

# Effects of Regular Physical Activity on Control of Glycemia in Pediatric Patients With Type 1 Diabetes Mellitus

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**Objective:** To evaluate the effect of regular physical activity (RPA) on the control of glycemia (glycosylated hemoglobin A<sub>1c</sub> level) and the frequency of severe hypoglycemia in a large cohort of patients with type 1 diabetes mellitus.

**Design:** Cross-sectional analysis of data for 19 143 patients, comparing control of glycemia and rate of hypoglycemia by frequency of RPA.

**Setting:** One hundred seventy-nine pediatric diabetes clinics in Germany and Austria.

**Participants:** Patients aged 3 to 20 years with type 1 diabetes mellitus.

**Main Exposure:** Patients were grouped by the frequency of RPA per week as follows: RPA0, none; RPA1, 1 or 2 times per week; and RPA2, 3 or more times per week.

**Main Outcome Measures:** Glycosylated hemoglobin A<sub>1c</sub> level, body mass index (calculated as weight in

kilograms divided by the square of height in meters) z score, and frequency of severe hypoglycemia.

**Results:** Glycosylated hemoglobin A<sub>1c</sub> level was higher in the groups with less frequent RPA (8.4% in group RPA0 vs 8.1% in group RPA2;  $P < .001$ ). This effect was found in both sexes and in all age groups ( $P < .001$ ). In female patients but not in male patients, the body mass index z score decreased from 0.60 in group RPA0 to 0.51 in group RPA2 ( $P < .001$ ). Multiple regression analysis revealed that RPA was one of the most important factors influencing the glycosylated hemoglobin level. No association was noted between frequency of RPA and frequency of severe hypoglycemia or hypoglycemia with loss of consciousness or seizure.

**Conclusions:** In pediatric patients with type 1 diabetes mellitus, frequency of RPA is a major factor influencing the control of glycemia without increasing the risk for severe hypoglycemia. Regular physical activity should be recommended in pediatric patients with type 1 diabetes mellitus.

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**Group Information:** For a current listing of the members of the DPV Science Initiative see <http://dpv.mathematik.uni-ulm.de>.

**P**HYSICAL ACTIVITY IS KNOWN to acutely reduce the blood glucose level and to increase insulin sensitivity in human beings with<sup>1-3</sup> and without<sup>4,5</sup> diabetes mellitus (DM). Furthermore, exercise increases insulin-stimulated glucose uptake in muscle, and this effect is higher in trained muscle than in untrained muscle.<sup>6,7</sup> It has been shown that exercise reduces the counterregulatory responses of epinephrine and the muscle sympathetic nerve activity during hypoglycemia the day after exercise.<sup>8,9</sup> Fewer hypoglycemic symptoms have been reported in groups that exercise compared with control groups.<sup>8</sup>

As a consequence, exercise might be a risk factor for hypoglycemia or severe hypoglycemia in patients with type 1 diabetes mellitus (T1DM) and, thus, endanger the patient. Regular physical activity (RPA)

can improve the lipoprotein profile, lower blood pressure, and improve cardiovascular fitness and quality of life in patients with T1DM.<sup>1,10</sup> The effect of physical activity training on the control of glycemia remains controversial, as some studies<sup>1,10</sup> have shown, and some studies<sup>2,11-14</sup> have failed to show, an independent effect of physical activity training on the control of glycemia as measured by the glycosylated hemoglobin (HbA<sub>1c</sub>) level in patients with T1DM. The present study evaluates the influence of RPA on the frequency of severe hypoglycemia and on metabolic control (HbA<sub>1c</sub> level) in a large cohort of 18 392 pediatric patients in a multicenter survey in Germany and Austria.

