA). Given that all patients had triglycerides less than 2 mM, LDL-C was computed using Friedewald’s formula, which is validated for use in T1D [16]. Leptin and adiponectin (radioimmunoassay, Linco Research Inc., St. Louis, MO, USA), lipoprotein(a), apolipoproteins A-1 (ApoA1) and B (ApoB) (immunonephelometry, Dade Behring S.A.S, Paris, France) and total insulin-like growth factor (IGF)-1 (radioimmunoassay, CIS Bio International, Saclay, France) were assayed in duplicate using frozen serum. For all samples analyzed, the intra-assay and interassay coefficients of variation were less than 8.3% and less than 9.3%, respectively. An EDTA tube was also taken to analyze HbA1c (high-performance liquid chromatography [HPLC], VARIANT™, Bio-Rad, Munich, Germany).
2.2. Dietary data

This was based on a 4-day diary (one school day, Wednesday, Saturday and Sunday). Written instructions were given to provide detailed information on the quantity and quality of all food items consumed. The subjects were asked to fill in their diary in the week preceding their visit to the laboratory; this was to be done directly after meals, except for lunch and snacks consumed during the school day, which could be recorded after school. The T1D girls were also asked to record the food they ate during hypoglycaemic episodes. On the day of their laboratory visit, the girls brought their diaries with them. After giving blood samples for the metabolic analyses and having breakfast, the girls were interviewed in a separate room by a research-trained dietitian, who gathered information to supplement the diaries. The dietitian elicited specific details related to the reported food intakes such as brand names, fat content and portion sizes, using a booklet containing photographs of food in bowls or plates. The dietitian also elicited any missing information about food intake (for example, to T1D girls: “Did you have any other hypoglycaemic episode not reported in the questionnaire and what did you eat then?”). After that, if possible, the parents were interviewed independently for more information on food preparation and recipes. Total duration of the interview with the dietitian was approximately 30 min. Macronutrient intakes reported in the diary were analyzed using PRoFIL v 6 software (C.I.A.M., Saint-Chouldard, France) based on the Ciqual (1995 version) composition table. Dietary intakes were averaged across the 4 assessment days.

2.3. Regular levels of physical activity

This was assessed using a structured validated questionnaire [17] adapted for Caucasian children [18]. Subjects were questioned about the time spent on sports in school, on extracurricular club-organized activities both in and outside of school, and on free spare-time activities, and the frequency of such activities. The average number of hours per week spent on each activity was calculated and totalled. To assess the energy requirement for each activity, the number of hours per week was then multiplied by an estimate of the metabolic cost of each activity (expressed as metabolic equivalents [METs], defined as the ratio of work metabolic rate to resting metabolic rate, with 1 MET = 1 kcal.kg\(^{-1}.h^{-1}\)) [19].

2.4. Quality of life

This was also assessed in the T1D group, using the diabetes quality-of-life (DQOL) questionnaire [20].

2.5. Statistical analyses

These were computed using STATISTICA 6.0 software (StatSoft, Tulsa, OK, USA). Normality was tested with the Kolmogorov-Smirnov test, and data were compared between T1D and healthy subjects using either Student’s unpaired t test (parametric data) or Mann-Whitney U test (non-parametric data). Pearson’s (or Spearman’s for non-parametric data) rank-order correlation coefficients were used to detect correlations between variables in T1D subjects, and \( P < 0.05 \) was considered statistically significant.

