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Abstract:	This study aimed to investigate the association of the anthropometric, clinical variables and maximal oxygen uptake with diabetes-specific health-related quality of life (HRQoL) in youths with type 1 diabetes; and to find the predictors of HRQoL and blood glucose control. A total of 239 youths with diabetes (124 boys and 115 girls) were recruited from diabetes summer camps. HRQoL assessment was carried out with PedsQL 3.0 Diabetes Module; VO2max was evaluated by conducting the 20-m shuttle run test. Higher VO2max and the insulin pump therapy were significant predictors of the HRQoL in the multiple regression analysis; other clinical and anthropometric variables had no effect. The better blood glucose control was explained only by the higher VO2max. The good cardiorespiratory fitness (expressed by VO2max) has clinical and quality of life benefits for paediatric patients with type 1 diabetes.

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ABSTRACT

This study aimed to investigate the association of the anthropometric, clinical variables and maximal oxygen uptake with diabetes-specific health-related quality of life (HRQoL) in youths with type 1 diabetes; and to find the predictors of HRQoL and ~~metabolic~~ blood glucose control. A total of 239 ~~diabetic~~ youths with diabetes (124 boys and 115 girls) were recruited from diabetes summer camps. HRQoL assessment was carried out with PedsQL 3.0 Diabetes Module; VO_{2max} was evaluated by conducting the 20-m shuttle run test. Higher VO_{2max} and the insulin pump therapy were significant predictors of the HRQoL in the multiple regression analysis; other clinical and anthropometric variables had no effect. The better ~~metabolic~~ blood glucose control was explained only by the higher VO_{2max}. The good cardiorespiratory fitness (expressed by VO_{2max}) has clinical and quality of life benefits for paediatric patients with type 1 diabetes.

Keywords: type 1 diabetes mellitus; diabetes-specific health-related quality of life; maximal oxygen uptake; children; adolescents

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune chronic disease that tends to occur in childhood, adolescents or early adulthood, but it may have its clinical onset at any age. It needs life-long diabetes treatment and care to avoid or delay short-term and long-term complications. Children with proper treatment and care can live productive lives, just like their healthy peers. However, diabetes has an impact on many aspects of life. It is important to understand how the disease and the clinical conditions influence on patients' health-related quality of life (HRQoL).

Generic measures evaluate and compare health status in patients with different diseases and provide valuable information for comparing outcomes between sick and healthy populations. Generic questionnaires are not sensitive to detect small but clinically significant changes in HRQoL (Chassany et al., 2002). The diabetes-specific measures are more suitable to assess the physical well-being, the health status of the patients as they are associated with diabetes management, including medical regimen adherence, ~~metabolic~~ blood glucose control, and risk for long-term complications of diabetes (Guttman-Bauman et al., 1998; Cameron et al., 2007). There is little evidence that quality of life measures are routinely used in clinical practice, but for health care

professionals is a key goal in diabetes management to help patients improve their quality of life (Clarke and Eiser, 2004).

The Pediatric Quality of Life Inventory (PedsQL) 3.0 Diabetes Module was developed for measuring diabetes-specific HRQoL for youths with T1DM. This module is a multidimensional instrument that assessed the broad age range of 2-18 years (Varni et al., 2003). While the original validation of the PedsQL Diabetes Module (DM) included only subscale scores, findings of Nansel et al. gave evidence for ~~use~~ using the total score of the module for assessing diabetes-specific HRQoL (Nansel et al., 2008). Generally parents of children with chronic diseases underestimate their children's quality of life (Eiser and Morse, 2001). The paediatric patients aged 5–18 years can reliably and validly self-report their HRQoL when an age-appropriate measurement instrument is utilized (Varni et al., 2007). In our study, we focused on disease-specific child self-report in order to examine the factors that influence the HRQoL in children and adolescents with T1DM.