## METHODS

Data were provided by the Pediatric Quality Initiative<sup>15</sup> and included anonymized longitudi-

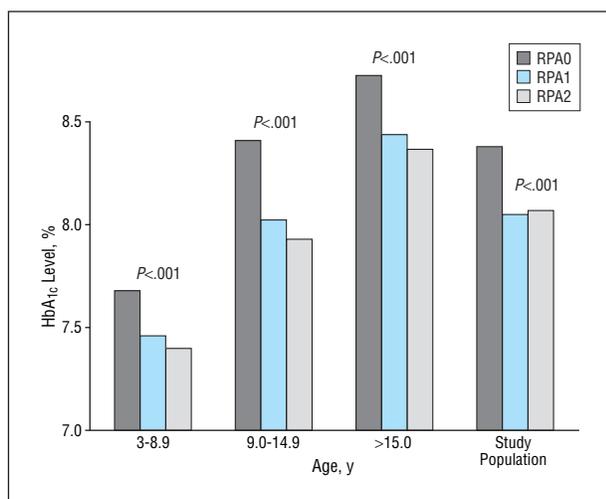
**Table 1. Characteristics of Study Population Stratified by Frequency of Regular Physical Activity\***

Variable	Age, y	T1DM Duration, y	HbA <sub>1c</sub> , %	Insulin Dosage, IU/kg per d	BMI z Score	Per 100 Patient-Years	
						Severe Hypoglycemia	Hypoglycemia With Loss of Consciousness
RPA0	12.9	4.8 ± 3.9	8.4 ± 1.9	0.85 ± 0.3	0.48 ± 0.9	23.5 ± 14.3	4.7 ± 31.9
RPA1	12.7	4.8 ± 3.8	8.0 ± 1.6	0.84 ± 0.3	0.44 ± 0.9	21.8 ± 8.2	5.1 ± 30.8
RPA2	14.0	5.2 ± 3.8	8.1 ± 1.6	0.84 ± 0.3	0.44 ± 0.8	23.6 ± 8.0	5.1 ± 28.3
P value†	<.001	<.001	<.001	<.005	<.05	<.01	.70

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HbA<sub>1c</sub>, glycosylated hemoglobin A<sub>1c</sub>; NS, not significant; RPA, frequency of regular physical activity per week; RPA0, none (n = 8589); RPA1, 1 or 2 times per week (n = 7056); RPA2, 3 or more times per week (n = 3498); T1DM, type 1 diabetes mellitus.

\*Data are given as mean ± SD.

†Statistical comparison by Kruskal-Wallis test followed by Bonferroni correction.



**Figure 1.** Glycosylated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level in age groups stratified by frequency of regular physical activity (RPA) per week. RPA0 indicates none; RPA1, 1 or 2 times per week; and RPA2, 3 or more times per week.

nal data for 19 143 patients aged 3 to 20 years (mean age, 12.8 years; 9140 female patients) with T1DM from 179 centers in Germany and Austria. Data are generated locally in an ongoing process by the participating centers using Diabetessoftware zur Prospektiven Verlaufsdokumentation (DPV) software (Diabetes Software for Prospective Documentation)<sup>16</sup> and transmitted in an anonymized form to the Pediatric Quality Initiative for central analysis. Twice a year the plausibility of these data is reviewed and inconsistent data are reconfirmed with the centers.

At every visit to the diabetologist, the DPV software requires information about the frequency of the patient's RPA. The patient or the parents of young children are asked about the patient's RPA and its frequency. Regular physical activity is defined as physical activity performed regularly at least once a week for at least 30 minutes. School sports are excluded. We included only patients for whom information on the frequency of RPA was available continuously for at least 1 year and evaluated the most recent year of complete documentation for each patient. Data obtained between January 1997 and December 2004 were included in this cross-sectional study. The study protocol was approved by the local human subjects committee of the University of Ulm, Ulm, Germany, and the study was carried out in accord with the Declaration of Helsinki.

Patients were grouped by the frequency of RPA per week as follows: RPA0, none (n=8589), RPA1, 1 or 2 times per week (n=7056), and RPA2, 3 or more times per week (n=3498). We divided the

total analyzed population into the following 3 age groups: 3 to 8.9 years (n=3530), 9 to 14.9 years (n=8458), and 15 years or older (n=7155). We excluded children younger than 3 years from the study because the extensive physical activity in this age group is performed spontaneously and cannot be defined as regular.