3. Results

Group demographics and metabolic profile data are summarized in Table 1. In T1D girls, long-acting daily insulin doses correlated positively with waist-to-hip ratios \((r = 0.66, P < 0.01)\), while total daily insulin doses \((IU.day^{-1})\) correlated negatively with serum adiponectin levels \((r = -0.55, P < 0.05)\). Time elapsed from menarche correlated negatively with adiponectin and HDL-C levels in T1D girls \((r = -0.75, P < 0.001\) and \( r = -0.56, P < 0.05, \) respectively) and positively with ApoB levels in the healthy controls \((r = 0.57, P < 0.05)\). Higher BMI scores and higher HbA1c levels were associated with the poorest quality-of-life scores in T1D girls (BMI with DQOL sections “worries about diabetes”, \( r = 0.61, P < 0.01 \) and “total score”, \( r = 0.46, P < 0.05 \); HbA1c with sections “satisfaction with life”, \( r = 0.60, P < 0.01, \) “satisfaction with diabetes”, \( r = 0.60, P < 0.01 \) and “total score”, \( r = 0.48, P < 0.05 \).
Macronutrient dietary intakes were comparable between groups except for protein intake, which was greater in T1D girls (Table 2). Also, in the T1D girls, total calorie intakes were negatively associated with BMI ($r = -0.50, P < 0.05$) and waist circumference ($r = -0.47, P < 0.05$). In addition, their relative intakes of protein correlated positively with markers of dyslipidaemia (ApoB/ApoA1: $r = 0.65, P < 0.01$; LDL-C/HDL-C: $r = 0.63, P < 0.01$) and insulin resistance (leptin: $r = 0.50, P < 0.05$), whereas their relative carbohydrate intakes correlated negatively with alterations in lipid profiles (ApoB/ApoA1: $r = -0.46, P < 0.05$; LDL-C/HDL-C: $r = -0.51, P < 0.05$). Proportions of saturated and unsaturated fatty acids did not correlate with markers of metabolic profile. Among the healthy controls, total calorie intakes were also negatively associated with BMI ($r = -0.50, P < 0.05$), and their relative protein and carbohydrate intakes did not correlate with their metabolic profile.

However, the T1D girls tended to be less active than the healthy girls (0.7 ± 1.0 vs. 1.4 ± 1.0 h/week of club-organized activities and 25.2 ± 21.1 vs. 29.1 ± 14.9 kcal.kg$^{-1}$.wk$^{-1}$, not significant [NS]). In T1D girls, the less time spent doing club-organized activities was associated with a higher waist-to-hip ratio ($r = -0.46, P < 0.05$) and lower adiponectin levels ($r = 0.57, P < 0.01$). Furthermore, the frequency of self-reported club-organized activity was associated with plasma HDL-C ($r = 0.48, P < 0.05$) and serum adiponectin ($r = 0.65, P < 0.005$) levels. Indeed, among T1D patients, the girls who devoted more time to watching television/videos presented with higher BMIs ($r = 0.61, P < 0.01$), higher percentages of body fat ($r = 0.60, P < 0.01$), and lower levels of protective lipoproteins (HDL-C, $r = -0.68, P < 0.001$) and apolipoproteins (ApoA1, $r = -0.74, P < 0.001$), and had a higher risk of insulin resistance (leptin, $r = 0.46, P < 0.05$; adiponectin, $r = -0.53, P < 0.05$). These significant correlations were not observed in the healthy control group.

### 4. Discussion

The present study of late-pubertal adolescent girls with T1D has highlighted the strong relationship between poor metabolic profiles and sedentary/low-physical-activity patterns, but not with unhealthy dietary habits.

The main strength of this report is its focus on strictly selected postmenarchal adolescent girls with and without T1D, and its inclusion of a wide spectrum of metabolic markers as well as dietary and physical-activity habits. Emphasis was placed on recruiting healthy and T1D girls who were closely matched by puberty stage, as the metabolic profile is known to deteriorate after menarche [1–3]. This deterioration was confirmed in our study by the correlations observed between time elapsed since menarche and insulin-resistance risk in the T1D group, and by the more atherosclerotic lipid profiles in both groups.

Changes in the metabolic profiles of the T1D adolescent girls in our present sample were alarming. Compared with their healthy matched controls, they had much higher levels of plasma glucose, despite comparable plasma insulin levels, as well as higher waist-to-hip ratios and higher levels of serum leptin, reflecting a high risk of insulin resistance. Although insulin resistance is carbohydrate-selective [21], insulin still has a role in protein synthesis and lipogenesis. This was illustrated in our T1D girls by a higher lean body mass/height-squared ratio and excess fat mass with truncal adiposity, which is significantly correlated with long-acting daily insulin injections. This marked alteration in body composition (higher BMI, larger waist circumference) and changes in glycaemic control (higher HbA$_1c$) had a negative impact on quality of life, as reflected by our correlations. Lipid profiles were also altered in T1D girls, as reflected by lower levels of cardiovascular-protective lipids and higher levels of atherosclerotic lipids. Moreover, contrary to what is usually observed in adults with T1D [22] and in prepubertal children with T1D [23], serum adiponectin, an important endogenous vasoprotective hormone, was not raised in the T1D adolescent girls compared with the healthy controls.