Cardiorespiratory fitness reflects the functions of the circulatory and respiratory systems providing adequate oxygen supply to the muscles during prolonged exercise. The maximal oxygen uptake (expressed by VO_{2max}) is widely accepted as the single best measure of cardiorespiratory fitness (Hyde and Gengenbach, 2007: 845). VO_{2max} is defined as the highest rate of oxygen delivery and extraction that can be achieved at a maximal level of exertion; and it is measured mostly in millilitres of oxygen per

kilogram of bodyweight per minute (ml/kg/min). There is some evidence that cardiorespiratory fitness is reduced in youths with T1DM compared with ~~non-diabetic~~ healthy peers (Huttunen et al., 1984; Maggio et al., 2010; Williams at al., 2011).

This study aimed to evaluate how diabetes-related clinical variables, anthropometric and cardiorespiratory fitness parameters were associated with self-rated diabetes-specific HRQoL of children and adolescents with T1DM. Furthermore, the study aimed to find the predictors of diabetes-specific health-related quality of life and ~~metabolic~~ blood glucose control.

METHOD

Patients

Participants in the age range 8 – 18 were recruited from diabetes-based summer camps. There were patients including 124 boys (aged 13.64 ±2.73) and 115 girls (aged 13.09 ±3.01). The mean diabetes duration was 5.64 ±2.41 years in boys and 6.06 ±2.99 in girls. The mean glycated haemoglobin (HbA_{1c}) was 8.45 ±1.57% in boys and 8.96 ±1.50% in girls. Inclusion criteria were to be diagnosed with type 1 diabetes mellitus at least two years, and aged 8-18. Exclusion criteria were physical problems that made the patient difficult to carry out the shuttle run test (due to musculo-skeletal, cardiac and

respiratory disorders). The camps were supported by foundations so the participation was made possible for everyone regardless of financial background of the families. Table 1 presents the sample characteristics. (Table 1)

Parents and their children were informed about the purpose and methods of the research verbally and in written form. Written consent was obtained from the parents and verbal assent from youths under age 18 before the completion of study measurement.

This research study was approved by the Borsod-Abaúj-Zemplén County Regional Scientific and Research Ethics Committee.

Measurements

Health-related quality of life measurement

The Pediatric Quality of Life 3.0 Diabetes Module (PedsQL™ 3.0 DM) was developed in 2003 by Varni et al. The questionnaire takes 5 to 10 minutes to complete. The twenty-eight-item scale encompasses five subscales: Diabetes symptoms (eleven items), Treatment barriers (four items), Treatment adherence (seven items), Worry (three items), and Communication (three items). The instructions ask how much of a problem each item has been during the past 1 month. A five-point Likert-scale is used (0 = never a problem, 1 = almost never a problem, 2 = sometimes a problem, 3 = often a problem, 4 = almost always a problem). Items are reverse-scored and linearly transformed to a 0-

100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0), so the higher scores indicate better HRQoL. The PedsQL 3.0 DM has been validated for Hungarian usage (Lukács et al., 2012).

Cardiorespiratory fitness

Cardiorespiratory fitness was measured by conducting the widely used 20 m shuttle run test. The participants ran back and forth between 2 lines 20 m apart, while running speed was dictated from CD audio beeps. Initial speed was 8.5 km/h and increased by 0.5 km/h at every minute. The participants were instructed to keep pace with the signal as long as possible. The test has been finished when the runner could not reach the line consecutively twice with the beep or stop voluntarily. The maximal oxygen uptake was predicted from the last stage using Léger's regression equation (Léger et al., 1988). The validity of the 20 m shuttle run test to predict VO_{2max} has been previously established (Léger et al., 1982; Ramsbottom at el., 1988; Liu et al., 1992). If blood glucose measured before the test was out of the target range (5-10 mmol/L), a new appointment was given to perform the test on ~~other day~~ second occasion.

Body mass index and ~~metabolic~~ blood glucose control

Height and weight were measured for calculating body mass index (BMI) (kg/m^2) and BMI z-score (adjusted for child age and sex). Z-score (or standard deviation score) was calculated according to the formula (Xi-Mx)/SD, where Xi is the actual measurement, Mx is the mean value for that age and sex, and SD is the standard deviation corresponding to that age and sex (National Institute of Child Health, 2012). The latest insulin dose and HbA_{1c} values for the ~~metabolic~~ blood glucose control were extracted from medical records of the participants during the study. The HbA_{1c} test is the most accepted measure of glycemic control, and diagnostic test for diabetes (American Diabetes Association, 2003).

