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Physical and psychosocial health in pediatric uveitis patients

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ABSTRACT

Background: To investigate the possible associations between childhood noninfectious uveitis and cardio-respiratory fitness, physical activity, health related quality of life and fatigue.
Methods: Cross-sectional analysis of 23 patients with noninfectious uveitis, aged 8–18 years. BMI, exercise capacity, muscle strength and physical activity were measured. Health-related quality of life and fatigue were assessed. The results were compared to standardized values for age matched healthy children.
Results: Twenty-three patients were included. Children with uveitis had a higher bodyweight and body mass index. Children with uveitis had lower cardio-respiratory fitness and they were less physically active, but they experienced a normal quality of life and normal fatigue. Parents of children with uveitis reported a lower quality of life and more fatigue for their children than parents of healthy children.
Conclusion: Our study indicates that children with noninfectious uveitis are at risk of developing lower physical and psychosocial health.

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Childhood uveitis; lower aerobic exercise capacity; reduced muscle strength; decreased physical activity; lower - parent reported - health related quality of life; more - parent reported – fatigue

Background

Uveitis is an inflammatory disorder of the eye, involving the uveal tract. In the western world the prevalence of pediatric uveitis is 30/100,000 and children account for 5–10% of the total uveitis population.[1] Uveitis may be caused by an infection, may be associated with a systemic auto-immune disease or may occur as an isolated auto-immune reaction without a known underlying cause.[2] In the developed countries, 87– 89% of the pediatric uveitis cases are noninfectious and the majority (41.5%) is related to juvenile idiopathic arthritis (JIA).[1,3]

Patients with auto-immune diseases are more physically inactive compared to the general population.[4] Also, aerobic fitness in children with different types of chronic conditions is reduced and they report more fatigue.[5–7] In juvenile idiopathic arthritis (JIA), children are also found to be less physically active and have reduced physical fitness levels[8] which does not restore after remission has been reached.[9,10] The causes of these persistent impairments of physical fitness and physical activity are not known, but it has been suggested that a combination of disease-related factors, treatment (e.g., medication) and deconditioning could be involved.[5,11,12]

The pathophysiology of noninfectious uveitis has not exactly been revealed.[13] It is not clear whether the inflammation in uveitis is really limited to the eye or may extend itself systemically.[14–17] A number of biomarkers have been identified in JIA-uveitis[18–20] and in auto-immune uveitis.[13] Also, in both idiopathic and JIA-uveitis a number of genetic predispositions have been found.[13,21]

Systemic treatment in children with idiopathic uveitis who do not respond sufficiently to topical therapy is comparable to that used in JIA. The first line of treatment in pediatric uveitis are local corticosteroids. If local corticosteroids are insufficient, a switch toward steroid sparing immunosuppressive therapy will be made in most cases. Systemic prednisone is started in case of severe uveitis and is given peri-operatively in case of intraocular surgery.

Because systemic inflammation can contribute to atherosclerosis,[22–24] there is concern that children with inflammatory disease are at higher risk for cardiovascular diseases. In addition to the inflammation itself, systemic corticosteroids have a negative impact on the cardiovascular risk profile. Well-known side effects are increased bodyweight, hypertension, and accelerated atherosclerosis.[25]

In the literature, information on the physical and psychosocial health of children with uveitis is scarce.[26–28] A recent study on the quality of life (QoL) in children with JIA showed that children with uveitis had poorer vision-related QoL and function when compared to those without uveitis.[29] Also, in

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Abbreviations: AGD = age and gender dependent; AqH = aqueous humor; BMI = body mass index; CHAQ = child Health assessment questionnaire; CO_2 = carbon dioxide; DI = disability index; FA = fluorescein angiography; HHD = hand-held dynamometry; HRmax = peak heart rate; HR-QoL = health related quality of life; JIA = juvenile idiopathic arthritis; Kg = kilogram; LogMAR = logarithm of the minimum angle of resolution; LPA = light physical activity; MRC = Medical research council; MTX = methotrexate; MVPA = moderate-to-vigorous physical activity; PA = physical activity; PedsQL = pediatric quality of life inventatory; PGA = physician global assessment; QoL = quality of life; SD = standard deviation; SPSS = statistical package for the social sciences; UMCG = university medical center of Groningen; VO_2peak = peak oxygen consumption; W_{peak} = peak work rate adolescents with noninfectious uveitis despite quiescence of disease and good visual function, certain factors, such as a high number of recurrences, chronicity of the uveitis and fear of blindness were correlated with a decreased health-related (HR)-QoL.[30,31]

