THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PH.D.)

Physical fitness and health-related quality of life in children and adolescents with type 1 diabetes mellitus

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DECLARATION

I declare that thesis entitled *"Physical Fitness and Health-related Quality of Life in Children and Adolescents with Type 1 Diabetes Mellitus"* is my own work and that all resources used or quoted in it have been indicated properly and acknowledged by means of complete references.

Lukács Andrea

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LIST OF ABBREVIATIONS

ADA	American Diabetes Association
BAH	Bent arm hang
BMI	Body mass index
CSII	Continuous subcutaneous insulin infusion
CSR	Child self-report
DCCT	Diabetes Control and Complications Trial
DKA	Diabetes ketoacidosis
DM	Diabetes Module
ESR	Endurance shuttle run
FLB	Flamingo balance
GCS	Generic Core Scale
HbA_{1c}	Haemoglobin A_{1c}
HGR	Hand grip
HRQoL	Health-related quality of life
ICCs	Intraclass correlations
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
ISPAD	International Society for Pediatric and Adolescent Diabetes
MDI	Multiple daily injections
PAQ-A	Physical Activity Questionnaire for Adolescents
PAQ-C	Physical Activity Questionnaire for Older Children
PA	Physical activity
PLT	Plate tapping
PedsQL	Pediatric Quality of Life Inventory
SAR	Sit and reach
SBJ	Standing broad jump
SD	Standard deviation
SHR	Shuttle run
SUP	Sit-ups
PPR	Parent proxy-report
T1DM	Type 1 Diabetes Mellitus
WHO	World Health Organization
VO_{2max}	Maximal oxygen consumption

1. INTRODUCTION AND LITERATURE REVIEW

1.1. Type 1 diabetes mellitus

1.1.1. Epidemiology and etiology

The rapidly rising incidence of diabetes mellitus of both types in the young population is clear evidence. The childhood type 1 diabetes mellitus (T1DM) in the last century was uncommon and the incidence was relatively low, but from the middle of the last century it increased worldwide affecting both the developed and developing countries. The average annual increase in Europe from 1989 to 2003 was 3.9%, especially rapid increase was observed in children under 5 years. (1, 2). There are huge differences between different countries, between regions and between different ethnic populations. Northern Europe is more affected than the Mediterranean regions in Europe; and the disease is least prevalent in East Asia. (The mean annual incidence rate in China is 0.1 and in Finland 57.6 per 100,000 in 0-14 year age group). T1DM is one of the leading chronic diseases of childhood in the developed countries (3-5). The latest survey about the incidence rate of childhood T1DM in Hungary presents a mean annual increase of 4.4% in the last two decades. The highest rate was observed in the youngest age group (6).

This is an autoimmune disease that tends to occur in childhood, adolescence or early adulthood, but it may have its clinical onset at any age. The symptoms and signs of T1DM characteristically appear abruptly; and immediate proper treatment is necessary for life-saving. Usually it presents with severe symptoms: high blood glucose levels, polyuria, polydipsia, polyphagia and weight loss, in association with glycosuria, ketonemia and ketonuria. The plasma glucose level>11.1 mmol/L diagnoses confirm the disease (7, 8). There is no recovery from the disease and the patient needs life-long exogenous insulin. It is yet unclear why the immune system turns against the pancreas, but susceptibility and environmental factors are assumed, although they are not precisely defined. A number of genes have been identified that are associated with the risk of developing T1DM (9). Some people are more genetically susceptible, but the disease might never develop, while others with low genetic risk may be affected. Eighty-five percent of children diagnosed with T1DM do not have first-degree relative with disease but the twin studies confirm the role of the genetic background. The disease risk is higher among monozygotic twins than in dizygotic ones (10-12). The pancreas β-cell destruction in T1DM usually leads to absolute insulin

deficiency. The rate of the β-cell destruction can be rapid (mainly in infants and children) and can be slow (mainly in adults). Besides of the immune mediated form of diabetes (Type 1A) there is a rare variant of the disease (5%), the idiopathic diabetes (Type 1B). There is no evidence of autoimmunity in these cases, but the clinical characteristics are similar to Type 1A; and the management is rather problematic (13).

1.1.2. Diabetes complications

The proper diabetes treatment and care is vital to avoid or delay the short-term and long-term complications from the very beginning. The diabetes complications are all related to blood glucose control (14). Short-term complications are hypoglycemia, hyperglycemia and diabetes ketoacidosis (DKA) (acidic by-product of the breakdown of fat molecules) (15). Ketoacidosis is much less common than hypoglycemia but it is a prominent cause of morbidity and mortality in diabetes (16). Hypoglycemic and hyperglycemic episodes accompany the diabetic children's life (17). Diabetic children and adolescents and their parents worry more about hypoglycemic than hyperglycemic episodes, although the hyperglycemia is associated with increased morbidity and mortality (18, 19). Symptoms of hyperglycemia include polydipsia, polyuria, weight loss, sometimes with blurred vision and polyphagia (13). Hyperglycemia left untreated can cause diabetic ketoacidosis or diabetic coma (16). This is life-threatening and needs immediate treatment. Symptoms include abdominal pain, nausea and/or vomiting, acetone breath, heavy or Kussmaul breathing and mental status changes (16). Symptoms of short or mild hypoglycemia are trembling, cold sweatiness, palpitation, anxiety, hunger, irritability; while prolonged or serious it can cause erratic behaviour, confusion, headache and nightmares (15). Especially severe cases may lead to irreversible brain damage, seizures, comas and death (20). Young patients should be educated to recognize the hypoglycemic symptoms in order to intervene before the condition becomes serious (15). The long-term complications of the disease include peripheral neuropathy (with risk of foot ulcers), nephropathy (that may lead to end-stage renal failure), and retinopathy (potential loss of vision) (20). The autonomic neuropathy can cause sexual dysfunction, cardiovascular problems, Charchot's joints, gastrointestinal and genitourinary symptoms in later age (21). Patients with diabetes are at high risk of developing atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are also potential problem in patients with diabetes (13).

1.1.3. Glycated haemoglobin (HbA_{1c})

The haemoglobin A_{1c} test is the most accepted measure of glycemic control, and diagnostic test for diabetes (22). It refers to non-enzymatic reaction between glucose and haemoglobin, which identifies average plasma glucose concentration in the blood over an 8-12 week period. Glucose binds non-enzymatically to the N-terminal valin residue of the β-chin of heamoglobin A in red blood cells. After spontaneous chemical modification irreversible product HbA_{1c} is formed. The higher the glucose levels over the previous 2-3 months, the higher the HbA_{1c} levels. The test is used as the gold standard for long-term follow-up of glycemic control, although it is only one of several available measurements (23). The Diabetes Control and Complications Trial (DCCT) in type 1 diabetes demonstrated that increasing level of HbA_{1c} is associated with greater risk of microvascular and macrovascular complications (24). General targets for HbA_{1c} of 6.5 – 7.5 % are recommended for patients. Usually it is measured every 3-6 months, according to the status and age of the patients (24-26). The HbA_{1c} is used in the clinical practice from the 1980s (27), and its potential utility in diabetes care is first mentioned in the 1985 WHO report (28). According to the International Expert Committee Report (2009) the HbA_{1c} test is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications (29, 30). The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) developed a new reference measurement system. The recommended new values will be presented only in mmol/mol instead of percentage. Converting equation is: HbA_{1c} mmol/mol = (HbA_{1c} % - 2.15)*10.929 (rounded to integers). The average plasma glucose level can be calculated from the HbA_{1c} % with the formula: (HbA_{1c} % * 35.6) – 77.3. According to the international nomination, the new unit will be used from 1 April of 2013 in Hungary, till then both forms, the IFCC reference and the DCCT units in percentage, will be reported (31).

Table 1 HbA_{1c} expressed in mmol/mol and in percentage, and average plasma blood glucose in mmol/L and mg/dl

HbA_{1c} (%)	13	12	11	10	9	8	7	6	5
HbA_{1c} (mmol/mol)	119	108	97	86	75	64	53	42	31
average plasma blood glucose (mmol/L)	21.4	19.5	17.5	15.5	13.5	11.6	9.6	7.6	5.6
average plasma blood glucose (mg/dl)	386	350	314	279	243	207	172	136	101

HbA_{1c} is used both as an index of mean glycemia and as a measure of risk for development of complications (32). Throughout our survey we used HbA_{1c} in percentage format.

1.1.4. Diabetes management

Immediately after the diagnosis of the disease, the child must be under continuous treatment, care and education by a multidisciplinary team involving ideally pediatric endocrinologist, healthcare experts, (diabetes educator, mental health professional), dietitians, integrated with family members, teachers and the patient. Since there is no cure or prevention for T1DM, life-long insulin replacement and monitoring of blood glucose levels are required (8). So patients will need treatment for the rest of their life. But with proper care and diabetes management, diabetic youths can live productive lives, just like their healthy peers (33). The children's positive attitude towards life can help to maintain the good metabolic control which contributes to the prevention of long-term complications, such as retinopathy, nephropathy and neuropathy (34). Successful diabetes management involves individualized insulin therapy, adjusted diet and regular exercise (8). In order to find the most appropriate insulin therapy for a patient, continuous monitoring of blood glucose levels is required. The frequency of blood glucose monitoring is correlated with improved HbA_{1c} levels (35). The ADA recommendation for children with T1DM is four to six tests per day (36).

The insulin can be delivered by syringe, pen or pump. Insulin requirements are usually based on age, weight and even on pubertal status (8). Nowadays, multiple daily injection (MDI) treatment is the most widely used method of the insulin administration (37). This regime 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. However, in younger children or within the remission phase, conventional therapy with premix insulin is also effective. A technological alternative to this method of insulin delivery is the continuous subcutaneous insulin infusion (CSII or insulin pump therapy). The insulin pump therapy can be used even in a very young age-group (38, 39).

The diabetes management depends on the proper collaboration between the physician and patient and parents who are involved in the child's management. The goal is the gradual transition toward the child's independence in management, although the parents' supervision remains important. Learning self-management requires ongoing education with sensitivity to the child's age and developmental stage (40, 41). Heller S. R. concluded that patients need the necessary knowledge and skills in order to manage their condition effectively. "The principles

of self-management include: 1. Understanding the effect of food, particularly carbohydrate on blood glucose. 2. Learning to calculate and match the right amount of insulin both to cover the effect of eating and to replace basal insulin secretion. 3. Recognising and self-treating hypoglycemia. 4. Adjusting both insulin and food in other situations (e.g. exercise, sick day rules)" This enables the patients even the children to maintain better metabolic control and quality of life (42).

Nutritional therapy is part of the diabetes care and education. For his reason it is recommended to have an educated dietitian as a team member who provides personalized nutrition care for diabetic patient. Planning the meal is the most challenging aspects of diabetes management: balance insulin and food while keeping the blood glucose level within a normal range. For children it is essential to ensure proper nutrition for growth and energy. The young patients also have to acquire how to measure portion size, calculate carbohydrates, protein and fat according to their daily activity. The ADA and the ISPAD have recommendations for the medical nutrition therapy (43, 44).

Integrated part of the diabetes management should be the regular exercise, with physically active lifestyle. Physiological, social and emotional benefits of regular exercise are well documented mostly in healthy population, but they are also prevalent for patients with T1DM (45). It helps to improve overall health and fitness; and reduces risk factors for vascular complications. Physically active diabetic youths have reduced blood glucose level and increased insulin sensitivity, primarily in the skeletal muscles, which leads to a reduced need for insulin (46, 47). According to the ADA statement, all levels of physical exercise can be performed by diabetic youths from leisure activities to competitive professional performance who do not have long-term complications and are in good blood glucose control (48). There are many sportsmen with T1DM in elite sport including the multiple Olympic swimming champion, Gary Hall Jr., Shannon Standridge M.D, competitor in triathlon, the Swedish soccer player Per Zetterberg or the ironman David Weingard. The diabetes management does not intend to educate competitive athletes, but the disease is not necessarily an obstacle to achieve considerable success in sports. There are several guidelines to discuss safe sport participation in children and adolescents with T1DM (47-53).