Intensive insulin therapy

The results of Diabetes Control and Complication Trial showed the benefits of intensive insulin therapy for achieving tight ~~metabolic~~ blood glucose control and reducing the risk of micro- and macrovascular complications (~~DCCT,~~ Diabetes Control and Complications Trial, 1993). Multiple daily injection (MDI) treatment is the most widely used method of the insulin administration. This ~~regime~~ method involves intermediate or long acting insulin once or twice a day as basal dose and rapid acting insulin at each meal time and patients need to administer at least three or more injections a day. A technological alternative to this method of insulin delivery is the continuous subcutaneous insulin infusion (CSII or insulin pump therapy). The insulin pump is a

programmable medical device that offers the most physiologic way of insulin delivery, and the amount of insulin delivered can be changed by user.

Statistical analyses

Data were analysed using SPSS 19.0 statistical analysis software. Data are presented as mean and ± standard deviation. Effect of indicator variables (gender and method of intensive therapy) on the HRQoL was analyzed with F-test. Correlation between the HRQoL and the different parameters was evaluated with the Pearson's coefficients. Multiple regression analysis with stepwise method was used to explore the effect of age, gender, duration of diabetes, insulin dosage, method of intensive therapy, maximal oxygen uptake, BMI z-score and HbA_{1c} on self-reported diabetes-specific HRQoL.

RESULTS

The gender significantly influenced the HRQoL. The boys had better perception of HRQoL than girls [boys (n=124): 72.76 ±13.04 vs. girls (n=115): 69.03 ±11.18; p=0.019]. The method of intensive insulin therapy also significantly influenced the HRQoL. Patients treated with continuous subcutaneous insulin infusion (CSII or insulin pump therapy) had significantly higher HRQoL score than patients on multiple daily

injections (MDI) (CSII (n=104): 73.12 ±11.66 vs. MDI (n=135): 69.31 ±12.56; p=0.017). We found significant correlation between the diabetes-specific HRQoL and VO_{2max} (r=0.435; p<0.001) and HbA1c (r=-0.185; p=0.004). In the multiple regression analysis, the maximal oxygen uptake (p=0.000) and the method of the intensive insulin therapy (p=0.054) were significant independent predictors of the self-rated diabetes-specific HRQoL. (Table 2) The ~~metabolic~~ blood glucose control, gender, age, insulin dosage, BMI z-score, and the duration of diabetes as independent variables were not significant in the model. When HbA_{1c} was used as dependent variable in the regression analysis, VO_{2max} proved to be the single significant predictor of the ~~metabolic~~ blood glucose control (B=-0.093, SE(B)=0.016, β=-0.353, t=-5.813; p<0.001) explaining 12.5% of the variance. Increase of the VO_{2max} associated with decrease of the haemoglobin A_{1c} in tendency nature. (Figure 1)

DISCUSSION

In this study, we examined the factors that could affect the diabetes-specific HRQoL in children and adolescents. There are several studies in the literature assessing the HRQoL of youths with T1DM, but we found no studies that evaluated parallel the effect of the diabetes-related clinical, anthropometric parameters and the cardiorespiratory fitness on diabetes-specific quality of life in younger ages.

