Alteration in sympathoadrenergic activity at rest and during intense exercise despite normal aerobic fitness in late pubertal adolescent girls with type 1 diabetes

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Received February 2007; accepted April 2007

Abstract

\textit{Background.} – An impaired sympathoadrenergic response to hypoglycaemic episodes has been described in young Type 1 diabetic subjects. It is unknown if this altered response occurs with exercise, and if it could influence aerobic power.

\textit{Methods.} – Body composition (skinfold thickness), physical activity (questionnaire) and aerobic power (PWC\textsubscript{170} and \textit{VO}\textsubscript{2}\textsubscript{max}) were assessed in 19 post-menarcheal Type 1 diabetic (T1D) girls (13.3–18.2 years) and 19 healthy siblings. At rest and at each stage of the graded exhaustive exercise, plasma glucose, insulin, epinephrine and norepinephrine, were monitored via an intravenous catheter.

\textit{Results.} – Only when expressed per kilograms of body weight, was aerobic power impaired in T1D girls compared to controls, probably because they were overweight. Throughout exercise, plasma glucose remained stable while plasma insulin decreased in the healthy girls, whereas glucose diminished significantly with no change in plasma insulin in T1D girls. During exercise catecholamines increased in the same way in both groups. However, at rest and throughout all stages of exercise, norepinephrine levels were significantly lower by a mean difference of 1.2 nmol/L, while epinephrine levels were significantly higher by a mean difference of 0.14 nmol/L, in T1D girls compared to healthy girls. Heart rates of T1D girls were not affected by the sympathoadrenergic alteration.

\textit{Conclusion.} – T1D adolescent girls display an altered sympathoadrenergic activity at rest and during intense exercise. Their reduced sympa-thetic activity, albeit probably compensated for by higher adrenomedullary responsiveness or sensitivity, does not affect their heart rate adaptations to exercise.

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alors que chez les adolescentes diabétiques la glycémie a diminué sans variation de l’insulinémie. Les catécholamines ont augmenté à l’exercice dans les mêmes proportions dans les deux groupes. Cependant, les concentrations de noradrénaline étaient significativement inférieures (en moyenne de 1,2 nmol/l) pour des concentrations d’adrénaline significativement supérieures (en moyenne de 0,14 nmol/l) chez les adolescentes diabétiques par rapport aux adolescentes non diabétiques, au repos et à tous les paliers d’exercice. Cela n’a pas affecté la fréquence cardiaque des adolescentes diabétiques.

Conclusion. – Les adolescentes diabétiques présentent une altération de la réponse sympathoadrénergique à l’exercice intense. Leur activité sympathique réduite, probablement compensée par une meilleure réponse et/ou sensibilité des glandes médullaires, n’affecte pas leur adaptation cardiaque à l’exercice.

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Keywords: Adolescent girls; Catecholamines; Exercise capacity; Sympathoadrenergic activity; Type 1 diabetes mellitus

Mots clés : Activité sympathoadrénergique ; Exercice physique ; Adolescentes ; Catécholamines ; Diabète de type 1 ; Puissance maximale aérobie

1. Introduction

At puberty, and more so at late pubertal stages, Type 1 diabetes mellitus (Type 1 DM) and female gender often lead to an excess of body weight, insulin resistance, glycaemic control deterioration and dyslipidaemia [1–3], which are important risk factors for cardiovascular diseases and long term complications. Regular physical exercise is usually considered an important therapeutic lifestyle intervention in the prevention and management of metabolic disorders [4,5]. From a practical point of view, it is often difficult to motivate adolescent girls to get involved in regular exercise, because this is partly influenced by their performance capacity [6,7]. Aerobic power is known to decrease from childhood to late puberty in healthy girls [8]. Capacity to exercise could be even more impaired in adolescent girls with Type 1 DM, given that Type 1 DM can affect metabolic and hormonal responses to exercise [9–13].

Most studies carried out in adults have reported reduced plasma catecholamine levels in subjects with Type 1 DM compared to healthy controls during maximal incremental exercise [9,11,12]. Plasma levels of catecholamines, which reflect sympathoadrenergic activity [14], are generally considered to be of great importance for the cardiorespiratory, circulatory and metabolic adjustments to exercise [14,15]. Thus, reduced catecholamine levels in adults with Type 1 DM were associated with an impaired aerobic power [16]. In younger subjects with Type 1 DM, i.e. children or adolescents, catecholamine levels have been described to be reduced during hypoglycaemic episodes compared to healthy controls [17]. However, it is not known if such an altered catecholamine response also occurs during intense exercise in adolescents with Type 1 DM, which would lead to impaired physiological responses to exercise.