Diabetic patients should be aware that exercise interferes with the glucose homeostasis, although there are individual differences in blood glucose response due to type, duration and intensity of the exercise, the pre-exercise level of counterregulatory hormones, and blood glucose concentrations (54, 55). Anaerobic exercise which lasts 1-2 minutes such as sprinting,

power sport and strength training can increase the blood glucose level. The aerobic exercise (running, cycling, swimming, rowing) may cause decrease in blood glucose level during the activity and post-activity (49). During the exercise both types of energy utilizations exist markedly depending on the intensity of exercise, but the activity is classified typically based on the predominantly used system. Aerobic exercise is used for training the cardiorespiratory system, while anaerobic is used for resistance training (52, 56). Exercise functions like insulin, so the balance between the insulin therapy and diet could be facilitated if the daily schedule for exercise and the exercise parameters are consistent, although this goal is difficult to obtain (57). Patients differ in tolerance to exercise and insulin requirements and it is impossible to give precise guidelines suitable for everyone with T1DM, but there are some points that should be taken into consideration. Patients need to monitor the blood glucose level before, during and after the exercise and evaluate their response to the physical exercise. Patients who can monitor themselves intensively around periods of activity can learn how to keep glucose levels in an acceptable range. If the blood glucose readings are < 5 mmol/L and not rising, the exercise-induced hypoglycemia is substantial. If fasting blood glucose is ≥ 14.0 mmol/L and ketone bodies are present or ≥ 15.0 mmol/L without ketone bodies, exercise is not recommended until satisfactory glycemic control has been restored (56, 58). Participation in sporting activity is safe for diabetic youths, although use of caution is advised and insulin-diet-exercise adjustment must be personalized and discussed with the child's endocrinologist (8).

1.2. Motor performances and cardiorespiratory fitness

Motor performance refers to the ability of the person to perform successfully sport-related movements. The primary physical characteristics measured by some of the physical fitness tests include balance, coordination, agility, speed, power and reaction time (59). Physical fitness refers to the capacity of the person to function effectively in physical work, training, and other activities without causing fatigue. The components of physical fitness are: body composition, flexibility, muscular strength and endurance, and cardiorespiratory fitness (aerobic fitness or aerobic endurance). Maintaining good physical fitness requires regular training, healthy nutrition and sufficient rest. Cardiorespiratory fitness is the most important component for health promotion. It 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 (60). VO_{2max} is defined as the highest rate of oxygen delivery and extraction that can be achieved at a maximal level of exercise; and it is measured in ml/kg/min (61, 61). Measuring VO_{2max} accurately requires laboratory circumstances under strict protocol of Bruce treadmill, bicycle ergometers or other exercise equipment that makes it difficult to assess large population (62). There are indirect tests used to estimate VO_{2max} such as 12-minute Cooper test, Balke 15-minute run, Six-minute walk test, 20-meter shuttle run test (63).

Exercise has been defined as any form of body movement that results in an increase in metabolic demand with the intention of developing one or more components of physical fitness. It is generally planned, structured and systematic (64). Physical activity is a broader term; it encompasses bodily movement produced by skeletal muscles which requires energy consumption. Physical activity can range from sports to any other lifestyle activities. There is evidence that behavioural patterns of physical activity in childhood are maintained throughout adulthood (65, 66). The relationship between physical activity and physical fitness in children is week to moderate. Stronger relationship can be found between vigorous physical activity (>6 MET) and physical fitness (67-71).

When physical fitness is tested, most body functions (skeletomuscular, cardiorespiratory, hematocirculatory, psychoneurological and endocrine-metabolic) are involved in the performance; and functional status of these systems is actually being checked. This is the reason that physical fitness is considered to be an important health marker, as well as a predictor of morbidity and mortality (72).

1.2.1. Physical activity and fitness of children and adolescents with type 1 diabetes mellitus

Despite of the importance of physical activity and fitness in youths with (and without) diabetes, very limited related data are available regarding children and adolescents with T1DM, and they are often conflicting and use small sample sizes. Valerio G. found diabetic children and adolescents less physically active than non-diabetic peers (73), while Massin experienced the opposite (74). Bernardini A. L. reported that 60% of children and teenagers were engaged in 1 hour physical activity daily that was sufficient to adhere to the physical activity prescribed by the health care professionals (75). Edmunds S. was dissatisfied with the result that 60% of boys and 23.5% of girls achieved the recommended 1 hour per day of moderate-to-vigorous physical activity (76). Särnblad S. in his small study found that adolescent girls approached the recommended level of 60 minutes of at least moderate

physical activity per day and although there was a tendency, but no significant difference between the diabetic and the control subjects in physical activity (77). Schweiger B. concluded that only 5% of the diabetic adolescent girl participants met the international recommendation of 60 minutes of moderate-to-vigorous activity per day (78). The discrepancy among the studies causes uncertainty in the diabetic youth adherence to the physical activity.

The effect of the physical activity on the glycated haemoglobin levels is also controversial in youths with T1DM. Some studies found improvement in HbA_{1c} with increased physical activity (73, 74, 78, 79), whereas others are failed to show this effect (76, 77, 80-83).

In a study from Finland, physical work capacity as measure of physical fitness was evaluated in children and adolescents with T1DM. Impaired work capacity was found in boys compared with non-diabetic boys, while no difference was observed between diabetic girls and control girls. Physical fitness inversely related to the metabolic control in diabetic boys, but not in girls (84). Lower cardiorespiratory fitness in conjunction with female gender was found in a cross-sectional study in different groups of children with chronic diseases, including T1DM (85). A small study from Poland investigating physical fitness by motor performance tests suggested that teenagers with T1DM have poorer results than the healthy local population (86). Another Australian study investigated cardiorespiratory fitness in children with T1DM and observed reduced levels in association with female sex (87). It has also been suggested that lower level of cardiorespiratory fitness in patients could be due to either lower physical activity level (85, 87), or pathophysiological changes resulting from diabetes, e.g. poor metabolic control (84, 87, 88). However, these studies used tests assessing cardiorespiratory function (84, 85, 87, 88) or motor performances (86) separately and no studies assessed these functions parallel.

1.3. Health-related quality of life

There is no definite consensus on the definition of health-related quality of life (HRQoL). All terms to be used are from the definition of health given by the WHO: “Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity” (89). Nevertheless, HRQoL refers to the physical and psychosocial functioning of the person and it is main concern of health care professionals. The perceived self-assessed health status is considered to be a predictor of mortality and morbidity (90, 91). The ultimate goal of health care is to maintain or improve the quality of life of patients. The treatment

effectiveness in chronic conditions is increasingly acknowledged by clinicians and pharmaceutical firms as a criterion for licensing new medications (92, 93).

HRQoL assessments help determine the burden of disease and provide valuable information regarding the risk factors and show the effectiveness of treatment. This is especially relevant for the management of patients with chronic diseases, where treatment is complicated and requires expensive interventions, continuous support of self-management, and monitoring of health outcomes (94). There are several considerations when determining which questionnaire to use. These include whether to use generic or disease-specific questionnaires, patient or parents' report versions. Generic questionnaires may encompass more common domains and allow comparisons to normative populations or to populations with different diseases, but they may not be sensitive disease-specific problems. Disease-specific questionnaire are more sensitive to symptoms experienced by patients, to the implications of different treatments, but they make impossible to compare groups with different diseases or healthy populations (92, 95). Jacobson A.M. compared a generic and a diabetes-specific measurement and found that generic questionnaire is less sensitive to lifestyle issues, but the two measurements can complete each other (96). Children versus parents' perspectives may produce different result in assessing HRQoL outcomes. WHO recommends using mostly child self-report in order to obtain the children's own perspectives (97). In large population survey children from age five could reliably and validly rate their HRQoL (98). There are some cases (age, developmental problems, illness, cognitive impairment) when children's reports may not be reliable. Eiser C. suggests obtaining information from both parents and children whenever possible (99).

At the beginning of HRQoL research in children, measures for adults had been modified to fit for children, but instruments originally developed for adults are not applicable to assess children's HRQoL (100, 101). The other problem, that most HRQoL instruments have been developed in the last decades and mostly in English-speaking countries. Developing a new instrument is time and money-consuming; therefore it is preferable to use a previously validated instrument (102). However an instrument must be culturally adapted in the country where it is intended to be used. It requires linguistic validation and evaluation of psychometric properties in the population concerned (103).

1.3.1. Health-related quality of life measurements in type 1 diabetes mellitus

Chronic condition like diabetes has an impact on many aspects of life. It is important to understand how the disease and the clinical conditions influence on patients' HRQol. Glycemic control reflects the physiological outcomes of diabetes management, whereas HRQoL represents the psychological perspective of treatment and care. Patients' overall quality of life can influence coping with their disease successfully in the short and over the long term. 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 control, and risk for long-term complications of diabetes (104, 105). 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 (106).

There are many scales and questionnaires available for diabetes adult population such as Diabetes Impact Measurement Scales, Problem Areas in Diabetes Scale, Audit of Diabetes-Dependent Quality of Life, Diabetes Impact Measurement Scales, Diabetes Quality of Life Clinical Trial Questionnaire, Diabetes Quality of Life Measure, Diabetes-Specific Quality-of-Life Scale, Questionnaire on Stress in Patients with Diabetes – Revised, Well-being Enquiry for Diabetics, Studying the Hurdles of Insulin Prescription, Norfolk Quality of Life Questionnaire, Functional Insulin Treatment Satisfaction Questionnaire, Patient Satisfaction with Insulin Therapy Questionnaire, Diabetes Clinic Satisfaction Questionnaire, Hypoglycemia Fear Survey. The Patient-Reported Outcome and Quality of Life Instruments Database provided the following instruments for quality of life assessments of youths: Well-being and Satisfaction of Caregivers of Children with Diabetes Questionnaire (WE-CARE), Impact of Child Illness Scale (ICI), Hypoglycemia Fear Survey (HFS) (in adolescents), Diabetes Self-Management Profile (DSMP), Diabetes Quality of Life Youth Scale (DQOLY), Diabetes Family Behavior Scale (DFBS), Appraisal of Diabetes Scale (ADS) (same as recommended for adults), PedsQL Diabetes Module. From 38 instruments listed in the database 7 were eligible for pediatric population (107). Only the PedsQL Diabetes Module met the criteria of being multidimensional, age-specific, easy-to-complete, and comprise parallel child self-report and parent proxy-report formats.

In the last two decades relatively few quality of life assessments have been conducted in youths with T1DM, mostly using generic questionnaires. It seems that regardless the type of

the questionnaires (generic or disease-specific) females are tending to report impaired HRQoL than males (108-113). Emmanoulididou E. could not find gender difference in Greek diabetic youths' HRQoL (114), and Upton found gender difference evaluating self-report, but not in proxy-report format (115). Amiri P. in Iranian and Chan in Japanese pediatric population found girls reporting higher HRQoL than boys (116, 117). Different results were demonstrated in surveys comparing diabetic youths with non-diabetic peers. Some studies showed similar quality of life or even better than the normative samples (115, 118-121), some of them observed worse quality of life in diabetic youths (108, 109, 122-124). The association of glycemic control with HRQoL is inconsistent across studies. The Hvidøre Study Group presented in its representative study that lower HbA_{1c} levels were associated with better quality of life in adolescents (111). This result was confirmed by other studies including children (105, 119, 122, 123, 125). Emmanoulididou E. and Graue reported no relationship between HRQoL and glycemic control in their studies (114, 126).

It should be noted that poor metabolic control may be associated with lower socioeconomic status and depression both in children and adolescents (127). Hood K. K. found that the depressive symptoms in diabetic children and adolescents is nearly double than in youth in general, and it causes poorer glycemic control (128). Higher mean HbA_{1c} level and hospitalization were associated with depressed mood in Lawrence's study, but the prevalence of depression among diabetic youths was similar to youth without diabetes (129). The psychological care of children and adolescents is important and highly recommended. Based on previous research the ISPAD Consensus Guidelines 2000 stated that "Psychosocial factors are the most important influences affecting the care and management of diabetes" (130). Family conflicts and negative communication regarding the diabetes management also may impact on children's HRQoL (131).

Nowadays the insulin pump therapy became a desirable way of treating patients with diabetes. Insulin pump was developed in the 1970s (132), but it gained popularity among diabetic patients in the 1990s when the DCCT gave evidence the benefits of intensive insulin therapy for achieving tight metabolic control and reducing the risk of micro- and macrovascular complications (133). Insulin pump therapy is a commonly used alternative to multiple daily injections (MDI). The portable insulin pump is a mechanical medical device that offers the most physiologic way of insulin delivery because it simulates the normal pattern of insulin secretion. The insulin pump gives flexibility to the patients in many areas of life (134).

Although the number of patients treated with CSII is growing rapidly, there is an issue about the clear advantages of insulin pump therapy over the MDI (135-138). The strength of evidence of the utilization data in the recent randomized controlled trials and meta-analyses was low or insufficient comparing CSII with MDI for HRQoL, metabolic control, and anthropometric measurement. There have been only a few studies assessing children and adolescents, and all trials suffered from limited sample sizes. Research into the use of CSII in children and adolescents is needed.