A number of studies suggest that males have better quality of life perception than females not only in chronic diseases (Riedinger et al., 2001; Wijnhoven et al., 2003; Mrus et al., 2005) but in healthy paediatric population as well (Bisegger et al., 2005; Michel et al., 2009). In our patient population, we also observed gender differences in HRQoL without age differences, although this ~~is also used to mention~~ latter often has been shown in other studies. Boys reported better quality of life perception than girls that is congruent with Kalyva et al. and the SEARCH for Diabetes in Youth Study Group's findings (Naughton et al., 2008; Kalyva et al., 2011). The diabetes-specific HRQoL questionnaire is sensitive to the ~~metabolic~~ blood glucose control, but the relationship between these parameters is rather ~~week~~ weak. When we analysed the different parameters in regression model we found that higher maximal oxygen uptake and the continuous subcutaneous insulin infusion had effect on the disease-specific HRQoL. We observed tendency that diabetic youths with impaired cardiorespiratory fitness had even unfavourable disease-specific HRQoL. The CSII therapy also seemed to be determinative factor on the HRQoL of young diabetic patients as was concluded in the SEARCH for Diabetes in Youth Study Group's examination (Naughton et al., 2008). The main task of the diabetes management is to achieve as near normal ~~metabolic~~ blood glucose control as possible. Using HbA_{1c} as dependent variable in the regression model, VO_{2max} was the only predictive parameter for ~~metabolic~~ blood glucose control and the other variables had no effect. These findings highlight the

importance of appropriate cardiorespiratory fitness both in improvement of HRQoL and in the care and treatment of diabetes. Our result of VO_{2max} being the only predictive parameter for HbA1c also suggest the importance of aerobic exercise in achieving and maintaining good glycemic control.

There are a few limitations in this study. The findings of this cross-sectional nonrandomized cohort study design may have been caused by selection bias, although the whole childhood population in the summer camps were invited to take part in the study. Cost effectiveness data to determine superiority of the insulin pump over the MDI and the socioeconomic status of the families were not available. The insulin pump is almost fully supported in paediatric population by the National Health Insurance in Hungary, so the use of an insulin pump device does not depend on the family's financial situation. Our investigated participants represented one ethnicity. These imperfections may limit the generalizability of the findings. The main strength of our study is that we used the same cohort and great sample size to evaluate diabetes-specific quality of life, cardiorespiratory fitness, clinical and anthropometric variables at the same time that is rather unique in the literature.

In conclusion, better diabetes-specific HRQoL is associated with male gender, treatment with insulin pump therapy, favourable ~~metabolic~~ blood glucose control, and better maximal oxygen uptake. Two dominant variables were observed that explained the favourable disease-specific HRQoL, namely the CSII therapy and the better

cardiorespiratory fitness. It is well defined that the major goal of diabetes care is to manage the patients' condition as much as possible with improving their quality of life. Treatment with CSII therapy has some restrictions and not all patients are willing to wear the insulin pump device, but most physical activities are recommended for type 1 diabetics (American Diabetes Association, 2004). Clinicians should encourage their young patients to exercise regularly – especially to do aerobic sport – for its clinical and quality of life benefits.

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Table 1 Characteristics of the study participants with type 1 diabetes mellitus by gender (mean ±SD) (N=239)

	Girls	Boys
sample size	115	124
age (yr)	13.09 ±3.01	13.64 ±2.73
Diabetes duration (yr)	6.06 ±2.99	5.64 ±2.41
HbA_{1c} (%)	8.96 ±1.50	8.45 ±1.57
VO_{2max} (ml/min/kg)	38.34 ±5.13	43.56 ±5.46
CSII : MDI therapy ratio	51 : 64	53 : 71
insulin dose (units/kg/day)	0.92 ±0.18	0.91 ±0.22
BMI z-score	0.39 ±0.82	0.35 ±0.80
PedsQL 3.0 Diabetes Module total score	69.03 ±11.18	72.76 ±13.04

Table 2 Summary of multiple regression analysis for self-rated diabetes-specific HRQoL (N=239)

Variables	B	SE(B)	β	t	p
(Constant)	36.303	5.188		6.997	0.000
VO_{2max} (ml/min/kg)	0.883	0.122	0.424	7.255	0.000
method of intensive insulin therapy CSII=0, MDI=1	-2.798	1.446	-0.113	-1.935	0.054

Note. Criterion variable is PedsQL Diabetes Module, child self-report. N=239; R=0.449, R^2=0.202

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections.

Figure 1 Improvement of ~~metabolic~~ blood glucose control (HbA_{1c}) depending on maximal oxygen uptake (VO_{2max})(N=239)