Catecholamines stimulate glucose production [15]. However, little is known about the effect of the hypothetical impaired catecholamine response, in combination with administration of exogenous insulin, on plasma glucose levels during exercise in patients with Type 1 DM. In these patients, plasma glucose levels often decrease after moderate exercise [18] or maximal graded exercise bout [10,13]. In a clinical setting a rapid drop in plasma glucose is able to trigger an adrenergic response and hypoglycaemia symptoms even in the absence of true biochemical hypoglycaemia [19]. Nevertheless, to our knowledge, the potential impact of glucose drop on tolerance to maximal exercise has never been studied in adolescents with Type 1 DM.

Adolescents with Type 1 DM are usually prone to temporary hyperglycaemic or ketotic episodes [20], which are known to be factors that contribute to fatigue [21]. In Type 1 DM patients with poor glycaemic control such as adolescent girls [2], it seems worth exploring whether their poor pre-exercise glycaemic state may lead to early fatigue.

The present study examined the catecholaminergic and glycaemic responses to an exhausting graded exercise in late pubertal girls with Type 1 DM. We hypothesized that (1) plasma epinephrine and norepinephrine levels would be reduced in girls with Type 1 DM compared with healthy girls and (2) high plasma glucose levels before exercise, low plasma catecholamine levels, and/or a large drop in plasma glucose concentrations during the graded exercise would impair tolerance to maximal exercise and/or aerobic fitness of the girls with Type 1 DM.

2. Material and methods

2.1. Subjects

Adolescent girls and their parents gave a written informed consent for the experimental protocol. This protocol was approved by the Ethics Committee of the University of Rennes (France). Among patients regularly attending the Unit of Pediatric Endocrinology (Rennes, France), all post-menarcheal adolescent girls with Type 1 DM, less than 18.5 years old, at Tanner’s pubic hair stages 4–5 [22], and having diabetes for at least one year were recruited. Nineteen Caucasian girls with Type 1 DM (T1D group) volunteered for the study. Duration of diabetes ranged from 1 to 14 years (mean 7.3 years). They were all on a conventional insulin regimen, consisting of both rapid (Novorapid™ or Humalog®) (0.63 ± 0.14 (SD) IU/kg per day) and long-acting (Lantus®) (0.42 ± 0.10 (SD) IU/kg per day) insulin analogues. Their mean glycated haemoglobin level (HbA1c) at the time of evaluation was 8.1 ± 1.3 (SD) % (range: 5.7–11.0) and they were free from microvascular diseases with negative microalbuminuria screening test and normal ophthalmoscopy.
A control group of 19 healthy Caucasian adolescent girls (CON group) was recruited among the friends and classmates of the T1D girls. They were selected to closely match the T1D group for age and pubertal development (Tanner stages 4–5) [22] (Table 1).

All the subjects were tested at the same period of the year (November). Their regular physical activity level was assessed using a structured validated questionnaire adapted for Caucasian children [23].

2.2. Laboratory testing

Subjects were requested to refrain from vigorous activity and from consumption of banana, tobacco, as well as alcohol, cocoa, tea, coffee and cola beverages for 48 h before the test. They presented to the laboratory at 7:45 am, after a 12-h overnight fast. Standing height, weight, body fat (estimated from triceps and subscapular skinfolds) [24] and pubertal stage [22] were determined. A normal electrocardiogram was a prerequisite for participation in exercise testing. During the medical examination a flexible Teflon catheter was introduced into a superficial cubital vein and kept patent with a saline solution. Then, the T1D girls injected their usual morning rapid insulin (Equilin, Lilly, Brussels, Belgium) and basal insulin (NovoRapid, Novo Nordisk, Bagsværd, Denmark) at the onset of exercise (at 8.00 am). Glucose was monitored every 15 min by a self-monitoring device (Contour, Bayer, Leverkusen, Germany).