2. AIMS OF THE RESEARCH

The general aims of our study were to evaluate physical fitness (both motor performances and cardiorespiratory fitness) and health-related quality of life in children and adolescents with type 1 diabetes mellitus and compare with non-diabetic age-matched control subjects. For obtaining adequate results we carried out the following assessments:

Physical fitness assessments:

1. We measured motor performances and cardiorespiratory fitness using the internationally recommended and widely used across Europe Eurofit fitness test battery.
2. For assessing anthropometric parameters:
    a. skinfold thickness measurements were made at four sites (biceps, triceps, subscapular and suprailiac) and they were summed to evaluate the body fat content
    b. height and weight were measured to evaluate body max index (kg/m^2)
    c. BMI z-scores adjusted to age and gender were computed using the national child health chart
3. We evaluated the physical activity using the Physical Activity Questionnaire for Older Children and Physical Activity Questionnaire for Adolescents. As these instruments were not translated into Hungary we carried out the linguistic validation of the questionnaires.
4. We looked for predictors of metabolic control (expressed by HbA_{1c}).
5. We looked for predictors of cardiorespiratory fitness (expressed by VO_{2max}).

Health-related quality of life assessments:

1. We culturally adapted the Pediatric Quality of Life Inventory 3.0 Diabetes Module designed for children and adolescents:
    a. We carried out the linguistic validation
    b. We evaluated the psychometric properties of the questionnaires (child and parent format) in Hungarian type 1 diabetic population.
        1. feasibility (missing item responses, floor and ceiling effect)
        2. internal consistency reliability (total scale – items and total scale – subscale scores)
        3. reproducibility (test-retest reliability)
        4. convergent validity (concordance between child self-report and parent proxy-report)
        5. discriminant validity (measuring the differences between three groups of participants according to the metabolic control levels)
        6. concurrent validity (intercorrelation between the PedsQL generic score scale and 3.0 diabetes module).
2. We evaluated the total quality of life scores and the subscale sores (diabetes symptoms, treatment barriers, treatment adherence, worry, communication) of diabetes module separately in girls and boys; and we compared the children and parental estimations.
3. We looked for factors affecting the patients' HRQol.
4. We compared HRQoL, metabolic control and cardiorespiratory fitness of diabetic participants treated with continuous subcutaneous insulin infusion to those being on multiple daily injections.
5. We compared the quality of life of diabetic patients with the non-diabetic participants using the PedsQL Generic Core Scale.

6. We looked for predictors of diabetes-specific and generic HRQoL from the clinical, anthropometric and cardiorespiratory fitness variables.

We obtained clinical parameters (HbA_{1c}, insulin dose, onset of diabetes, method of intensive therapy) from medical records of the study participants during the study.

3. MATERIAL AND METHODS

3.1. Subjects

Subjects were recruited in two steps. For the physical fitness assessment 106 type 1 diabetic and 130 non-diabetic children and adolescents were measured. For the validation process of the PedsQL 3.0 Diabetes Module 355 youths with T1DM and 294 control participants were evaluated. In the HRQoL assessments we enlisted 239 diabetic participants from 355 who had diabetes duration at least two years.

3.1.1. Study participants for the physical fitness assessments

One hundred and six diabetic (53 girls and 53 boys) and one hundred and thirty (69 girls and 61 boys) non-diabetic children and adolescents participated in the physical fitness survey. All the participants were between aged 8-18 years. There were no significant age differences between the diabetic and control groups. Table 2 and Table 3 present the data of the subjects by age and gender.

Table 2 Characteristics of female participants for the physical fitness assessments

	Diabetic girls	Control girls	Diabetic girls	Control girls
mean, SD (±)	8-12 y/o	8-12 y/o	13-18 y/o	13-18 y/o
n	27	32	26	37
age (years)	10.60 ±1.53	10.80 ±1.15	15.79 ±1.81	16.01 ±1.84
diabetes duration (years)	4.86 ±2.78	-	5.73 ±2.80	-
HbA_{1c} (%)	8.49 ±1.39	-	8.96 ±1.20	-

Table 3 Characteristics of male participants for the physical fitness assessments

	Diabetic boys	Control boys	Diabetic boys	Control boys
	8-12 y/o	8-12 y/o	13-18 y/o	13-18 y/o
n	25	28	28	33
age (years)	10.53 ±1.50	11.02 ±1.13	15.76 ±1.75	15.41 ±1.71
diabetes duration (years)	3.76 ±2.74	-	6.14 ±4.02	-
HbA_{1c} (%)	8.22 ±1.61	-	8.52 ±1.53	-

Exclusion criteria for diabetic participants were cognitive disabilities or another serious chronic illness impacting the patient's ability to perform the motor tests. Diabetic patients were recruited from the patient population of the Pediatric Diabetes Centre of Borsod-Abaúj-Zemplén County University Hospital providing diabetes care for the Northern-East region of Hungary. The diabetes duration was at least 1 year and the participants had no evidence of diabetes complications by regular assessments for retinopathy (fundal photography), nephropathy (microalbuminuria) and neuropathy (nerve conduction velocity and cardiovascular reflex tests).

3.1.2. Study participants for PedsQL 3.0 Diabetes Module validation process

A total of 355 diabetic children and adolescents (171 girls and 184 boys) and 328 parents took part in this survey. The youths were between 8-18 years old. The participants have had T1DM for more than six months. The mean duration of the diabetes was 5.69 ±3.44 years in girls, and 5.15 ±2.93 years in boys. The mean glycated haemoglobin value was 8.86 ±1.41 % in girls and 8.45 ±1.72 % in boys. The diabetic patients were from diabetes-based summer camps which were supported by foundations; so the participation was made possible for everyone regardless of financial background of the families. Patients completed the questionnaire in the camps, parents were asked to complete the proxy-report at home and send back to the outpatient care or to the University of Miskolc. There were 27 parents whose report did not arrive. They were asked to think about the last month of the school year when

completing the school domain. There were 294 randomly chosen non-diabetic children and adolescents (aged 8-18 years) from primary and secondary schools of different parts of Hungary including 157 girls (13.93 ±2.63 y/o) and 137 boys (13.87 ±2.47 y/o) and their parents (n=294). The age of the patients and the controls did not differ significantly. The control participants and their parents completed the questionnaires in the academic year at school where the children studied.

3.1.3. Study participants for the HRQoL assessments

For HRQoL assessments we picked out participants from diabetes camps who had diabetes duration at least two years. 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 HbA_{1c} was 8.45 ±1.57% in boys and 8.96 ±1.50% in girls. Table 3 and Table 4 present the sample characteristics according to gender and intensive therapy treatment, respectively. There were 15 parents who did not send back the parent proxy-report.

Table 4 Characteristics of study participants with type 1 diabetes mellitus by gender for HRQoL assessments (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
BMI z-score	0.39 ±0.82	0.35 ±0.80
insulin dose (U/kg/day)	0.92 ±0.18	0.91 ±0.22
CSII : MDI therapy ratio	51 : 64	53 : 71

Table 5 Characteristics of study participants with type 1 diabetes mellitus treated with continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) (mean ±SD) (N=239)

	patients treated with CSII therapy	patients treated with MDI therapy
n	104	135
girls : boys ratio	51 : 53	64 : 71
age (yr)	13.29 ±2.85	13.44 ±2.90
diabetes duration (yr)	6.03 ±2.52	5.70 ±2.85
HbA_{1c} (%)	8.63 ±1.49	8.75 ±1.60
BMI z-score	0.38 ±0.84	0.36 ±0.79
insulin dose (U/kg/day)	0.90 ±0.21	0.93 ±0.19

3.1.4. Ethical approval

All parents and their children were informed about the purpose and the method of the research and the voluntary nature of participation in the study verbally and in written form. Written consent was obtained from the parents and assent from the youths before the completion of the study measurement. This research was approved by the Borsod-Abaúj-Zemplén County Regional Scientific and Research Ethics Committee.

3.2 Health-related quality of life measurements

The Pediatric Quality of Life Inventory is a multidimensional HRQoL measurement for healthy and chronically or acute ill youths. It was developed in the United States by James W. Varni (139). The scale is brief and contains developmentally appropriate child self-report (5-18 years) and parent proxy-report (2-18 years) versions. This instrument has been used to describe the quality of life of healthy children and children suffering from various illnesses (diabetes, extreme obesity, cancer, asthma, cerebral palsy, brain tumour, fatigue, end stage renal disease, cardiac problems, rheumatology problems, neuromuscular problems, etc.) The modules are created as a self-administered instrument. It took 5-10 minutes to complete.

3.2.1. PedsQL 4.0 Generic Core Scale

The 23-item GCS encompasses four subscales: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items) and school functioning (5 items). The Scale takes 5-10 minutes to complete and it is comprised of parallel self-report and parent proxy-report format. The participants rate how much of a problem they have had in the previous month on a five-point Likert response scale. (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 scale ranging from 0 to 100 (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Total scores and subscale scores were computed as the sum of the items divided by the number of items answered. The higher score indicate better quality of life. If more than 50% of the items on the scales are missing, the scale score is not computed. This HRQoL measurement can be used in clinical practice, clinical trials and research and school health settings (140).

3.2.2. PedsQL 3.0 Diabetes Module

PedsQL 3.0 DM was developed to measure disease-specific HRQoL for T1D youths in 2003. The original scales were developed through focus groups, cognitive interviews, pretesting and field testing. The multidimensional 28-item DM encompassed 5 subscales including Diabetes symptoms (11 items), Treatment barriers (4 items), Treatment adherence (7 items), Worry (3 items) and Communication (3 items). The scoring method is the same as the GCS (122). Based on research of Nansel we used the total score of the DM for evaluating diabetic patients' global HRQoL, and for comparing them by age and gender (141).

3.2.2.1. Linguistic validation of the PedsQL 3.0 Diabetes Module

For assessing the HRQL of the Hungarian young diabetic population we carried out the linguistic validation. We translated the questionnaire and made sure that both understandable and applicable in Hungary. For evaluating the cultural differences between the original and Hungarian versions of the questionnaires we conducted cognitive interviews both with children and parents.

The linguistic validation of the 3.0 DM was carried out according to the linguistic validation guidelines of PedsQL and in close ongoing collaboration with the Mapi Research Institute's translation team (142, 143). The linguistic validation process consisted of 3 phases: forward translation, backward translation and patient testing.

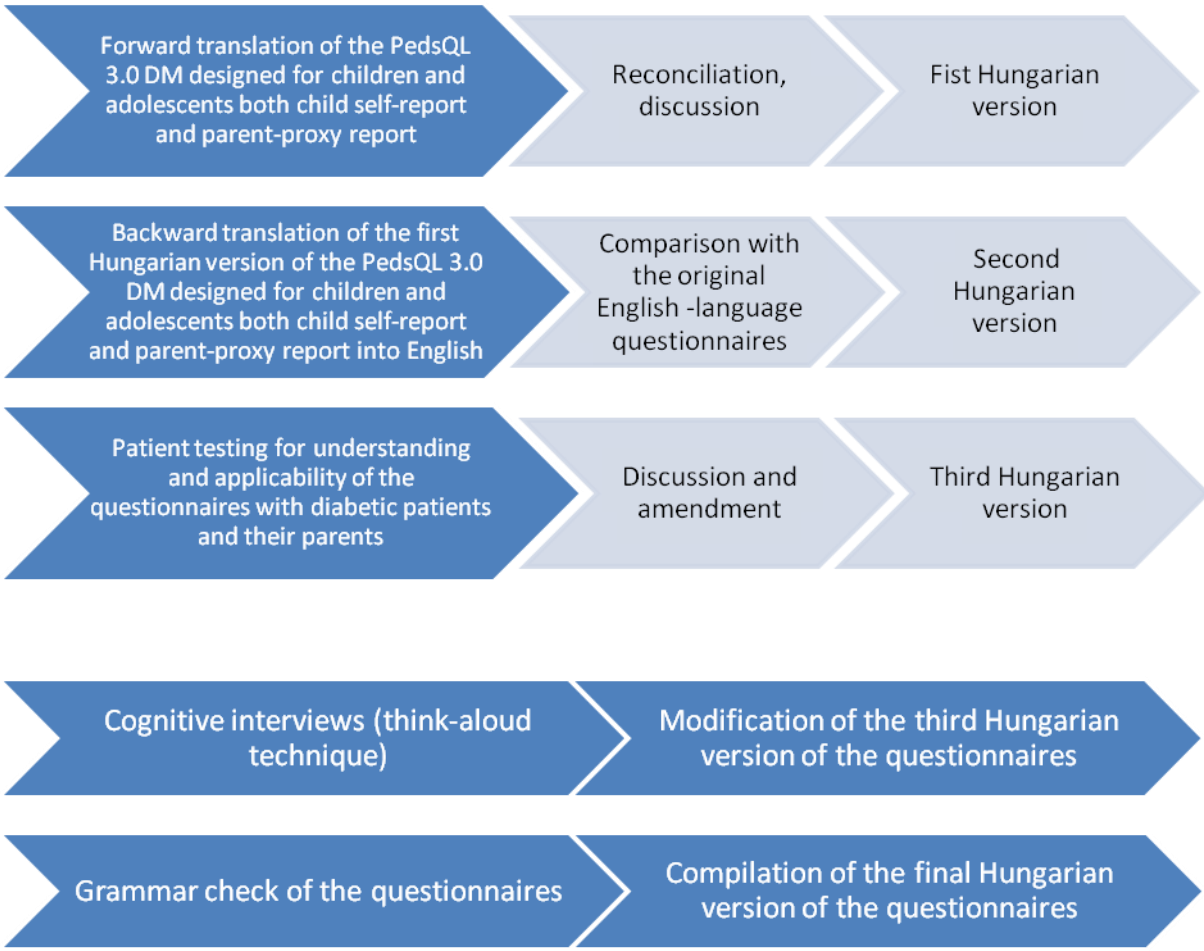
1. Forward translation - The first group, included two English teachers and an English-speaking endocrinologist, translated the questionnaires (both child self-report and parent-proxy report) into Hungarian independently of each other. They discussed the differences in translations and prepared the first Hungarian versions of the questionnaires.