Taken altogether, these results underscore the high level of potential risk factors for atherosclerosis and cardiovascular disease in late-puberty T1D adolescent girls. To improve therapeutic interventions in this young population, it is probably essential to understand the involvement of lifestyle factors in metabolic profile alterations.

Concerning dietary habits, as reported in another study [13], macronutrient dietary intakes were comparable in both groups except for a greater proportion of calories derived from protein in T1D girls. Compared with the French dietary recommendations, both the T1D and healthy control girls consumed fewer calories than recommended. However, considering that underestimation of nutrient intakes during self-reporting may be commonplace in
adolescents [13], this result should be viewed with caution. Nevertheless, the T1D girls were already accustomed to accurately keeping their 4-day dietary diaries with the dietitian as part of the therapeutic education of patients. In addition, measures were taken to minimize any tendency towards selective reporting; for example, a separate room was reserved for the interviews. Furthermore, the absence of any judgement and the confidentiality of the study data were emphasized by being both written in the diary and given as a verbal reminder by the dietitian. During the interview, there were no closed questions and no questions or comments that could be considered judgmental.

To minimize the effect of underreporting, energy intakes derived from carbohydrates, fats and proteins were adjusted in relation to total energy intake (%). In our study, both groups met the dietary requirements for carbohydrates and protein, but exceeded the recommendations for saturated fat and cholesterol, while fibre intakes were below the recommended amount [24]. This was in accordance with the results of other studies including both T1D children and adolescents [25]. However, rather surprisingly in our present study, the T1D girls who had healthier diets (in terms of quantity and quality) were also those suffering more from excess weight and metabolic dysfunction. Thus, it might be hypothesized that adolescent girls with T1D become more compliant with dietary recommendations when their metabolic profiles deteriorate. Such a result is consistent with other studies highlighting the link between more intense dietary restraints and increases in BMI and HbA1c from adolescence to adulthood among T1D girls [26].

Thus, future research using food-frequency questionnaires could perhaps supplement our present results. Bortsov et al. [27] recently found that male and female youths (aged 10–22 years) with T1D who drank at least one sugar-sweetened or diet beverage a day had higher levels of blood cholesterol, LDL-C and triglycerides than those who never drank such beverages.

Although the differences in physical activity between our two groups were not statistically significant, among the T1D girls, there were strong relationships between low club-organized physical activity and more time spent watching television with fat mass excess, insulin resistance and dyslipidaemia. To the best of our knowledge, this link has never been thoroughly studied in late-puberty T1D girls. Indeed, only the relationship between physical activity and HbA1c has previously been considered [13], and the results were in agreement with our present findings: there was no correlation. However, the impact that the lack of regular exercise has on long-term glycaemic control [28] could be explained by a fear of hypoglycaemia during exercise [29], which could perhaps cause patients to make inappropriate dietary and/or insulin adaptations. Furthermore, the strong association between less physical activity or more physical inactivity and lower serum adiponectin levels, as observed in the present study, merits further investigation. As adiponectin is an important endogenous vasoprotective agent, it may be that this hormone represents an underlying mechanism that might explain the relationship, reported in a recent study, between atherosclerosis (as reflected by a non-invasive marker, arterial flow-mediated vasodilation) and levels of physical activity in children and adolescents (aged 10.2–12.8 years, with the majority being Tanner stage 1 puberty) with T1D [30].

Through various correlations, our present study has suggested that physical inactivity could be one of the factors leading to non-elevated adiponectin levels in T1D adolescent girls in contrast to T1D prepubertal children [23] or adults [22]. However, this peculiarity of adiponectin in T1D adolescent girls might be explained by other factors; for example, adolescent girls with T1D are compelled to strongly increase insulin doses throughout puberty to counteract worsening insulin resistance as a result of growth hormone hypersecretion [2]. As exposure to insulin is known to downregulate adiponectin synthesis in vitro [31], it is possible that the higher insulin doses administered to late-puberty T1D girls compared with T1D prepubertal children or adults trigger a relative decrease in circulating adiponectin levels. This hypothesis was corroborated in our study by the significant inverse relationship between insulin doses and serum adiponectin levels.

In conclusion, the present study provides documentation that physical inactivity is more strongly linked to metabolic dysfunction than poor dietary habits in contemporary late-puberty T1D adolescent girls. This indicates that, for these patients, physical exercise accompanied by appropriate insulin treatment guidelines should be seen as an important therapeutic adjunct in the prevention and management of metabolic and cardiovascular risks.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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