They presented to the laboratory at 7:45 am, after a 12-h overnight fast. Exercise began at 30 Watts and resistance was increased by 24 Watts every 30 s. Unless hypoglycaemia occurred, the test was terminated at the point when the pedalling rate could no longer be sustained. All subjects received verbal encouragement from the testing staff. Breath-by-breath gas monitoring (CPX, Cardioware, Sweden) at a constant rate of 60 rpm. Exercise began at 30 Watts and resistance was increased by 24 Watts every 2 min. Unless hypoglycaemia occurred, the test was terminated at the point when the pedalling rate could no longer be sustained. All subjects received verbal encouragement from the testing staff. Breath-by-breath gas monitoring (CPX, Cardioware, Sweden) at a constant rate of 60 rpm.

Ninety minutes after the end of breakfast, T1D girls’ urine was tested with a test strip (Keto-Diastix®, Bayer Diagnostics) for the presence of sugar or ketone bodies and the incremental exercise test to exhaustion was carried out. Subjects pedalled on a mechanically braked cycle ergometer (Monark, 814E, Sweden) at a constant rate of 60 rpm. Exercise began at 30 Watts and resistance was increased by 24 Watts every 2 min. Unless hypoglycaemia occurred, the test was terminated at the point when the pedalling rate could no longer be sustained. All subjects received verbal encouragement from the testing staff. Breath-by-breath gas monitoring (CPX, Cardioware, Sweden) at a constant rate of 60 rpm.

Plasma was assayed for norepinephrine and epinephrine levels by high-performance liquid chromatography (Waters, St Quentin en Yvelines, France; Chromosystems, Munich, Germany) with electrochemical detection (ESA, Coulombem II, France). The intra-assay coefficients of variation (CV) were 4–5.8% for norepinephrine and 4.3–5.4% for epinephrine. The interassay CV were 3.9–6.1% for norepinephrine and 5.8–5.6% for epinephrine.

2.3. Biochemical analysis

Plasma was assayed for norepinephrine and epinephrine levels by high-performance liquid chromatography (Waters, St Quentin en Yvelines, France; Chromosystems, Munich, Germany) with electrochemical detection (ESA, Coulombem II, France). The intra-assay coefficients of variation (CV) were 4–5.8% for norepinephrine and 4.3–5.4% for epinephrine. The interassay CV were 3.9–6.1% for norepinephrine and 5.8–5.6% for epinephrine.

Statistics were computed using Statistica 6.0 software. Normality was tested using Kolmogorov-Smirnov tests. Descriptive and anthropometric data, physical activity levels, aerobic power were compared between groups by using either Student’s unpaired t-tests (parametric data) or Mann-Whitney U-tests (non-parametric data). Hematocrit levels, plasma glucose, and catecholamine concentrations (parametric for all) were compared within and between groups by two-way ANOVAs (group xexercise level) with repeated measures on the second factor. If significant main effects were observed, Duncan’s multirange post hoc tests were applied to examine specific pairwise differences. Plasma insulin concentrations (non-parametric) were analysed using Friedman ANOVAs in each group separately. If a significant change with exercise

__Table 1__

<table>
<thead>
<tr>
<th>General characteristics of the girls with Type 1 DM and healthy controls</th>
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<tbody>
<tr>
<td><strong>CON girls (N = 19)</strong></td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Time elapsed from menarche (years)</td>
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<td>Age at menarche (years)</td>
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Data are means ± SD. * P < 0.05, ** P < 0.01. CON girls: healthy adolescent girls, T1D girls: adolescent girls with Type 1 DM.
level was detected, specific differences between exercise levels were determined using Wilcoxon Matched Pairs tests. Specific between groups differences of insulin were analysed using Mann-Whitney U-tests. Pearson (or Spearman for non-parametric data) rank order correlation coefficients were used to detect correlations between variables. *P* < 0.05 was considered statistically significant. Results are reported as means ± SD except where otherwise indicated.

3. Results

3.1. Subjects characteristics

General characteristics of the girls are shown in Table 1. The T1D girls were heavier than the CON girls due to an excess of body fat mass.

Except for leisure time sport activities, the T1D girls appeared to be less active than the CON girls (Table 2).

3.2. Exercise testing

3.2.1. Aerobic power

The results of exercise testing are presented in Table 3. Out of the 19 subjects in each group, only 12 T1D and 8 CON girls were able to reach maximum effort during the test. In these girls, PWC170 was achieved at a comparable relative workload in T1D (78.3 ± 2.6%HRR) and CON (76.7 ± 3.6%HRR) girls.