2. The second working group, included two English teachers and a Hungarian speaking English lector, reversed the first version into the source language. This working group had no access to the original English version. The aim of the backward translation was to detect any misunderstandings, mis-translations or inaccuracies in the forward version of the questionnaire.

3. The third step was to administer the translated questionnaire to a sample of respondents (patients and their parents) to determine whether the translation is acceptable, whether it is understood and whether the language used is simple and appropriate.

The last work phase was the cognitive interviewing using the PedsQL Cognitive Interviewing Methodology^{SM} (Clauzoni, S. personal communication, September 2, 2010). The goal of the cognitive interviewing was to understand the thought processes and to pass this knowledge on to the author who can construct, create and ask better questions. We used the think-aloud interviewing technique (144, 145). Patients and their parents were interviewed separately during the outpatient visits. The interview took 45-60 minutes per participant. Item 20 ('It is hard for me to wear id bracelet.') had to be adjusted to the Hungarian custom, since the Hungarian diabetic youth used diabetes identity cards instead of id bracelets. The reports of the linguistic validation and the cognitive interviews were sent to the translation team for approval. The Hungarian version of the PedsQL DM is compatible and took 5-10 minutes to complete, just like the original version. The Mapi Research institute (France) accepted the Hungarian version of the PedsQL 3.0 DM. The flowchart demonstrates the algorithm of the translation and the linguistic validation process. (Table 1)

Figure 1 Flowchart of the linguistic validation process



On the basis of the PedsQL linguistic validation guideline

3.3 Physical Activity Questionnaire for Older Children and Adolescents

The Physical Activity Questionnaire for Older Children (PAQ-C) and the Physical Activity Questionnaire for Adolescents (PAQ-A) were developed for assessing physical activity at various ages. These are self-administered, 7-day recall instruments that provide general measure of physical activity for youths from ages 8-19. They classify children and adolescents into five different activity levels. There are nine items in the PAQ-C: physical activities during spare time, intensity of physical education class, recess time activities, lunch time activities, after-school activities, evening activities, weekend activities, activities in the past seven days, and activities on specific days of the week. The PAQ-A is a slightly modified version of PAQ-C, one item (recess time activities) has been removed. Calculating the mean

of the 8 or 9 items will result the final score, where a score of 1 indicates low, whereas a score of 5 indicates very high physical activity. The last item ("Were you sick last week, or did anything prevent you from doing your normal physical activities?") is not included into the scoring method. The instruments do not provide an estimate of caloric expenditure or frequency, time and intensity of exercise (146-148).

There are no validated questionnaires for evaluating physical activity for children and adolescents in Hungary. For this reason we carried out the linguistic validation of PAQ-C. PAQ-A is a shorter version of PAQ-C so we focused only on PAQ-C validation.

3.3.1. Linguistic validation of Physical Activity Questionnaire for Older Children

We performed the linguistic validation of the questionnaire. Because of the relatively small sample size the psychometric properties of the questionnaire were not measured. Two English teachers (one of them is English native speaker) translated the questionnaire from English into Hungarian independently. They discussed the translation and agreed on a single version. English version was translated back by two other English teachers who were not associated with the first translation phase. After comparison with the original questionnaire and after revision, the new version was tested on 8 children (4 girls and 4 boys). The purpose of this test was to ensure that the words chosen by the translators are easily and accurately understood by participants (144). Translation of the American sports made difficulties into Hungarian as some sports were unknown or not popular in Hungary.

3.4 Eurofit Fitness Test Battery

The Eurofit Physical Fitness Test Battery was devised by the Committee of Experts for Sports Research of the Council of Europe (1988). This standardized test battery examines nine tests: eight motor performances and the cardiorespiratory fitness. Motor performance tests consist of the evaluation of the body balance (Flamingo test, FLB), the speed and coordination of upper limb movement (Plate tapping test, PLT), general flexibility (Sit and reach test, SAR), explosive strength of legs (Standing broad jump test, SBJ), static strength of the hand and forearm (Hand grip test, HGR), abdominal muscle strength (Sit-up test, SUP), upper body strength (Bent arm hang test, BAH), running speed (10 x 5 meter shuttle run test, SHR) (149). The hand grip was measured with calibrated hydraulic Baseline dynamometer. Test for cardiorespiratory fitness utilizes the maximal oxygen consumption (VO_{2max}) as the single best

measure of maximal aerobic power. Cardiorespiratory fitness was measured by 20 meter progressive shuttle run test. (150, 151). 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 it progressively 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 shuttle run test was carried out 08.00-10.00 AM and if morning home blood glucose result of the patient was out of the target range (5-10 mmol/l), a new appointment was given to perform the test on other day. The maximal oxygen consumption was computed from the last completed stage using the regression equation of Léger et al. (1988). The validity of the test in prediction of maximal oxygen consumption has been previously established (151-154). Nowadays there is some doubt about the underestimation of VO_{2max} in adolescents and adults, but this test is used in most recent surveys for evaluating cardiorespiratory fitness in children and adolescents. The Eurofit tests were conducted with the same instructors, with the same instruments in gym halls according to the Eurofit protocol. Table 6 presents the Eurofit test battery.

Table 6 Eurofit test battery

Dimension	Factor	Test	Description
Cardiorespiratory endurance/fitness	Cardiorespiratory endurance	20 m progressive shuttle run	running until exhausted
Strength	a) Static strength	Hand grip	In standing position squeeze the dynamometer as forcefully as possible with the preferred hand. 2 attempts
	b) Dinamic strength (explosive muscular strength)	Standing broad jump	Jump forward as long as possible with two legs using arm swing and knee bend before jumping. 2 attempts
Muscular endurance	a) Functional strength (upper limb muscular endurance)	Bent arm hang	The body lifted to a height so that the chin is level with a horizontal bar. Holding this position as long as possible. Time is recorded. 1 attempt
	b) Trunk strength (abdominal muscular endurance)	Sit-ups in 30 sec	Lying position with knees bent, feet are held by a partner. Upper body to be lifted vertically and return to the floor back as quickly as possible during 30 sec. 1 attempt
Flexibility	Extent of flexibility (articulo-muscular range of movement)	Sit and reach	Sitting with legs stretched out straight ahead and reaching the box with fingers without. Distance is measured in cm. 2 attempts
Speed	Speed of limb movement (segmental repetitive velocity)	Plate tapping time for 25 cycles	Moving the preferred hand back and forth between 2 discs at 80 cm distance over the hand in the middle as quickly as possible 25 times. Time is recorded. 2 attempts
	Running speed (total body velocity)	Shuttle run 10 x 5 meters	Sprint 5 m distance as quickly as possible 10 times without stopping. Time is recorded. 1 attempt
Balance	Total body balance (coordination of total body equilibrium)	Standing on one foot on a beam for 1 min	Balancing on the preferred leg, the other is flexed close to the buttocks. When balance is lost, stopwatch is stopped. Number of falls in 1 min is counted. 1 attempt

On the basis of Testing Physical Fitness Eurofit Experimental Battery Provisional Handbook (Strasbourg 1983)

3.5. Anthropometric Assessments

3.5.1. BMI z-score

Height was measured (to the nearest 0.5 cm) and weight was measured (accurate to 0.1 kg) with medical digital scale with column (Soehnle 7831, Germany) in light sport clothing without shoes. Body max index (BMI) (kg/m^2) was calculated and each BMI value was standardized by conversion to a z-score (BMI z-score) adjusted for child age and sex, using the national child health chart (155). Z-scores (or standard deviation scores) 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.

3.5.2. Skinfold thickness

All measurement were taken in standing position, on the right side of the body in the standard manner using a Harpenden skinfold calliper (HSB-BI, British Indicators Ltd., UK) according to the International Society for the Advancement of Kinanthropometry (156). Two non-consecutive measurements for four sites (triceps, biceps, subscapular and suprailiac) were performed and mean values were used for data analyzing. As there is no gold standard to evaluate the body fat content in percentage for children and adolescents the four skinfold thicknesses were summed, and the total was used as a measure of total body fat.

3.6. Glycated haemoglobin

The haemoglobin A_{1c} (HbA_{1c}) values were extracted from medical records. HbA_{1c} levels are recorded as a percentage of the total haemoglobin. Currently there is not a scale to determine the clinical severity of T1DM, as our participants had no complications. Therefore, the disease status was determined according to the target indicators of glycemic control recommended by ISPAD: HbA_{1c} values below 7.5% were considered as optimal metabolic control, values between 7.5-9% were considered as suboptimal metabolic control, and values above 9% were defined as high risk metabolic control (157).

3.7. Statistical analysis

SPSS 19.0 statistical analysis software was used for data analyses and p values at ≤0.05 were considered statistically significant. Descriptive characteristics (mean and standard deviation) were performed for all parameters. Correlation between the different fitness and anthropometric parameters was evaluated with Spearman's coefficients. In order to compare the diabetic and the healthy control groups as well as the different age or gender groups of the diabetic patients, t-test was employed. Physical activity level (ordinal scale) was compared with Chi-squared test. Multiple regression analysis with stepwise method was carried out to establish predictors of physical fitness, metabolic control, generic and disease-specific health-related quality of life.

The psychometric properties of the PedsQL 3.0 DM designed for children and adolescents were analyzed jointly. Feasibility was determined from the percentage of missing values for each subscales of the PedsQL 3.0 DM and the floor and ceiling effects for both CSR and PPR versions (158, 159). Internal consistency reliability was characterized by Cronbach's coefficient alpha using total-items and inter-subscales methods (160). Reliability coefficient of 0.70 or higher is considered acceptable between groups and 0.90 or higher are acceptable for interpreting individual scores (161, 162). Reproducibility was measured with test-retest reliability using the Pearson correlation coefficient between total scales and subscales. The construct-related evidence was assessed using convergent and discriminant validities. The convergent validity was determined through correlation coefficients between CSR and PPR. The Pearson correlation coefficient effect sizes are designated as small (0.10–0.29), medium (0.30–0.49), and large (≥0.50) (163). Intraclass correlations (ICCs) were also computed, designated as ≤0.40 poor to fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good agreement, and 0.81–1.00 excellent agreement (164, 165). The discriminant validity was evaluated through the metabolic control and the DM total scores, whether HbA_{1c} was related to HRQoL of the patients. We used one-way ANOVA and LSD post-hoc multiple comparisons. In order to establish concurrent validity we selected the PedsQL GCS, that measure different aspect of the HRQoL and we tested if scores on the subscales of the DM would correlate with the total scores of the GCS**.** Intercorrelation was expected to demonstrate moderate to large effect sizes (166).