For the occurrence of hypoglycemic episodes, we differentiated between severe hypoglycemia requiring help from another person and hypoglycemia with occurrence of seizure or loss of consciousness. For purposes of comparison, body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) was expressed as BMI z score<sup>17</sup> and HbA<sub>1c</sub> values were transformed to Diabetes Control and Complications Trial normal values<sup>18</sup> using the LMS transformation of Cole.<sup>19</sup>

## STATISTICAL ANALYSES

The incidence of severe hypoglycemia or hypoglycemia with seizure or loss of consciousness is expressed as frequency per hundred patient-years. Data about insulin dosage are given as the mean daily dose per kilogram of body weight.

Data were evaluated statistically using the Kruskal-Wallis test for comparison between groups followed by the Bonferroni step-down correction in cases of multiple comparison, using SAS for Windows software (SAS Institute Inc, Cary, NC). Multiple linear regression analysis was performed to extract possible explanatory variables affecting the frequency of hypoglycemia and the HbA<sub>1c</sub> level. *P* < .05 was considered statistically significant.

## RESULTS

The frequency of RPA ranged from 0 to 9 (mean, 1.3) times per week. The general characteristics of the RPA groups are given in **Table 1**. The mean duration of DM was 4.9 years; the mean HbA<sub>1c</sub> level was 8.2%. In group RPA2, the mean age of patients was higher and the mean duration of DM was longer than in groups RPA0 and RPA1.

### HbA<sub>1c</sub> LEVEL

The HbA<sub>1c</sub> level differed among the RPA groups (*P* < .001) and was lower in the groups with more frequent RPA. This difference was present in all age groups (*P* < .001 in each age group) (**Figure 1**) and in both sexes (*P* < .001 in female and male patients).

A multivariate model with HbA<sub>1c</sub> level as the dependent variable and with age, BMI z score, sex, RPA, insulin dosage, and duration of T1DM as independent variables revealed that RPA was one of the most important

factors influencing the HbA<sub>1c</sub> level. Other factors influencing HbA<sub>1c</sub> level were age, sex, and insulin dosage (**Table 2**). Thus, the HbA<sub>1c</sub> level was lower in patients with more frequent RPA, in male patients, in younger patients, and in patients receiving a higher insulin dosage. Body mass index had no influence on HbA<sub>1c</sub> level. After statistical control of all of these factors, the HbA<sub>1c</sub> level decreased by 30% from RPA0 to RPA1 and by 37% from RPA1 to RPA2.

### BODY MASS INDEX

In female patients but not in male patients, the BMI z score was lower in the groups with more frequent RPA ( $P < .001$ ) (**Figure 2**). The main difference in BMI z score in female patients was found between the RPA0 group (0.60) and the RPA1 group (0.50). In the RPA2 group, the mean BMI z score (0.51) was not lower than in the RPA1 group.

### INSULIN DOSAGE

In male patients but not in female patients, the insulin dosage differed among the RPA groups ( $P < .01$ ). Insulin dosage was higher in the groups with less frequent RPA. For male patients, the mean daily insulin dosage in the RPA0 group was 0.02 IU/kg higher than in the RPA1 group and was 0.02 IU/kg higher in the RPA1 group than in the RPA2 group. Analysis of the different age groups confirmed this effect in patients aged 9 to 15 years ( $P < .001$ ) or 14.9 years or older ( $P < .001$ ) but not in patients aged 3 to 8.9 years, the youngest age group.