Aerobic power was assessed with \( \text{VO}_2 \text{max} \) in the girls having achieved maximum effort and with PWC170 in all the subjects. Aerobic power was comparable in both groups, except when expressed per kilograms of body weight (Table 3).

Before the start of exercise test, 15 T1D girls had glycosuria (ranging from 5.5 to 280 mmol/L) and three girls had acetonuria (ranging from 0.5 to 8 mmol/L). A poor short-term glycaemic control was associated with low peak values (e.g. glycosuria with peak \( \text{VO}_2 \) in L per min: \( R = -0.57, P < 0.01 \) or with peak absolute workload: \( R = -0.56, P < 0.01 \); resting plasma glucose with peak heart rate: \( R = -0.60, P < 0.01 \). Resting plasma glucose levels of the T1D girls who reached maximum effort (\( n = 12 \)) were lower than those of the T1D girls who stopped the test before maximum effort (\( n = 7 \)) (10.8 ± 3.3 vs. 16.8 ± 4.4 mmol/L, \( P < 0.01 \)). In contrast, PWC170 was not associated with short-term glycaemic control.

In T1D girls neither peak \( \text{VO}_2 \), \( \text{VO}_2 \text{max} \), or PWC170 were correlated to HbA1c levels, i.e. long-term glycaemic control.

Heart rates as well as calculated relative workloads did not differ between the two groups at each stage of the exercise (Fig. 1).

![Relative workloads (%HRR) at every stage of the incremental exercise in T1D and CON girls.](image)

Table 3

| Physical testing results in adolescent girls with Type 1 DM compared to healthy controls |
|----------------------------------|------------------|------------------|
| Exercise time (min)              | CON girls (\( N = 19 \)) | T1D girls (\( N = 19 \)) |
|                                  | 11.4 ± 1.3       | 11.0 ± 1.4       |
| Peak heart rate (bpm)            | 188.0 ± 9.2      | 188.1 ± 10.0     |
| Peak workload (W)                | 138.9 ± 17.8     | 132.4 ± 17.2     |
| Peak RER                         | 1.09 ± 0.09      | 1.05 ± 0.08      |
| Peak \( \text{VO}_2 \)            |
| L/min                            | 1.99 ± 0.30      | 1.98 ± 0.25      |
| mL/min per kg                    | 35.1 ± 6.0       | 30.8 ± 3.8 **    |
| mL/min per kg of LBM             | 45.7 ± 6.4       | 44.7 ± 5.0       |
| \( \text{VO}_2 \text{max} \)     |
| L/min                            | 2.01 ± 0.21      | 1.90 ± 0.26      |
| mL/min per kg                    | 55.6 ± 6.9       | 30.6 ± 4.0 *     |
| mL/min per kg of LBM             | 46.2 ± 6.8       | 43.8 ± 4.9       |
| PWC170                           |
| W                                | 113.2 ± 18.4     | 107.6 ± 26.2     |
| W/kg                             | 1.99 ± 0.30      | 1.66 ± 0.34 **   |
| W/kg LBM                         | 2.62 ± 0.35      | 2.41 ± 0.51      |

Data are means ± SD. CON girls: healthy adolescent girls, T1D girls: adolescent girls with Type 1 DM. LBM: Lean body mass, RER: Respiratory Exchange Ratio. *P* < 0.05, **P* < 0.01 compared to healthy controls.

\( a \) \( N = 8 \).
\( b \) \( N = 12 \).

3.2.2. Metabolic and hormonal data during the incremental exercise

Hematocrit levels rose significantly in T1D and CON groups during the exercise test (exercise level effect, \( P < 0.001 \); exercise level-by-group interaction: NS) from 0.40 ± 0.03 to 0.42 ± 0.03 in T1D girls and from 0.36 ± 0.07 to 0.40 ± 0.03 in CON girls. Therefore, metabolic and hormonal...
concentrations have been corrected to account for plasma volume changes. Hematocrit levels were higher in T1D compared to CON girls, both at rest and during all stages of exercise (group effect, \( P < 0.05 \)).

Plasma glucose and insulin concentrations were significantly higher in T1D girls compared to CON girls at rest and during exercise (Fig. 2).