4. RESULTS

4.1. Eurofit tests of children and adolescents with type 1 diabetes mellitus compared with non-diabetic controls

4.1.1. Anthropometric characteristics and physical activity levels

No significant differences in body composition expressed by skinfold thickness and BMI z-score were observed between the diabetic and age-matched control groups. (Table 7)

Table 7 Anthropometric characteristics of diabetic and control groups

	Diabetic girls	Control girls	Diabetic girls	Control girls
	8-12 y/o	8-12 y/o	13-18 y/o	13-18 y/o
n	27	32	26	37
BMI z-score	0.64 ±0.81	0.57 ±0.80	0.68 ±0.76	0.65 ±0.84
sum of skinfolds (mm)	62.56 ±23.58	56.44 ±27.45	92.02 ±27.91	83.48 ±27.10
	Diabetic boys	Control boys	Diabetic boys	Control boys
n	25	28	28	33
BMI z-score	0.39 ±1.16	0.43 ±1.39	0.36 ±0.89	0.35 ±0.99
sum of skinfolds (mm)	57.62 ±24.93	63.44 ±31.47	56.97 ±26.58	52.49 ±22.41

Physical activity levels of the diabetic groups did not differ significantly from the control youths as assessed by PAQ-C and PAQ-A (Table 8).

Table 8 Crosstabulation of the physical fitness level of the participants by age and gender

	younger girls		older girls		younger boys		older girls		
PAQ score	diabetic n=27	control n=32	diabetic n=26	control n=37	diabetic n=25	control n=28	diabetic n=28	control n=33	∑
1	8	5	13	13	6	6	7	4	62
2	8	14	6	14	7	6	6	7	68
3	7	9	3	8	2	9	6	9	53
4	1	1	1	1	1	2	3	3	13
5	3	3	3	1	9	5	6	10	40
∑	27	32	26	37	25	28	28	33	

4.1.2. Physical fitness

Eurofit test results in 5 and 4 of 9 tests applied were poorer in the groups of younger and older girls with diabetes as compared with their healthy peers, respectively. Younger girls with diabetes had significantly poorer results of PLT test, SUP test, BAH test, SHR test and VO_{2max} than control younger girls. Older girls with diabetes had significantly poorer results of PLT test, SUP test, BAH test and VO_{2max} than control older girls. Table 9 presents results obtained by the Eurofit battery for girls with diabetes and their age-matched controls.

Table 9 Eurofit test results of diabetic girls compared with control groups (mean±SD)

	girls (8-12 y/o)			girls (13-18 y/o)		
Tests	Diabetic (n=27)	Control (n=32)	p value	Diabetic (n=26)	Control (n=37)	p value
FLB† (No of error)	8.33 ±4.35	6.63 ±6.01	0.095	9.65 ±6.52	9.03 ±6.28	0.716
PLT†† (sec)	16.60 ±3.23	14.89 ±3.48	0.022	14.32 ±1.80	13.13 ±1.82	0.013
SAR (cm)	19.17 ±5.48	19.66 ±4.42	0.951	22.52 ±6.40	20.65 ±6.21	0.250
SBJ (cm)	133.41 ±21.02	137.56 ±18.17	0.419	150.31 ±24.86	143.22 ±23.90	0.259
HGR (kg)	19.44 ±4.73	19.72 ±4.80	0.826	30.31 ±4.73	29.57 ±4.17	0.514
SUP (attempt)	16.11 ±5.78	20.63 ±5.43	0.001	16.77 ±5.57	19.41 ±4.19	0.036
BAH (sec)	2.61 ±2.83	5.98 ±7.39	0.025	1.77 ±2.55	4.58 ±5.41	0.008
SHR (sec)	24.30 ±2.06	23.16 ±2.09	0.040	23.42 ±2.13	23.28 ±2.25	0.806
VO_{2max} (ml/min/kg)	43.14 ±4.33	46.42 ±4.17	0.006	33.27 ±4.80	36.48 ±5.96	0.015

†-numbers of steps down from the beam losing the balance
††-time for touching two discs 25 times back and forth

FLB, Flamingo balance; PLT, Plate tapping; SAR, Sit and reach; SBJ, Standing broad jump; HGR, Hand grip; SUP, Sit-ups; BAH, Bent arm hang; SHR, 10 x 5 m Shuttle run

Results in 4 and 5 of 9 tests applied were poorer in the groups of child and adolescent boys with diabetes as compared with their non-diabetic controls, respectively. Younger boys with diabetes had significantly lower achievement of PLT test, SAR test, HGR test and SUP test than control younger boys. Older boys with diabetes produced significantly poorer results of

PLT test, SAR test, SUP test, BAH test and VO_{2max} than control older boys. Table 10 presents results of Eurofit tests for boys with diabetes and the age-matched control boys.

Table 10 Eurofit test results of diabetic boys compared with control groups (mean±SD)

	boys (8-12 y/o)			boys (13-18 y/o)		
Tests	Diabetic (n=25)	Control (n=28)	p value	Diabetic (n=28)	Control (n=33)	p value
FLB† (No of error)	9.68 ±5.23	7.18 ±6.01	0.054	9.39 ±6.57	6.58 ±5.75	0.066
PLT†† (sec)	17.39 ±3.40	15.54 ±3.00	0.025	13.16 ±1.47	11.87 ±1.97	0.006
SAR (cm)	14.58 ±5.44	18.23 ±4.41	0.009	16.50 ±7.77	20.63 ±7.46	0.038
SBJ (cm)	146.64 ±24.57	151.25 ±28.65	0.535	195.50 ±24.46	201.15 ±31.15	0.440
HGR (kg)	21.04 ±6.06	23.79 ±5.91	0.050	39.64 ±8.52	42.24 ±8.80	0.248
SUP (attempt)	19.80 ±4.97	22.89 ±5.45	0.036	23.39 ±4.18	26.12 ±4.13	0.013
BAH (sec)	6.01 ±5.61	6.00 ±5.96	0.979	13.36 ±11.56	19.60 ±12.92	0.030
SHR (sec)	22.39 ±2.48	21.80 ±3.32	0.103	20.45 ±1.70	19.96 ±2.51	0.386
VO_{2max} (ml/min/kg)	45.58 ±3.30	46.89 ±5.60	0.298	38.72 ±5.20	44.80 ±7.29	<0.001

†-numbers of steps down from the beam losing the balance
††-time for touching two discs 25 times back and forth

FLB, Flamingo balance; PLT, Plate tapping; SAR, Sit and reach; SBJ, Standing broad jump; HGR, Hand grip; SUP, Sit-ups; BAH, Bent arm hang; SHR, 10 x 5 m Shuttle run

4.1.3. Predictors of metabolic control and cardiorespiratory fitness

Out of the 9 Eurofit tests applied, VO_{2max} (ρ=-0.413; p<0.001), SUP test (ρ=-0.215 p=0.027), SHR test (ρ=0.192 p=0.049) and the skinfold thickness (ρ=0.231; p=0.017) correlated significantly with HbA_{1c} as measure of metabolic control. When HbA_{1c} was used as dependent variable in the multiple regression model, better VO_{2max} proved to be the single significant predictor of favourable HbA_{1c} (B=-0.077, SE(B)=0.021, β=-0.343, t=-3.726, p<0.001; R^2=0.118). Age, gender, diabetes duration, BMI z-score, skinfold thickness, physical activity level, general balance, flexibility, speed of limb movement, running speed, static strength, dynamic strength and muscular endurance (independent variables) were not

significant in the model. Therefore, in further analysis to establish predictors of physical fitness, VO_{2max} was used as dependent variable. In diabetic subjects, older age, female gender, higher skinfold thickness, lower physical activity level and higher HbA_{1c} proved to be significant independent predictors of poorer VO_{2max} explaining 65.1% of its variance (Table 11). Age, BMI z-score and skinfold thickness as independent variables were not significant in the model.

Table 11 Summary of multiple regression analysis for VO_{2max} (N=106)

Variables	B	SE(B)	β	t	p
skinfold thickness	-0.037	0.015	-0.168	-2.543	0.013
age	-1.261	0.126	-0.606	-10.001	<0.001
HbA_{1c}	-1.037	0.272	-0.233	-3.811	<0.001
gender	2.248	0.820	0.176	2.740	0.007
physical activity	0.737	0.269	0.171	2.742	0.007

$R=0.807$, $R^2=0.651$

4.2. Reliability and validity of PedsQL 3.0 Diabetes Module

For evaluating the psychometric properties of the PedsQL 3.0 DM in patient and control subjects, feasibility, internal consistency reliability, reproducibility, convergent, discriminant and concurrent validities were evaluated.

4.2.1. Feasibility

For the PedsQL 3.0 DM, the percentage of missing item responses as a whole was 1.10% for CSR and 0.61 for PPR, respectively. The scale range was 0.00-4.23% in CSR and 0.35-1.16% in PPR. There were minimal floor effects in both versions (ranged 1.07-3.10% in CSR and 1.13-3.70% in PPR). However, moderate ceiling effects existed; the largest effects were for Treatment adherence (56.46% in CSR and 55.49% in PPR) and for Communication (48.17% in CSR and 46.50% in PPR). Table 11 displays the descriptive statistics of the mean

subscales scores for CSR and PPR versions as well as the floor-ceiling effects and missing data in percentage. (Table 12)

Table 12 Subscales descriptive statistics, floor and ceiling effects, missing data of the child self-report (n=355) and parent proxy-report (n=328) in the PedsQL Diabetes Module

Total score and subscale scores of the	Mean score		Floor effect (%)		Ceiling effect (%)		Missing data (%)	
3.0 DM mean ±SD	CSR	PPR	CSR	PPR	CSR	PPR	CSR	PPR
Total score	71.38 ±12.71	68.91 ±11.84	1.91	2.08	37.0	36.10	1.10	0.61
Diabetes symptoms	63.77 ±13.56	62.45 ±12.57	1.74	1.82	23.62	22.91	0.47	0.35
Treatment barriers	69.51 ±19.94	65.33 ±20.12	3.10	3.70	34.48	33.98	0.00	0.53
Treatment adherence	82.53 ±14.46	79.90 ±14.58	1.07	1.13	56.46	55.49	1.56	1.16
Worry	69.17 ±20.50	62.78 ±21.36	2.77	3.17	32.83	31.70	0.67	0.47
Communication	77.36 ±22.43	76.77 ±22.53	2.10	2.03	48.17	46.50	4.23	0.57

4.2.2. Internal consistency reliability

The total-items and subscales reliability is demonstrated in Table 12. Cronbach's alpha coefficients for the subscales of the DM ranged from 0.698 to 0.795 in CSR and from 0.747 to 0.848 in PPR. Subscales scores on the module exceeded the 0.70 standard. The Cronbach's alpha in total-items reliability approached the criterion of 0.90 recommended for analyzing individual patient scores (0.904 in CSR and 0.892 in PPR). (Table 13)

Table 13 Subscales and total-items internal consistency reliability for PedsQL 3.0 DM in child self-report (CSR) and parent proxy-report (PPR)

N=355	items	Cronbach's α	Cronbach's α
3.0 DM	CSR/PPR	CSR	PPR
Total-items	28	0.904	0.892
Diabetes symptoms	11	0.775	0.767
Treatment barriers	4	0.707	0.763
Treatment adherence	7	0.742	0.747
Worry	3	0.698	0.769
Communication	3	0.795	0.848

4.2.3. Reproducibility

To examine test-retest reliability, a random sample of 29 respondents (16 girls, aged 14.33 ±2.66 y/o and 13 boys, aged 14.01 ±3.33 y/o) and their parents were selected. The participants completed the questionnaires 3-4 weeks apart. The health condition of the children was clinically similar in the second administration. Test-retest reliability was assessed through Pearson correlation coefficient between the total scores and between the subscales scores. The Pearson correlation coefficient ranged between 0.586-0.840 in CSR subscales, and 0.432-0.822 in PPR subscales. The correlations between the total scores were 0.877 in CSR and 0.834 in PPR. The lowest correlation (0.432) was found in the Communication subscale in PPR.

4.2.4. Convergent validity

Concordance between CSR and PPR is demonstrated in Table 3. The effect size was large in all subscales of the DM; the Pearson correlation coefficients were between 0.617 and 0.764 in all subscales and 0.807 between the total scores (<0.001). The ICCs were between 0.763 and 0.865 in the subscales and 0.893 in the total items (Table 14).