In our clinical experience, fatigue is often reported by children with uveitis or by their parents. In adults, fatigue has been shown to be a barrier for being physically active.[32] Fatigue is highly present in patients with JIA and is related to many factors including physical activity, physical fitness and HR-QoL of which cause and effect are not exactly known.[33] Therefore, uveitis may have a large impact on a child's life and can alter their QoL.[26,27,30,34]

To optimize treatment for children with uveitis it is of great importance to get insight in risk factors that have a negative impact on physical and psychosocial health. Regarding the possible negative effects of uveitis, we therefore studied levels of cardio-respiratory fitness, physical activity, muscle strength, HR-QoL and fatigue in pediatric noninfectious uveitis patients.

Patients and methods

The Medical Ethical Committee of the University Medical Center of Groningen (UMCG) approved the study. Patients were included from the departments of pediatric rheumatology and ophthalmology of the UMCG (the Netherlands) from July till December 2014. Patients aged 8–18 years, known with idiopathic or JIA-associated uveitis were eligible for this study. Patients with infectious uveitis were not included. Patients with co-morbidities, not related to the uveitis, that could influence the outcome of the exercise test, like pulmonary or cardiac diseases, were excluded from the study. All investigations were carried out on the same day following the regular visit. Informed consent was obtained from the parents and from the child if the child was ≥ 12 years old.

Patient characteristics

Information regarding patient characteristics (gender, age), disease characteristics (location of the uveitis, etiology, time since diagnosis, disease status), current treatment (medication, dose, route of administration), complications, and surgery was retrospectively gathered by consulting the medical charts of the patients. Median duration of active disease was recorded. Active disease was defined as observed cells in the anterior chamber or in the vitreous.[35] The diagnosis of posterior and panuveitis was made by fundoscopy and in some cases fluorescein angiography (FA) was performed.

Disease control was defined as an observable inactive disease in the affected eye for longer than 3 months without the use of systemic corticosteroids or local steroid injections (subtenon or subconjunctival).[35] During this period, local steroid medication such as eye drops or ointment were allowed in a maintenance dosage of maximum of 4 times a day.

Patients were examined by an ophthalmologist to determine the activity of the uveitis. The visual acuity was measured with a Snellen chart and was converted to LogMAR-acuity for calculation and statistical purposes.[35,36] Visual field examination to assess the amount of glaucomatous damage, due to increased intraocular pressure, was only performed if the age of the child permitted perimetry. Unfortunately, because of the young age of our patients, measurement of optic disc cupping-changes and perimetry were not routinely performed. Blindness was defined as a visual acuity less than 0.01 (or LogMAR > 1.3) or a visual field ≤ 10º.[37] Visual impairment was defined as a visual acuity ≥ 0.05 (LogMAR ≤ 1.30) and < 0.3 (LogMAR > 0.50).[37]

Disease activity of JIA was scored on a 0–10 Physician Global Assessment (PGA) scale by a pediatric rheumatologist. Height and bodyweight were measured and body mass index (BMI = bodyweight(kg)/height^2 (m)) was calculated. These measurements were compared with the reference values of Dutch children.[38] Overweight was defined as ≥ 1SD above the mean reference BMI and obesity as >2SD above the mean reference BMI.[39]

Physical fitness

Physical fitness was assessed by measuring exercise capacity and muscle strength. Exercise capacity was measured with a cardiopulmonary exercise test using an electronically braked cycle ergometer, and was expressed by peak oxygen consumption (VO_{2peak}) and peak work rate (W_{peak}). We used a ramp version of the Godfrey protocol[40] in which the work rate increased gradually over time with 10, 15 or 20 Watt/min depending on the body height of the patient, as described by Bongers et al.[41] All patients were verbally encouraged to cycle until exhaustion. Maximal exertion was defined as a heart rate of > 180 beats per minute and a respiratory exchange ratio of more than 1.0.[41] The absolute values obtained during the test were compared with the reference values of healthy Dutch children.[41] VO_{2peak} - and W_{peak} per kg bodyweight were calculated and these relative values were also compared with the reference values.[41]