An interaction between exercise level and group was detected for plasma glucose \( (P < 0.05) \). Plasma glucose concentrations were stable during the test in CON girls, while they fell during the exercise test in T1D girls \((-1.6 \pm 1.4 \text{ mmol/L}, \text{ or } -13.1 \pm 9.6\% \text{ from baseline values}; \ P < 0.001) \) (Fig. 2). However, no hypoglycaemic episodes occurred during the test in the T1D girls. The decrease in their plasma glucose during the exercise test did not correlate with any markers of aerobic power.

Whereas plasma insulin concentrations declined during exercise in CON girls \( (P < 0.001) \), they did not significantly change in T1D girls (Fig. 2).

Plasma concentrations of norepinephrine and epinephrine rose significantly with exercise level in T1D and CON girls \( (P < 0.001) \) with no differences between the groups (exercise level-by-group interaction: NS) (Fig. 3). An adrenergic threshold appeared for most of the subjects at comparable relative workloads in T1D and CON girls \((65 \pm 17 \text{ and } 62 \pm 11\%\text{HRR}, \text{ respectively})\). At rest and across all workloads, norepinephrine concentrations were lower in T1D compared to CON girls (group effect, \( P < 0.05 \)), while epinephrine levels were higher in T1D girls (group effect, \( P < 0.05 \)) (Fig. 3).

4. Discussion

This study shows that in late pubertal girls with Type 1 DM compared to healthy controls, levels of plasma epinephrine are higher despite reduced levels of plasma norepinephrine at rest and during intense exercise. However, this altered sympathoadrenergic activity is not accompanied by an impairment of absolute aerobic power.

We assessed aerobic power using both maximal \( (\dot{V}O_2\text{max}) \) and submaximal (PWC\(_{170}\)) recordings. \( \dot{V}O_2\text{max} \) was obtained in only 20 of the 38 subjects, while only a peak \( \dot{V}O_2 \) was measured at exhaustion in the remaining 18 girls. In T1D group high pre-exercise levels of glycaemia or glycosuria were associated with low peak \( \dot{V}O_2 \). Thus, a poorer short-term glycaemic control could lead to a premature fatigue in girls with Type 1 DM, as previously suggested [21]. As short-term glycaemic control varies from day to day, it seems that peak \( \dot{V}O_2 \) should not be an accurate index of aerobic power in adolescents with Type 1 DM. PWC\(_{170}\) was not influenced by short-term glycaemic control and it correlated to \( \dot{V}O_2\text{max} \) in the 12 T1D girls that reached maximum effort (e.g. when both markers are expressed in kg per LBM: \( R = 0.86, \ P < 0.001 \)). Therefore PWC\(_{170}\) can be considered as an acceptable aerobic power index [25]. PWC\(_{170}\) and \( \dot{V}O_2\text{max} \) expressed in absolute terms were not impaired in T1D girls compared to CON girls. When expressed per kilograms of body weight, PWC\(_{170}\) and \( \dot{V}O_2\text{max} \) were reduced in T1D girls presumably because of their excess of fat mass (Table 1) [2]. Behavioural aspects such as a lack of participation in

![Fig. 2. Plasma concentrations of glucose (A) and insulin (B) during the incremental exercise in T1D and CON girls.](image-url)
sports activities – as observed in TID girls (Table 2) – could partly be implicated in their fat mass excess [30].

Although absolute aerobic fitness was not impaired in adolescent TID girls, their plasma levels of glucose, insulin, and catecholamines during exercise were affected by the disease.

The higher plasma glucose levels despite higher plasma insulin levels in TID vs. CON girls are consistent with the well-documented insulin-resistance among adolescent girls with Type 1 DM [1]. The higher levels of plasma glucose in TID girls may have contributed to enhance their hematocrit levels, a mild dehydration being anticipated with hyperglycaemia [31].

In TID adolescent girls maximal incremental exercise induced a drop in plasma glucose levels while these levels were maintained in CON adolescent girls. In CON girls the decrement in plasma insulin levels probably contributed to the stability of plasma glucose, as already asserted in healthy adults even in case of intense exercises [32]. In TID girls exercise testing was conducted at the time of peak action of the morning insulin analogue and plasma exogenous insulin did not decrease during the exercise. This may have contributed to their plasma glucose drop [32]. Catecholamines are also important regulators of glucose production during intense exercise [15]. It is assumed that the onset of the sharp increase in plasma epinephrine (i.e. adrenergic threshold) during a graded exercise will initiate the increase in muscle glycogenolysis [33]. Thus, in our TID girls, the higher the plasma epinephrine concentrations at the adrenergic threshold were, the less plasma glucose decreased thereafter ($R = 0.54$, $P < 0.05$). This effect of epinephrine on glucose occurred even in presence of high insulin levels, as already reported in insulin-treated adults [34].