Table 14 Intercorrelations between child self-report and parent proxy-report in PedsQL 3.0 DM with Pearson correlation and intraclass correlations coefficients

PedsQL 3.0 DM	Pearson correlation coefficients	Intraclass correlation coefficients
Total scores/total items	0.807*	0.893*
Diabetes symptoms	0.757*	0.860*
Treatment barriers	0.725*	0.841*
Treatment adherence	0.764*	0.865*
Worry	0.617*	0.763*
Communication	0.740*	0.851*

p<0.001 (2-tailed)

4.2.5. Discriminant validity

To assess whether the measure could differentiate between patients with varying degrees of disease severity, patients were categorized into 3 groups according to the HbA_{1c} values as having optimal (<7.5%) (n=70), suboptimal (7.5-9%) (n=166) and high risk metabolic control (>10%) (n=119). Using one-way ANOVA we found significant differences among three sizes of HRQL, F(2, 352)=3.099, p=0.046 in CSR and F(2, 325)=3.080, p=0.047 in PPR. LSD post-hoc multiple comparisons of the three groups indicate that the group of optimal metabolic control (M=74.73, 95% CI [72.09, 77.37]) in CSR and (M=72.31, 95% CI [69.54, 75.07]) in PPR gave significantly higher HRQL scores than the group of suboptimal metabolic control (M=70.73, 95% CI [68.77, 72.69]); p=0.027 in CSR and (M=68.03, 95% CI [66.09, 69.98]); p=0.018 in PPR; and the group of high risk metabolic control (M=70.33, 95% CI [67.92, 72.74]); p=0.021 in CSR and (M=68.31, 95% CI [66.13, 70.48]); p=0.034 in PPR, respectively.

4.2.6. Concurrent validity

The concurrent validity was examined through an analysis of the intercorrelation between the PedsQL GCS total scores and the PedsQL 3.0 DM subscales scores. Intercorrelations ranged from 0.463 to 0.593 in CSR and from 0.440 to 0.692 in PPR with medium to large effect size range. The smallest intercorrelations were observed between the GCS and Worry subscale

both in CSR and PPR. The intercorrelation between GCS and DM total scores were 0.689 in CSR and 0.762 in PPR. (Table 15)

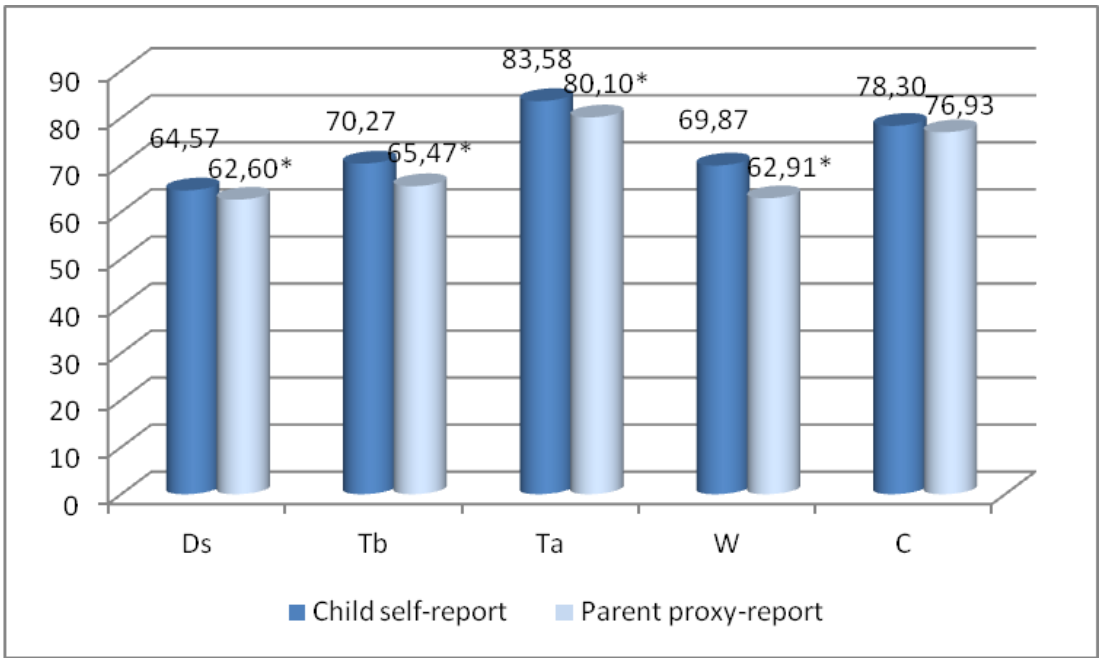
Table 15 Intercorrelation between PedsQL GCS total scores and DM subscale scores and total score in child self-report (CSR) and parent proxy-report (PPR)

	Diabetes symptoms	Treatment barriers	Treatment adherence	Worry	Communication	DM total score
GCS - CSR	0.593	0.526	0.557	0.463	0.524	0.689
GCS - PPR	0.692	0.583	0.563	0.440	0.449	0.762

4.3. Health-related quality of life of children and adolescent with type 1 diabetes mellitus

With the PedsQL Diabetes Module we evaluated the diabetic youths' HRQoL both from the children and from the parents' perspective. When we compared the HRQoL of diabetic boys and girls, we observed that boys had significantly better quality of life perception than girls (boys (n=184): 72.77 ±12.95 vs. girls (n=171): 69.89 ±12.31; p=0.033). This was confirmed by the parents' answers (boys (n=170): 70.82 ±11.24 vs. girls (n=158) 66.86 ±12.16; p=0.002). The parents significantly underestimated their children's HRQoL globally (CSR: 72.08 ±12.35 vs. PPR: 68.91 ±11.84; p<0.001) and in all subscales except of Communication subscale (Diabetes symptoms: CSR: 64.57 ±13.27 vs. PPR: 62.60 ±12.30; p<0.001, Treatment barriers: CSR: 70.27 ±19.81 vs. PPR 65.47 ±20.03; p<0.001, Treatment adherence: CSR: 83.58 ±13.32 vs. PPR: 80.10 ±14.17; p<0.001, Worry: CSR 69.87 ±20.43 vs. PPR: 62.91 ±21.30; p<0.001, Communication: CSR:78.30 ±22.17 vs. PPR: 76.93 ±22.39; p=0.123). Analyzing the subscale scores of the DM we found that patients with T1DM had no problem with the treatment adherence and communication, but they had low scores in the diabetes symptoms, treatment barriers and the worry subscales. Similar pattern was found in the PPR. (Figure 2)

Figure 2 Diabetic children and their parents' concordance on the basis of Diabetes Module subscales (N=328)



**Child self-report vs. parent proxy-report in Ds=Diabetes symptoms, Tb=Treatment barriers, Ta=Treatment adherence and W=Worry subscales; p<0.001,*
C=communications

We put the items into order according to the item scores. We found that treatment adherence /eating snack (86.60), taking insulin shots (85.90), carry fast-acting carbohydrate (84.21), exercise (82.87), taking blood glucose tests (82.75) and wearing id card (79.34)/ have no problems for the diabetic youths. Only exception is one item, keeping track of carbohydrates or exchanges (67.43) that can be problematic for the children. Patients have no real communication difficulties, they tell the doctors and nurses how they feel (80.32), ask questions (77.46), but reluctant to explain the illness to other people (74.34). The most problems are due to the somatic symptoms /getting sweaty (66.74), going to bathroom too often (65.81), getting shaky (64.24), getting irritable (56.94), feeling tired or fatigued (55.21), feeling thirsty (52.78), feeling hungry (49.88)/. The worst symptom is the hypoglycaemic episode (48.83). The diabetic youths seem to worry very much about the long-term complications (57.86).

4.4. Health-related quality of life of children and adolescents treated with continuous subcutaneous insulin infusion versus multiple daily injections

We grouped the patients according to the method of the intensive therapy. We measured the CSII and MDI groups both with the GCS and the DM. We observed significant differences in HRQoL between them regarding both the child self-report (CSR) ($p<0.001$) and the parent-proxy report (PPR) ($p=0.001$) according to the GCS total scores. The same significant differences were found in DM, both in CSR ($p=0.020$) and PPR ($p=0.033$). Youth with CSII therapy had higher scores. The difference was caused by the divergent emotional functioning (CSR: $p<0.001$; PPR: $p<0.001$) and better physical functioning (CSR: $p=0.008$; PPR: $p=0.005$) between the two groups. The youths treated with CSII reported significantly better school functioning than those with MDI therapy (CSR: $p=0.004$). Regarding the diabetes-specific subscales, we found that CSII patients had significantly higher subscale index in Diabetes symptoms (CSR: $p=0.001$; PPR: $p=0.001$) and in Worry subscale (CSR: $p<0.001$; PPR: $p=0.002$). The GCS total score and subscale scores and DM total score and subscale scores are presented in Table 16 and Table 17.

Table 16 Total score and subscale scores of Generic Core Scales for child self-report and parent proxy-report in patients treated with CSII and MDI (mean±SD)

	Child self-report		Parent proxy-report	
	CSII therapy	MDI therapy	CSII therapy	MDI therapy
	n=104	n=135	n=97	n=127
GCS total score	82.14***	76.99	79.34***	74.91
	±9.17	±9.97	±8.98	±10.12
Physical functioning	84.59 **	80.82	81.14**	77.45
	±9.81	±11.05	±9.48	±9.79
Emotional functioning	75.82***	67.02	72.77***	63.80
	±15.19	±15.97	±14.97	±14.90
Social functioning	90.61	87.59	88.30	85.65
	±13.60	±15.28	±13.40	±17.51
School functioning	75.85**	70.33	74.07	71.16
	±14.24	±14.95	±14.22	±15.01

*p<0.05 **p<0.01 ***p<0.001

Table 17 Total score and subscale scores of Diabetes Module for child self-report and parent proxy-report in patients treated with CSII and MDI (mean±SD)

	Child self-report		Parent proxy-report	
	CSII therapy n=104	MDI therapy n=135	CSII therapy n=97	MDI therapy n=127
DM total scores	73.06* ±12.17	69.25 ±12.66	69.90* ±11.95	66.54 ±12.08
Diabetes symptoms	67.18*** ±12.55	61.36 ±13.49	65.70*** ±11.93	60.01 ±12.48
Treatment barriers	72.49 ±19.78	68.40 ±19.21	68.73 ±19.43	66.07 ±18.93
Treatment adherence	82.87 ±14.29	81.81 ±14.14	79.81 ±14.94	77.80 ±13.37
Worry	71.43*** ±20.66	62.00 ±19.13	66.89** ±20.90	57.09 ±21.70
Communication	77.15 ±21.20	76.54 ±22.68	74.83 ±20.86	76.51 ±21.32

*p<0.05 **p<0.01 ***p<0.001

We computed the maximal oxygen consumption (VO_{2max}) separately by gender and found no significant difference between the CSII and MDI groups either in boys or girls. The metabolic control between the CSII and MDI groups were similar without any notable differences. (Table 5)

4.5. Health-related quality of life of children and adolescents with type 1 diabetes mellitus compared with non-diabetic peers

Comparing the diabetic and the non-diabetic groups by gender on the basis of PedsQL GCS we found no statistically significant differences in quality of life neither in CSR or PPR, except of the Physical functioning in boys by the PPR. The parents rated the physical functioning significantly better for control boys than diabetic boys (p=0.005). (Table 18)

Table 18 PedsQL Generic Score Scales in diabetic and the control groups in child self-report (CSR) and parent proxy-report (PPR) by gender (mean±SD)

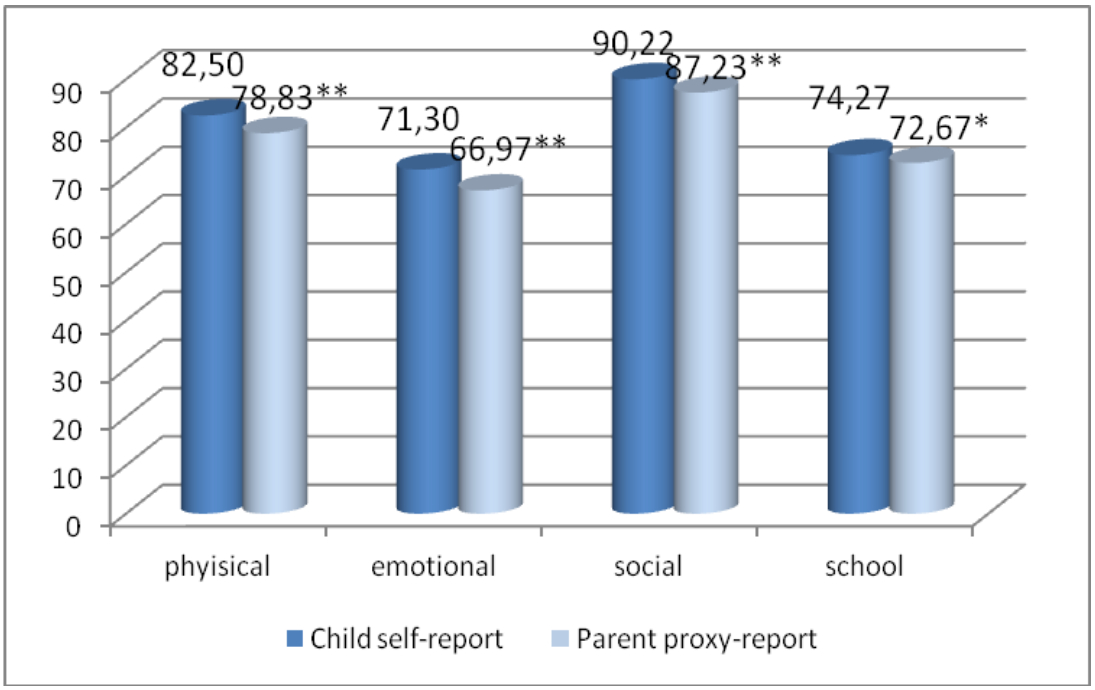
	Girls				Boys			
	CSR		PPR		CSR		PPR	
Subscales of GCS	diabetic n=171	control n=157	diabetic n=158	control n=157	diabetic n=184	control n=137	diabetic n=170	control n=137
Physical	81.05 ±70.74	80.06 ±12.45	78.05 ±10.35	77.66 ±13.98	84.20 ±10.80	84.63 ±12.82	79.56* ±10.10	83.55 ±13.92
Emotional	66.87 ±10.74	66.11 ±14.92	64.68 ±16.24	67.51 ±13.70	74.02 ±16.73	73.72 ±16.90	69.09 ±16.23	71.72 ±15.55
Social	88.83 ±15.60	86.18 ±14.32	86.35 ±16.00	86.78 ±13.62	90.04 ±12.84	87.49 ±13.65	88.06 ±14.17	87.41 ±15.85
School	72.66 ±15.33	70.82 ±15.17	73.48 ±13.72	73.22 ±15.35	74.12 ±14.51	73.67 ±14.23	71.91 ±15.68	71.82 ±15.65
Total score	77.89 ±10.23	76.35 ±10.17	75.93 ±10.10	76.45 ±10.58	81.07 ±10.02	80.51 ±11.39	77.49 ±9.96	79.27 ±11.92