### HYPOGLYCEMIA

The mean frequency of severe hypoglycemia was 22.9 per hundred patient-years in the analyzed population, and the mean frequency of hypoglycemia with occurrence of seizure or loss of consciousness was 4.9 per hundred patient-years. Multiple regression analysis (Poisson distribution) with frequency of severe hypoglycemia as the dependent factor and RPA, age, sex, BMI z score, HbA<sub>1c</sub> level, mean insulin dosage, and T1DM duration as independent factors revealed no influence of any of these factors on severe hypoglycemia. The same results were found for the frequency of hypoglycemia with occurrence of seizure or loss of consciousness. Thus, the frequency of RPA had no significant influence on the frequency of severe hypoglycemia or hypoglycemia with occurrence of seizure or loss of consciousness.

### COMMENT

This study evaluated the influence of the frequency of RPA on metabolic control (HbA<sub>1c</sub> level), frequency of severe hypoglycemia, insulin dosage, and BMI in a large cohort of 19 143 patients with T1DM.

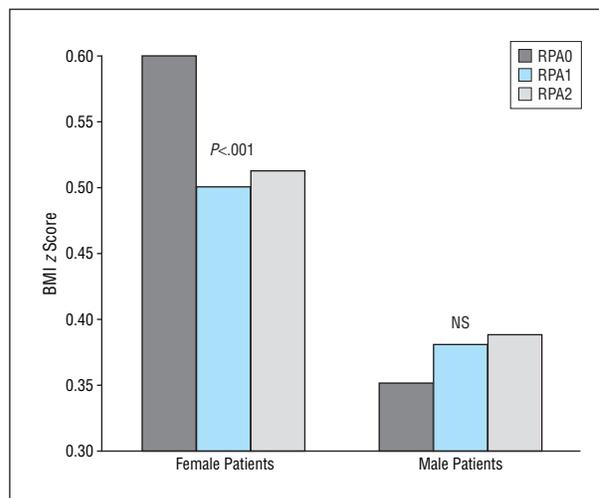
### HbA<sub>1c</sub> LEVEL

Our results show that the frequency of RPA is one of the most important factors influencing the HbA<sub>1c</sub> level. The

**Table 2. Results of Multiple Regression Analysis With Glycosylated Hemoglobin Level as the Dependent Variable**

Variable	Regression Coefficient $\beta$	95% CI for exp( $\beta$ )	P Value
RPA	-0.302	-0.434 to -0.247	<.001
Age, y	0.074	0.067 to 0.081	<.001
Sex	-0.097	-0.145 to -0.049	<.001
Insulin dosage	0.990	0.904 to 1.077	.001

Abbreviations: CI, confidence interval; RPA, frequency of regular physical activity per week.



**Figure 2.** Body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) z score in female and male patients stratified by frequency of regular physical activity (RPA) per week. NS indicates not significant; RPA0, none; RPA1, 1 or 2 times per week, and RPA2, 3 or more times per week.

HbA<sub>1c</sub> level was lower in the groups with greater RPA frequency. This effect was found in both sexes and in all age groups. Previous publications revealed controversial results; some studies<sup>1,10,20,21</sup> have shown an independent effect of physical activity training on the control of glycemia as measured by the HbA<sub>1c</sub> level in patients with T1DM, whereas other studies<sup>2,11-14,22,23</sup> have failed to show this effect. Most of the previous studies were designed as intervention studies and assessed the effect of an exercise program on HbA<sub>1c</sub> level during a defined period. The controversial results might be because of the different methodological approaches or because of few patients.<sup>1,2,10,13,20-23</sup> The FinnDiane Study<sup>24</sup> included a larger cohort of patients with T1DM (1030 adults) and assessed leisure time physical activity during 12 months. A lower HbA<sub>1c</sub> level was found in physically more active women but not in men. In another study,<sup>14</sup> 142 children and adolescents with T1DM were interviewed about their physical activity using a structured questionnaire. Performing intensive sports activity or taking part in competitive sports was not associated with better or worse metabolic control. Our study includes a large cohort of patients. However, the definition of the physical activity used in our study is based on the DPV questionnaire. This definition is not specific because it includes the patient's self-reported frequency of physical activity but does

not consider the individual kind or intensity of the activity. This might limit our results and affect the strength of the association of the analyzed parameters.