General muscle function was assessed by manual muscle testing using the scale of the Medical Research Council (MRC). This scale ranges from 0 till 5, in which 0 means no muscle contraction and 5 means normal muscle power.[42] Isometric muscle strength of four muscle groups was assessed bilaterally by hand-held dynamometry (HHD): the biceps, triceps, iliopsoas, and quadriceps muscles. The assessed values were converted to a total z-score of the four muscle groups and compared with the reference values of healthy children.[43]

Physical activity

Physical activity (PA) was subsequently measured by an accelerometer (Actical, Philips respironics). The accelerometer was given on the day of the regular visit and research measurements. The Actical measures accelerations in any plane of movement which are translated into activity counts as a reflection of physical activity. Counts were summed in 1-minute periods. Cutoff points were used to categorize activities as sedentary, light physical activity (LPA), and moderate-to-vigorous physical activity (MVPA).[44] Patients were instructed to wear the accelerometer during 7 days, for all hours except during sleep and wet-activities (showering, swimming). Patients were also asked to record their physical activities in a diary during the same 7 days as they were wearing the accelerometer. In the diary, patients scored their dominant activity of each 15 minute period of every 24 hours of the day The parents were allowed to help the child with filling out the diary.[45] Patients were asked to register in the diary at which moment they put the accelerometer on and off. Because non-wearing time of the accelerometer can be mistakenly categorized into sedentary activity, we corrected non-wearing time with the information provided in the activity diary. Patients were included in the analysis if they had minimally 4 valid days of wearing the accelerometer. A valid day was defined as a wearing time of minimally 8 hours on a weekday or minimally 6 hours on a weekend day. Measurements were validated if there was concordance between the measurements of the accelerometer and diary. Mean daily counts were determined by the sum of the total daily counts divided by the number of valid days. The mean amount of time spent in the four different categories of physical activity per day was compared to the values of healthy Canadian youth.[46]

Functional ability

Functional ability was assessed by using the Child Health Assessment Questionnaire (CHAQ38). Functional ability was expressed in the disability index (DI) which was calculated as the mean of the maximum scores of all domains. A higher score suggests more disability (range 0– 3). The DI of the patients was compared to the DI of healthy Dutch children.[47,48]

Health related quality of life

Health related quality of life (HR-QoL) was evaluated with the Pediatric Quality of Life Inventatory (PedsQL 4.0). The PedsQL measures HR-QoL in four domains: physical, emotional, social and school functioning.[49] The questionnaire consists of a child self-report and a parent proxy report part and was completed by the child and the parent. A higher score (range 0–100) represents a higher quality of life. The scores of the patients were compared to the scores of healthy children.[49,50]

Fatigue

The level of fatigue in the patients was measured by the PedsQL Multidimensional Fatigue Scale, which measured fatigue in three domains: general fatigue, sleep/rest fatigue and cognitive fatigue.[50] The questionnaire consists of a child self-report and a parent proxy report part and was completed by the child and the parent. A higher score (range 0–100) indicates less fatigue. The scores of the patients were compared to the scores of healthy children.[49,51]

Statistical analysis

Statistical analyses were performed by using SPSS software (version 22). Descriptive statistics were used to present mean and standard deviation (SD) or median and range if data were abnormally distributed. The variables of the children were compared to the reference values of healthy children. Z-scores were calculated for age and gender dependent outcome measures as length, weight, BMI, peak oxygen consumption, peak work rate, and muscle strength. A z-score represents the amount of standard deviations the value differs from the age and gender specific reference value. A z-score above 0 means that the value measured in the study group is higher than in the reference group. A z-score below 0 is the other way around. The one sample t-test was used to compare the normally distributed outcomes of the patients with healthy controls, in case of abnormal distribution of the outcome parameters the one-sample Wilcoxon Signed Rank Test was used. To examine the possible relations between the outcome measurements, we analyzed which measurements were correlated to VO_{2peak}, muscle strength, and quality of life. In all analyses a $P < .05$ was considered statistically significant.