* Diabetic boys vs. control boys in physical functioning by PPR; $p<0.01$

The children and the parents' concordance showed similarity in healthy groups (Physical functioning CSR: 82.19 ±12.81 vs. PPR: 80.4 ±14.24, Emotional functioning CSR: 69.66 ±16.30 vs. PPR: 69.47 ±14.72, Social functioning CSR: 86.79 ±14.01 vs. PPR: 87.07 ±14.68, School functioning CSR: 72.15 ±14.78 vs. PPR: 72.57 ±15.48).

The parents of the diabetic group significantly underestimated their children' HRQoL in all subscales of the GCS (Physical functioning CSR: 82.50 ±10.90 vs. PPR: 78.83 ±10.23; $p<0.001$, Emotional functioning CSR: 71.30 ±16.73 vs. PPR: 66.97 ±16.36; $p<0.001$, Social functioning CSR: 90.22 ±13.86 vs. PPR: 87.23 ±15.08; $p<0.001$, School functioning CSR: 74.27 ±14.78 vs. PPR: 72.67 ±14.76; $p=0.003$). (Figure 3)

Figure 3 Diabetic children and their parents' concordance on the basis of General Score Scales (N=328)



*p<0.01 **p<0.001

4.6. Predictors of health-related quality of life and metabolic control

In the multiple regression models we analysed both the generic and diabetes-specific quality of life. The higher maximal oxygen uptake and the method of intensive insulin therapy were significant independent predictors of the better self-rated generic HRQoL. (Table 19) The metabolic control, gender, age, insulin dosage, BMI z-score, and the duration of diabetes as independent variables were not significant in the model.

Table 19 *Summary of stepwise multiple regression analysis for HRQoL. (Criterion variable is PedsQL Generic Core Scales, child self-report) (N=239)*

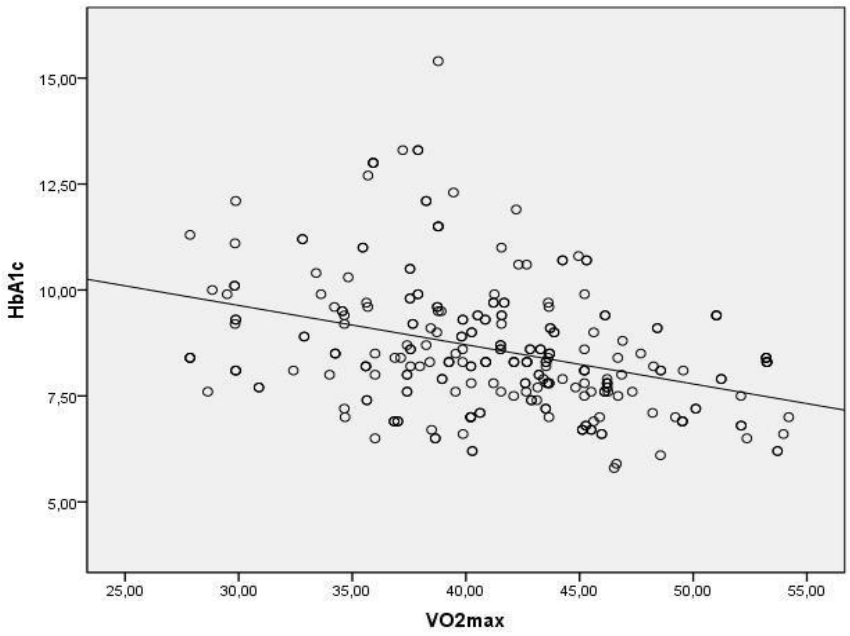
Variables	B	SE(B)	β	t	p
(Constant)	55.046	4.163		13.331	<0.001
VO_{2max}	0.650	0.098	0.386	6.654	<0.001
therapy	-4.410	1.160	-0.220	-3.800	<0.001

R=0.462, R^2=0.214 (CSII=0, MDI=1)

When we put the self-rated DM into the model as dependent variable the higher maximal oxygen uptake (B=0.883, SE(B)= 0.122, β=0.424, t=7.255; p<0.001) and the method of intensive insulin therapy (B=-2.798, SE(B)=1.446, β=-0.113, t=-1.935; p=0.054, R=0.449, R^2=0.202) were significant predictors.

We ran the regression analysis again on the HbA_{1c}, because we had now greater sample size and we analyzed the intensive therapy method as well. The result was similar to the previously got outcome. Predictors of the metabolic control (expressed by HbA_{1c}) was the maximal oxygen consumption (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 4)

Figure 4 Improvement of hemoglobin A_{1c} depending on maximal oxygen uptake



5. DISCUSSION

In this research work we investigated the physical fitness including motor performances and cardiorespiratory fitness using the standardized Eurofit test battery, anthropometric characteristics of children and adolescents with T1DM and compared the results with age-matched control groups; we also evaluated the clinical parameters. We determined the predictors of the metabolic control (expressed by HbA_{1c}) and the cardiorespiratory fitness (expressed by VO_{2max}). We carried out the linguistic validation of the Physical Activity Questionnaire. We culturally adapted the Pediatric Quality of Life Inventory 3.0 Diabetes Module designed for children and adolescents. We evaluated diabetes-specific quality of life and found the factors influencing on quality of life of patients with T1DM. We compared the diabetic patients' HRQoL and cardiorespiratory fitness treated with CSII versus to MDI. We assessed the children and parents' concordance on the basis of generic and diabetes-specific quality of life questionnaires. We compared the diabetic youths' HRQoL with the age-matched non-diabetic peers using generic instrument. We found the predictors of the generic and disease-specific HRQoL.

5.1. Physical fitness

Diabetic patients of both sexes produced substantially poorer physical fitness levels in several tests than their non-diabetic peers. Female gender, increasing age, higher skinfold thickness, lower physical activity level and poor metabolic control were significant independent predictors of lower VO_{2max} as a measure of cardiorespiratory fitness. Furthermore, out of the Eurofit tests, anthropometric and physical activity parameters used, VO_{2max} influenced independently the metabolic control.

Few previous studies addressed assessment of physical fitness in children with T1DM. These studies investigated cardiorespiratory fitness comparing results with non-diabetic children. Except for one study, in which prepubertal boys were investigated (167), all investigations observed reduced cardiorespiratory fitness in children and adolescents with diabetes (84, 85, 87, 168). To our knowledge, this is the first trial, in which parallel assessments of motor performances, and cardiorespiratory function were carried out in youths with T1DM by the use of Eurofit test battery. These tests are standardized and widely used methods to estimate complex physical fitness of children and adolescents. According to the present results, all diabetic groups had impaired speed and coordination of upper limb movement and abdominal

muscle strength. In addition, all girls with diabetes had less upper body strength and maximal oxygen uptake; furthermore, younger diabetic girls had poorer running speed as well. Moreover, all boys with diabetes had poor general flexibility and younger diabetic boys had poor static strength of hand and forearm and older diabetic boys showed less upper body strength and lower maximal oxygen uptake. In a previous study, diabetic children had lower achievement in body balance, long jump and handgrip tests; however this study did not investigate cardiorespiratory fitness (86). In another study, pre-pubertal diabetic boys had normal cardiorespiratory fitness (167) similarly to the present study where younger diabetic boys also had no impairment of this parameter.

The reason why diabetic youths showed impaired performances of various tests for physical fitness is not clear. It has been suggested that lower physical activity or physiological changes resulting from the diabetes pathology itself could result in reduced fitness in children (85, 87). In the present study, physical activity level and skinfold thickness also influenced cardiorespiratory performance in healthy and diabetic subjects. Nevertheless, the diabetic groups did not differ from the control groups regarding body composition and physical activity level. Despite these facts, it is conceivable that diabetic youths, due to the fear of hypoglycaemia as a consequence of exercise, participate less intensively in sport activities, have less daily physical activity, and may have less skill to perform such tests than non-diabetic peers. However this concept should be assessed prospectively in the future.

Another assumption is that metabolic control influences the fitness of diabetic patients. Previous studies showed that poor metabolic control is associated with poor cardiorespiratory fitness in children with diabetes (84, 87, 88). In our study, HbA_{1c} was independent predictor of VO_{2max}. Interestingly, the VO_{2max} was the only predictive parameter for metabolic control and the other tests representing motor performances had no effect. This finding emphasizes the importance of physical fitness in the care of diabetes and suggests that improvement in physical condition may contribute to better diabetes control which in turn leads to further improvement in physical performance. Our finding of VO_{2max} being the only predictive parameter for HbA_{1c} also suggest the importance of aerobic exercise in achieving and maintaining good glycemic control. Although, children and adolescents need all types of movements for improving different physical abilities and strengthen muscle groups, but the glycemic control seems to be influenced primarily by the aerobic exercise. This underlines the importance of the aerobic exercise in the treatment and care of type 1 diabetes in childhood.

Further possibility is that early subclinical complications of diabetes may contribute to reduced physical fitness achievements. Early complications can be present in children with diabetes and in a previous trial cardiovascular autonomic dysfunction interfered with exercise testing results (169). Subtle microangiopathic vascular lesions and peripheral nerve dysfunction may lead to disturbed muscle innervations and some impairment in motor performances. However, in the present study patients with early complications were not involved. In order to investigate whether very early microvascular or neuropathic alterations may contribute to the impairment of motor or cardiorespiratory performances further studies are necessary.

Both motor performances and cardiorespiratory fitness can be impaired in youths with T1DM. Independent relationship exists between metabolic control and cardiorespiratory fitness underlying the importance of life style interventions in the complex treatment and care of childhood diabetes. Regular and parallel assessments of motor and cardiorespiratory functions by the Eurofit battery tests may help to identify the individual needs of special exercise activities which contribute to better physical condition and metabolic control of children and adolescents with T1DM. However, further studies are necessary to explain the mechanisms by which diabetes leads to reduced fitness and to examine the effect of lifestyle intervention on the feasibility of improving cardiovascular fitness.

5.2. Cultural adaptation of PedsQL 3.0 Diabetes Module

The PedsQL 3.0 DM designed for children and adolescents has been translated into Hungarian and accepted by the Mapi Research Institute. We fulfilled the requirements of the validation process for both CSR and PPR. Based on the results of the psychometric evaluation, it was confirmed that the Hungarian versions of the PedsQL 3.0 DM are generally comparably feasible, reliable and valid. There were hardly any unanswered items on the DM. Both patients and parents were able to complete the questionnaires and provide sufficient data regarding the child's HRQoL. The instrument has excellent internal consistency reliability. We demonstrated the test-retest reliability of the questionnaires that was missing in the original scales. We found great agreement between the children's and the parents' answers. The PedsQL 3.0 DM was able to differentiate between HRQoL of optimal, suboptimal and high risk metabolic control in the young patients. This result is underpinned by the answers of the parents. Good metabolic control is important primarily to avoid complications; furthermore, favourable metabolic control may be associated with good perception of

HRQoL. The diabetic participants and their parents completed the PedsQL GCS and the DM on the same occasion, beginning with the GCS. The DM subscales and the GCS total scale correlated well, except for the Worry subscale, both in CSR and PPR. The intercorrelations were from medium to large effect size that confirmed the concurrent validity of the instrument. The worry about the short- and long-term complications and the worry about the treatment efficacy are special characteristics of the diabetes disease, which explains why this subscale does not match the generic total score.