Besides their role in glucose regulation, catecholamines are implicated in most of the physiological adaptations to intense exercise [14,15]. Since plasma catecholamine levels could be impaired by Type 1 DM, we investigated epinephrine and norepinephrine levels at rest and during the maximal incremental exercise.

In TID versus CON girls, norepinephrine levels were reduced while epinephrine levels were increased at rest and at each exercise stage (corresponding to comparable relative workloads in two groups).

Since the experimental protocol was the same for both groups, the influence of stress, posture, or diet may not contribute to the differences found. Also, the amount of active muscle mass [35,36] did probably not account for the differences in catecholamine levels between the two groups, since lean body mass was comparable in TID and CON girls.

Plasma norepinephrine levels are considered an indicator of average sympathetic outflow [37]. Therefore in TID adolescent girls the lower norepinephrine concentrations probably reflect a reduced sympathetic activity. Diminished plasma norepinephrine levels have already been observed during incremental exercise in adults with Type 1 DM and were assumed to be caused by sympathetic neuropathy [9,16]. This might suggest the presence of a subclinical sympathetic neuropathy in the TID adolescent girls [38]. Contrary to what is observed in adults with Type 1 DM [16], the reduced sympathetic activity did not alter heart rate adaptations to exercise in the TID girls. This discrepancy between adults and adolescents could be explained by a possible increased cardiac sensitivity to sympathetic influx during the first years of disease [39].

Basal epinephrine levels are known to decline with puberty [40]. This effect of puberty is probably not involved in the difference of resting epinephrine levels between TID and CON groups, since our population was homogeneous concerning pubertal development (all girls at Tanner stages 4-5). Gschwend and colleagues [41] found that hyperglycaemia did not induce any increase in epinephrine levels in adolescents with Type 1 DM. Therefore, the higher plasma epinephrine levels in TID girls may not be attributed to their higher plasma glucose levels. We cannot exclude a possible adrenergic response to the decrease in plasma glucose levels during exercise in TID girls. However, this is probably not responsible for the differences in plasma epinephrine levels observed between
the two groups for several reasons. Firstly, the degree of glucose drop from rest to peak exercise did not correlate to peak epinephrine levels in TID girls. Secondly, the between-groups difference in epinephrine levels was evident throughout the exercise protocol.

To a large extent plasma epinephrine reflects the production of epinephrine by adrenal medulla glands in response to sympathetic outflow [14,42]. Therefore the present study shows that the reduced sympathetic activity of adolescent girls with Type 1 DM – as reflected by lower norepinephrine levels – is compensated for by a greater sensitivity and/or responsiveness of the adrenal medulla glands – as reflected by higher epinephrine levels. As reported in previous studies, this compensation could be progressively attenuated with age and disease progression, since norepinephrine as well as epinephrine are reduced in adults with Type 1DM during maximal graded exercise [9,11,12,16].

5. Conclusion

Despite a normal aerobic fitness, adolescent girls with Type 1 DM display reduced sympathetic activity at rest and during maximal graded exercise, which seems to be compensated for by an increased sensitivity and/or responsiveness of adrenal medulla glands. Comparing our results to those in adults, it seems that the sensitivity (and/or responsiveness) of tissues, such as adrenal medulla glands or myocardium, may progressively change from over-sensitivity at the beginning of the disease to reduced-sensitivity with age and disease progression. This hypothesis has already been postulated for the sympatho-drenergic response to hypoglycaemia [39], but additional research in the field of exercise is needed to confirm our assumptions.

The results of this study might eventually lead to guidelines or strategies to prevent a possible decrease in tissue sensitivity and hence in aerobic fitness with age and Type 1 DM. It may be therefore important to encourage young Type 1 DM patients practice regular physical exercise.

Acknowledgements

This study was supported by grants from Novo Nordisk. We thank H. Youssef, C. Toutain, E. Marcoux, A. Ruelland, M.-T. Gougeon, D. Paul for laboratory assistance, Luk Buyse for revising the manuscript, A. Content for statistical assistance, G. Cox and A. Kinnucan for revising the English.

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