Results

Forty-two patients were eligible for the study, 24 of whom (57.1%) were willing to participate (Figure 1). One patient was excluded because of pulmonary comorbidities. Thirteen patients (56.5%) had idiopathic uveitis and the other 10

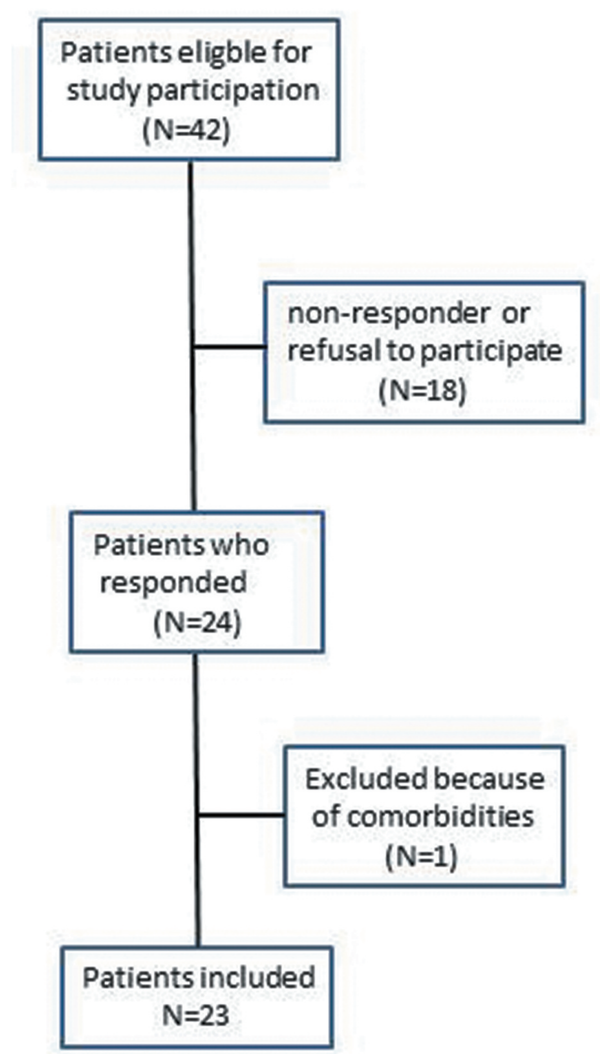

Figure 1. Patient selection.

patients (43.5%) had JIA-associated uveitis. Patients with JIA had no clinically important systemic disease activity at the time of study participation (median PGA 0.0, range 0.0– 0.5).

At the time of study participation 20 patients (87.0%) had disease control on medication with regard to their uveitis. Three patients, 2 with JIA-uveitis and 1 with idiopathic uveitis, had mild uveitis activity. Eighteen patients (78.6%) used eye drops, 8 of these used steroid eye drops, one patient used anti-glaucoma medication and 9 patients used a combination of steroid eye drops and anti-glaucoma medication (Table 1) . Fourteen (60.9%) patients used systemic medication, 7 of whom used methotrexate (MTX), 6 were treated with a combination of adalimumab and MTX and 1 patient used 5 mg systemic corticosteroids daily next to MTX (Table 1). The majority (n = 20) of the patients were treated with systemic corticosteroids in the past. On average, these patients were treated with > 0.5 mg/kg systemic corticosteroids for 16.3 (range 0– 77) weeks. At the moment of investigation high dose corticosteroids (> 0.5/mg/kg) were ceased for a median of 243.3 (range 0– 464) weeks.

In total 8 patients developed visual loss. Three patients experienced visual loss due to the uveitis, two of whom (8.7%) had unilateral visual impairment and one (4.3%) unilateral blindness. Visual field loss due to glaucomatous optic nerve damage caused by elevated intraocular pressure was found in 7 patients, 2 of whom had already lost visual acuity. Because of the complications, 9 patients (39.1% of total study population) had undergone surgery; seven of whom (30.4% of total study population) had needed re-surgery (Table 2).

Mean weight and body mass index of the patients were statistically significantly higher when compared to the reference population (Table 1, Figure 2). Nine patients had higher BMI than the reference population, three of whom (13.0%) were obese and six were (26.1%) overweight. Patients with JIA-associated uveitis had a significantly higher BMI z-score than patients with idiopathic uveitis (z-score 1.26 vs 0.22, p =.02).

At the cardiopulmonary exercise test, patients reached a mean peak heart rate (HR_{max}) of 191 (±11) beats per minute. At maximal exertion, four patients did not reach a heart rate of > 180 beats per minute, but all patients reached a respiratory exchange ratio of more than 1.0,

Table 1. Patient characteristics and outcome measurements compared to reference values.