The main strength of this validation process is that we have measured the psychometric properties of the PedsQL 3.0 DM with a wide range of methods and statistical analyses. The potential limitation is that we have examined the questionnaires designed for children and adolescents, but did not measure the psychometric properties of the questionnaires for toddlers (aged 2-4) and young children (aged 5-7). The nationally adapted versions of PedsQL 3.0 DM designed for children and adolescents are reliable and valid instrument for assessing HRQoL of children and adolescents with T1DM.

5.3. Health-related quality of life of children and adolescents with type 1 diabetes mellitus

Most researchers known to us employed generic HRQoL questionnaire in their studies that are less sensitive to the impact of specific diseases than are disease-specific questionnaires.

To our knowledge this is the first study that evaluated the effect of cardiorespiratory fitness parallelly with the diabetes-related clinical and anthropometric parameters on the youths' diabetes-specific quality of life from both children and parents' perspective.

Both our diabetic and non-diabetic female groups reported significantly poorer HRQoL perception than males. Multiple studies have shown these gender differences not only in healthy population (113, 170), but in chronic diseases as well (171-173) including diabetes (108, 109). These differences are rather due to perception of health than the actual health status as there were no significant differences in clinical parameters in our patients.

We found that parents underestimated their diabetic children's HRQoL. This parental underestimation is known from the literature (108, 109, 174), and our survey confirms these findings on the basis of both DM and GCS. We did not find this underestimation in the healthy youths. It raises the assumption that the parents may overprotect their diabetic children.

The diabetic patients cope with the treatment adherence very well and have no communication problems, but the presence of the diabetes symptoms and the worry about the short-term and long-term consequences of the disease has negative impact on their quality of life. The long-term parental fear may limit the diabetic child's self-esteem and build panic issues in children as well (175). Hypoglycaemia episodes have the greatest negative influence in the diabetic youths' HRQoL.

It is generally agreed that to achieve optimal glycemic control patients should be treated with intensive insulin therapy either with CSII or MDI. It is not clear if one of these two treatments is superior to the other in clinical practice. In our study, there was no considerable difference in HbA_{1c} between the two investigated groups suggesting that the method of the intensive therapy had no effect on metabolic control. We had no comparison data from the literature regarding the maximal oxygen consumption between the CSII and MDI groups. Studies examining the physical fitness in patients with T1DM did not distinguish between the methods of intensive insulin therapy. Our result is unique in this field; the physical fitness level of the patients is independent from the method of the intensive therapy. However, patients treated with insulin pump therapy had better HRQoL than those treated with MDI. This result was confirmed by the parents' answers. Recently, SEARCH for Diabetes in Youth Study from the United States had similar result using the PedsQL GCS (110). Both the child self-report and the parent proxy-report indicated significantly more stable emotional and physical functioning due to flexibility of the use of insulin pump. Youths with CSII therapy reported better school achievement, although this was not confirmed by the parents' answer, and less diabetes-related somatic problems. Youths with CSII therapy and their caregivers worry less about the efficiency of the medical treatment, the short and long-term complications.

Two dominant variables were observed that explained the favourable generic and diabetes-specific quality of life, the higher level of maximal oxygen uptake and CSII therapy. The HbA_{1c} was no predictive factor of the HRQoL and the CSII therapy did not predict the better HbA_{1c} level. Although CSII therapy had no effect on metabolic control and cardiorespiratory fitness, this type of treatment influenced the HRQoL positively which is a remarkable finding. This could be due to greater emotional balance and less fear of diabetes related symptoms. The main goal in diabetes management is to achieve good metabolic control and improve the young patients' quality of life. CSII therapy seems to be more effective way to make the

young patient feel better mainly to give psychological stability and disburden diabetes-related anxiety.

When we measured the diabetic youths' HRQoL with the GCS we found great similarity to their age-matched peers. Physical and psychosocial factors did not indicate differences between the diabetic and control youths, indicating that patients live similar lives as their non-diabetic peers. This may be due to the appropriate care of diabetes including proper continuous patient and parent education in Hungary.

6. CONCLUSION AND CLINICAL IMPLICATIONS

- Both motor performances and cardiorespiratory fitness can be impaired in type 1 diabetes youths without differences in body composition. Independent relationship exists between metabolic control and cardiorespiratory fitness underlying the importance of life style interventions in the complex treatment and care of childhood diabetes. Regular and parallel assessments of motor and cardiorespiratory functions by the Eurofit tests may help to identify the individual needs of special exercise activities which contribute to better physical condition and metabolic control of children and adolescents with T1DM.
- The nationally adapted versions of PedsQL 3.0 DM designed for children and adolescents are reliable and valid instruments for assessing HRQoL of children and adolescents with T1DM. This is the only validated instrument in Hungary that can be applied for HRQoL assessments of Hungarian diabetic youths with age range 8-18.
- HRQoL is similar in type 1 diabetic and non-diabetic children and adolescents. With proper care and diabetes management diabetic youths can live as happy and productive lives as their non-diabetic peers. We assume that the diabetes care and management in Hungary is satisfactory.
- Both diabetic and healthy boys have better HRQoL than girls. These differences are rather due to perception of health than the actual health status or due to biological and psychological differences between the genders.
- Parents underestimate HRQoL of their diabetic children, but this is not the case in healthy population that may suggest parents overprotect their chronically ill children.
- Diabetic youths' quality of life is especially influenced by the presence of diabetes somatic symptoms and the worry about the improper medical treatment, long-term complications and hypoglycaemic episodes.
- Diabetic youths treated with CSII therapy have better HRQoL than those treated with MDI. It may be due to the better physical and emotional functioning and less fear of improper medical treatment, long-term complications and hypoglycaemic episodes. The physical fitness level and the metabolic control of the patients seem to be independent from the method of the intensive therapy.

- Good physical fitness has an important role in achieving better metabolic control and health-related quality of life which underlines the importance of the regular aerobic exercise in the treatment and care of type 1 diabetes in childhood.

7. SUMMARY AND KEYWORDS

Type 1 diabetes mellitus is one of the commonest chronic diseases in childhood affecting more and more children worldwide. In the routine care of diabetes, mainly the clinical parameters are controlled and little attention is paid to the physical fitness status and quality of life assessment.

In our research work we evaluated the physical fitness (both motor performances and cardiorespiratory fitness), anthropometric characteristics and health-related quality of life in children and adolescents with type 1 diabetes mellitus and compared with non-diabetic age-matched control subjects. To be able to use a genuinely validated age- and disease specific health-related quality of life questionnaire in Hungary we carried out the linguistic validation and measured the psychometric properties in Hungarian type 1 diabetic pediatric population. The results demonstrated the feasibility, reliability and validity of the nationally adapted instrument for assessing health-related quality of life of children and adolescents with type 1 diabetes mellitus.

There were no differences between the diabetic and non-diabetic participants in anthropometric characteristics and physical activity, but the motor performances and the cardiorespiratory fitness were reduced in diabetic patients. Independent relationship existed between the metabolic control and cardiorespiratory fitness underlying the importance of life style interventions in the complex treatment and care of childhood diabetes. The health-related quality of life of diabetic youths was similar to the age-matched controls. The parents underestimated their diabetic child's health-related quality of life that was not the case in non-diabetic subjects. Both diabetic and non-diabetic boys had better health-related quality of life perception than girls. The presence of diabetes symptoms and the worry about the treatment efficacy, hypoglycemia and long-term complications adversely influenced the health-related quality of life of diabetic boys and girls. The better cardiorespiratory fitness and the insulin pump therapy are explaining factors of the favourable health-related quality of life on the basis of both generic and disease-specific modules.

This research work gave evidence that good physical fitness had an important role in achieving better metabolic control and health-related quality of life which underlined the importance of the regular aerobic exercise in the treatment and care of type 1 diabetes in

childhood. Clinicians should encourage their young patients to exercise regularly – especially to do aerobic sport – for its clinical and quality of life benefits.

Keywords: type 1 diabetes mellitus, health-related quality of life, physical fitness, glycemic control, children, adolescents

SUMMARY IN HUNGARIAN

A rutin diabetes gondozás során az egészségügyi szakemberek elsősorban a klinikai paramétereket ellenőrzik és kevésbé fordítanak figyelmet a fizikai képességek és az egészséggel összefüggő életminőség vizsgálatára.

Kutatómunkánk során megvizsgáltuk az 1-es típusú diabeteses gyermekek és serdülők fizikai fittségét (motoros képességeket és a kardiorespiratórikus állóképességet egyaránt), antropometriai jellemzőiket és az egészséggel összefüggő életminőségüket, valamint összehasonlítottuk eredményeiket azonos korú kontroll csoportokkal. Az angol nyelven validált kor- és betegség-specifikus egészséggel összefüggő életminőséget vizsgáló kérdőívet magyarországi használatra validáltuk. Elvégeztük a kérdőív lingvisztikai validálását és megnéztük pszichometriai tulajdonságait 1-es típusú diabeteses magyar gyermekközösségben. Az eredmények a kérdőív használhatóságát, megbízhatóságát és érvényességét támasztották alá az 1-es típusú diabeteses gyermekek és serdülők életminőség-méréséhez.

A diabeteses és a kontroll résztvevők antropometriai jellemzői és fizikai aktivitásuk között nem találtunk lényeges különbséget, de a diabeteses betegek motoros képességei és a kardiorespiratórikus fittségük gyengébb volt. Összefüggést fedeztünk fel a metabolikus kontroll és a kardiorespiratórikus fittség között, ami kiemeli az életformaváltás jelentőségét a gyermekkori diabetes komplex kezelésében és gondozásában. A gondozottak életminősége hasonló volt nem diabeteses kortársaikéhoz. A szülők kedvezőtlenebbnek ítélték meg diabeteses gyermekük életminőségét, mint maguk a gyermekek. Ezt a kontroll csoport esetén nem tapasztaltuk. A diabeteses és a kontroll fiúknak is jobb volt az életminőség-érzésük a lányokénál. A diabetes tünetek megléte és az aggódás a kezelés hatékonysága, a hypoglikémia és a késői szövődmények miatt hátrányosan befolyásolta a diabeteses fiatalok életminőségét. A jobb kardiorespiratórikus fittség és az inzulin pumpa terápia szignifikáns magyarázó tényezője volt a kedvezőbb életminőségnek az általános és a betegség-specifikus kérdőív alapján is.

Kutatómunkánk rávilágított, hogy a jó kardiorespiratórikus fittség fontos szerepet játszik a kedvezőbb metabolikus kontroll és az egészséggel összefüggő életminőség elérésében, ami kiemeli a rendszeres aerob mozgás fontosságát az 1-es típusú gyermekkori diabetes kezelésében és gondozásában. A klinikusoknak ösztönözni kell fiatal betegeiket a rendszeres

testmozgásra – legfőképpen aerob sportolásra – a klinikai és az életminőségre gyakorolt előnyei miatt.

Kulcsszavak: 1-es típusú diabetes mellitus, egészséggel összefüggő életminőség, fizikai fittség, glikémia kontroll, gyermekek, serdülők

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10. PUBLICATIONS

List of publications related to the dissertation

1. **Lukács, A.**, Varga, B., Kiss-Tóth, E., Soós, A., Barkai, L.: Factors influencing the diabetes-specific health-related quality of life in children and adolescents with type 1 diabetes mellitus.
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The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenezy Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

17 April, 2013

DEBRECENI EGYETEM KENÉZY ÉLETTUDOMÁNYI KÖNYVTÁRA EGYETEMI ÉS NEMZETI KÖNYVTÁR

10. ANNEX

8-12 éves GYERMEKEK ÖNÉRTÉKELÉSE

8-12 éves GYERMEKEK SZÜLŐI ÉRTÉKELÉSE

13-18 éves SERDÜLŐK ÖNÉRTÉKELÉSE

13-18 éves SERDÜLŐK SZÜLŐI ÉRTÉKELÉSE

GYERMEKEK FIZIKAI AKTIVITÁSÁT VIZSGÁLÓ KÉRDŐÍV

SERDÜLŐK FIZIKAI AKTIVITÁSÁT VIZSGÁLÓ KÉRDŐÍV