### BODY MASS INDEX

Our study revealed a positive effect of RPA on BMI in female patients but not in male patients. This is important because, during puberty, adolescents with T1DM tend to become overweight<sup>25</sup> and girls with T1DM have a higher risk for gaining weight than are boys with T1DM.<sup>26</sup> Our data suggest that for weight normalization, girls benefit from RPA more than boys do. This might be caused by a greater lipolytic response to exercise in female patients compared with male patients.<sup>27</sup> However, we are not absolutely certain about which is the cause and which is the effect. Physical activity might keep the BMI low, but it might also be that girls with low BMI perform more physical activity. However, a reduction in weight due to exercise has been shown in a previous intervention study: Lehmann et al<sup>1</sup> found a decrease in BMI, waist-hip ratio, and body fat after a 3-month program of RPA in patients with T1DM. There is one more important detail in our results: in female patients, the BMI z score in the group exercising more than 3 times per week was not lower than in the group exercising once or twice a week. The main difference in BMI z score in female patients was found between those performing no RPA and those performing RPA once or twice weekly. Thus, it seems that for weight, the regularity of physical activity has a greater effect than does frequency. In male patients, however, we found a slight (not significant) weight gain in the group with more frequent RPA. We suggest that this higher BMI is not due to greater body fat mass but to greater muscle mass.

### INSULIN DOSAGE

An effect of exercise on insulin dosage has been shown.<sup>14,28</sup> Our data confirm that RPA is associated with a lower insulin dosage as a long-term effect. However, we found this effect only in male patients and only in those 9 years and older. The FinnDiane Study<sup>24</sup> found the same sex difference and revealed an association between greater physical activity and lower use of exogenous insulin in men but not in women. The authors speculated that men tend to reduce their insulin dosage to prevent exercise-induced hypoglycemia more than women do. We believe this issue should be followed up in further studies.

In our study, in the younger age group (<9 years), we found no difference in insulin dosage among the RPA groups. One reason might be that in this age group a higher proportion of patients still are in remission and, therefore, factors other than physical activity exert a major influence on insulin dosage.

### HYPOGLYCEMIA

Better control of glycemia (lower HbA<sub>1c</sub> level) is related to more frequent mild and severe hypoglycemia.<sup>29,30</sup> Thus, one might argue that RPA, by lowering the HbA<sub>1c</sub> level, indirectly bears the risk for a higher incidence of hypo-

glycemia in patients with T1DM. We analyzed the influence of RPA on the occurrence of severe hypoglycemia and of hypoglycemia with loss of consciousness or seizure. Mild hypoglycemia was not assessed in our study. Our data show that the frequency of RPA does not constitute an independent risk factor for severe hypoglycemia or hypoglycemia with loss of consciousness. One reason might be that RPA enables the patient to implement management strategies to prevent exercise-induced hypoglycemia. It has been shown that the intrasubject blood glucose response to moderate exercise is reliable and repeatable when preexisting meal, exercise, and insulin regimens are kept constant.<sup>31</sup> Thus, the well-educated patient with T1DM is able to learn about his or her individual glucose response to RPA and can establish an individual strategy (ie, intake of carbohydrates or reduction of insulin dosage before exercise) to prevent exercise-induced hypoglycemia.

Our results are influenced by the educational status of the analyzed patients concerning glucose management before exercise. However, preventing exercise-induced hypoglycemia is only possible in cases of planned exercise by a reasonable patient. This is not the case in very young children, who exert physical activity spontaneously and often unexpectedly by the parents. These children were not the subject of our study and might be at higher risk for hypoglycemia due to physical activity.

### CONCLUSIONS

Regular physical activity should be recommended in patients with T1DM. Regular physical activity results in better control of glycemia, including a lower HbA<sub>1c</sub> level and, in female patients, lower BMI. The risk for severe hypoglycemia or hypoglycemia with loss of consciousness or seizure is not elevated in pediatric patients with a high frequency of RPA.

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