	Number (%)	Mean (±SD)/Median (range)	Reference value	Z-score	Sig.
Age (yrs)		12.7 (± 2.7)			
Female	13/23 (56.5%)				
Anthropometrics					
Height (cm)		156.7 (± 17.5)	*AGD*[23]	−0.19	p = .46
Weight (kg)		50.3 (± 17.7)	*AGD*[23]	0.58	**p = .02**
BMI		19.9 (± 4.0)	*AGD*[23]	0.67	**p = .02**
Underlying systemic disease					
juvenile idiopathic arthritis (JIA)	10				
PGA JIA activity	0 (0–10)				
Uveitis[a]					
Idiopathic	13/23 (56.5%)				
Time since diagnosis (yrs)		5.88 (1.28– 12.71)			
Remission duration (yrs)[b]		2.09 (0.17– 8.35)			
Duration of active disease (yrs)		3.19 (0.55– 11.91)			
Active disease (uveitis)	3 (13%)				
Local medication	18				
Steroids	8 (44.4%)				
Anti-glaucoma	1 (5.6%)				
Steroids and anti-glaucoma combined[c]	9 (50%)				
Systemic medication	14				
MTX[d]	7 (50%)				
Biological (adalimumab)	1 (7.1%)				
MTX and adalimumab combined	6 (42.9%)				
Duration of systemic medication (mos)		54.4 (1.8– 112.4)			
Physical fitness					
VO_{2peak} (l/min)		2.1 (± 0.84)	*AGD*[44]	−0.40	p = .11
VO_{2peak}/kg (l/min/kg)		41.3 (± 8.1)	*AGD*[44]	−0.47	p = .07
W_{peak} (Watt)		163 (± 65.5)	*AGD*[44]	−0.49	**p = .04**
W_{peak}/kg (Watt/kg)		3.3 (± 0.6)	*AGD*[44]	−0.40	**p = .05**
HDD (Newton)		200.3 (± 68.2)	*AGD*[46]	−0.58	***p* = .001**
Questionnaires					
Functional ability		0.22 (0– 1.44)	0.20[51]		p = .15
HR-QoL Child		84.2 (± 10.0)	83.91[50,51]		p = .76
HR-QoL Parent		77.0 (± 11.7)	82.29		**p = .04**
Fatigue Child		82.9 (± 12.1)	80.49[52]		p = .25
Fatigue Parent		72.0 (± 18.0)	89.63		***p* < .001**
Physical activity (N = 21)[e]					
Light physical activity (min)		182 (± 75)	256[49]		**p < .001**
MVPA (min)		36 (± 16)	54[49]		**p < .001**

SD = standard deviation, *AGD* = age and gender dependent, yrs = years, mos = months, min = minutes, BMI = body mass index, PGA = physician global assessment, MTX = methotrexate, VO_{2peak} = oxygen consumption at peak exercise, VO_{2peak}/kg = peak oxygen consumption per kg bodyweight, W_{peak} = peak work rate, W_{peak}/kg = peak work rate per kg bodyweight, HHD = hand held dynamometry, MVPA = moderate-to-vigorous physical activity, HR-QoL = health related quality of life. [a] See Table 2 for further specifications. [b] Remission on medication. [c] In 1 patient mydriatic eye drops were used as treatment next to steroid and anti-glaucoma eye drops. [d] One patient used low dose (5 mg) systemic corticosteroids next to MTX. [e] In 2 patients the measurement of physical activity was invalid.

meaning that the exercise is intense because carbon dioxide (CO_2) production by the working muscles becomes greater and more of the inhaled oxygen (O_2)gets used rather than being expelled. Median VO_{2peak} was comparable to VO_{2peak} of healthy children. Mean VO_{2peak} per kilogram bodyweight, median W_{peak}, and mean W_{peak} per kilogram bodyweight were all significantly lower than the reference value of healthy children ($p < .05$) (Table 1, Figure 2).

All patients had a normal general muscle power (MRC-scale 5). However, in comparison to healthy children of the same age maximal isometric muscle strength was significantly reduced in patients (p <.01).[43] There was no difference in physical fitness (VO_{2peak}, W_{peak}, and muscle strength) between patients with JIA-associated uveitis and patients with idiopathic uveitis.

Measurement of physical activity by the accelerometer was valid in 21 children (91.3%). Patients were physically active during 182 (light) and 36 minutes (moderate-to-vigorously) per day, respectively. This is significantly lower than in healthy Canadian children ($p < .001$) (Table 1).[30] There was no difference in the amount of moderate-to-vigorous physical activity (MVPA) between patients with JIA-associated uveitis and patients with idiopathic uveitis.

Parents indicated that their children had a lower quality of life compared to a reference group of parents of healthy children. Children themselves reported an equal HR-QoL compared to their healthy peers(Table 1). Children with uveitis did not experience more fatigue than healthy children, but their parents judged their children were more fatigued compared to parents of healthy children. Patient and parent scores on HR-QoL and fatigue did not differ between patients with JIA-associated and idiopathic uveitis.

The correlation-coefficient between VO_{2peak} and W_{peak} was 0.94 ($P = < 0.001$), VO_2peak was therefore used and interpreted as a measure for exercise capacity (Table 3). Muscle strength (HDD) was correlated with higher VO_2peak. Older age and higher BMI were correlated with higher muscle strength. Higher BMI was not correlated with previous corticosteroid use. Higher child reported HR-QoL was correlated with higher muscle strength and less fatigue. Higher disability was correlated with lower HR-QoL. Longer duration of active disease was correlated with lower HR-QoL reported by the parents about their child. Less fatigue was associated with a higher HR-QoL reported by the parents about their children. None of the outcome parameters correlated with the visual loss found in 8 patients.

Table 2. Ocular features.

	Number of patients (N = 23)	Percentage	Median	Range
Uveitis localization				
Anterior	15	65.2%		
Intermediate	4	17.4%		
Posterior	0	–		
Panuveitis	4	17.4%		
Bilateral disease	16	69.6%		
Visual acuity (LogMAR*)				
Worse eye			0.05	−0.08– 2.48
Better eye			0.00	−0.08– 0.22
Unilateral impairment**	2	8.7%		
Unilateral blindness**	1	4.3%		
Complications**	19	82.6%		
Cataract	13	56.5%		
Glaucoma	13	56.5%		
Posterior synechiae	10	43.5%		
Band keratopathy	5	21.7%		
Amblyopia	1	4.3%		
Surgery***	9	39.1%		
Cataract extraction	8	34.8%		
Baerveldt-implantation (anti-glaucoma treatment)	8	34.8%		
Re-surgery	7	30.4%		

LogMAR = Logarithm of the Minimum Angle of Resolution.
* A lower LogMAR visual acuity score corresponds to higher Snellen visual acuity and vice versa
** Visual impairment was defined as a visual acuity ≥ 0.05 (LogMAR ≤ 1.30) and < 0.3 (LogMAR > 0.50), blindness was defined as a visual acuity less than 0.01 (or LogMAR > 1.3) or a visual field ≤ 10º.[37]
*** Because some patients had more than one complication, surgery or medication, the cumulative percentages
can be different from the total percentages.

Discussion

Patients with uveitis have higher BMI compared to healthy children, they are at risk for reduced physical fitness levels as indicated by a lower aerobic exercise capacity and reduced muscle strength when compared to the healthy pediatric population. Also, children with uveitis are less physically active (PA), and their parents report a lower quality of life (HR-QoL) and more fatigue for their children when compared to parents of healthy children. In contrast, the children themselves report a normal HR-QoL and fatigue. The children with JIA-uveitis have a statistically significantly higher BMI than the children with idiopathic uveitis. No differences are found between JIA and idiopathic uveitis patients in physical fitness levels.

We found a significantly higher percentage of overweight (26%) and obese (14%) patients compared to the Dutch population, 13–15% and 2.2%, respectively.[38] In patients with JIA-uveitis BMI was significantly higher compared to non JIA uveitis. Corticosteroids are a well-known cause of weight gain,[12] however in our study only one patient used low dose (5 mg) systemic corticosteroids and most of the patients had not used systemic steroids for a median of 243.3 (range 0– 464) weeks . Also, no correlation was found between previous systemic corticosteroids and higher BMI. In JIA, contradictory results concerning obesity have been found and the cause has not been revealed yet.[53,54] A possible explanation is a more sedentary lifestyle which we also found in this study. There are indications that obesity in JIA can result in higher inflammatory markers and an increased risk of atherosclerosis.[11,12,52] It is reasonable to assume that this risk is comparable in patients with uveitis, so healthcare professionals and carers should be aware of weight gain in patients with uveitis.

Children with uveitis have lower aerobic exercise capacity levels than their healthy peers, but relatively well preserved levels when compared to children with other chronic conditions,[5,6] such as children with end stage renal disease, spina bifida, achondroplasia, acute lymphoblastic leukemia,

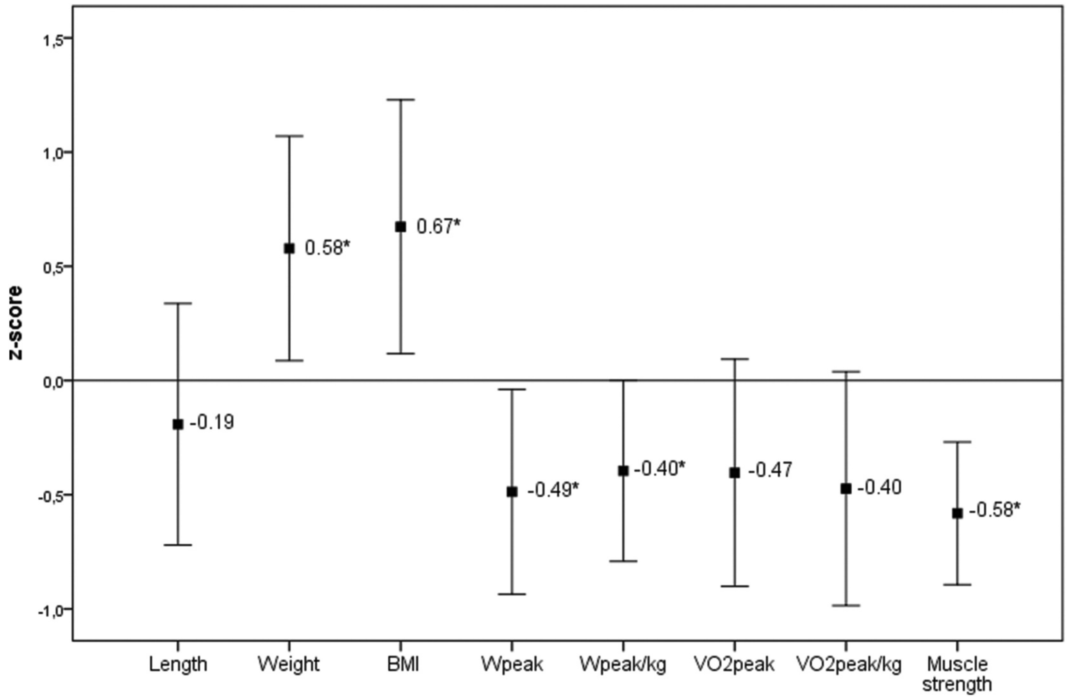

Figure 2. Z-scores. The z-score represents the amount of standard deviations the value differs from the age and gender specific reference value. Values are presented as mean with 95% confidence interval. Weight = weight for age, BMI = body mass index, Wpeak = peak work rate, Wpeak/kg = peak work rate per kg bodyweight, VO2peak = oxygen consumption at peak exercise, VO2peak/kg = oxygen consumption per kg bodyweight, Muscle strength = the sum of biceps, triceps, iliopsoas, and quadriceps muscles divided by eight as measured by hand-held dynamometry. * Significant at $p < .05$ (see Table 1)

osteogenesis imperfecta, cystic fibrosis and cerebral palsy.[5] When comparing the exercise capacity found in our study to the reported exercise capacity of children with JIA without uveitis in the literature,[5] the children in our study perform relatively well.

Interestingly, we found no differences in aerobic exercise capacity between JIA and idiopathic uveitis patients. The arthritis of the ten patients with JIA uveitis was in remission. It is known that the aerobic exercise capacity in patients with JIA does not restore after remission has been reached.[9] We assume that comparable underlying mechanisms could play a causative role in uveitis but their nature has not yet been revealed . The general assumption is that reduced levels of aerobic fitness are caused by a combination of disease-related pathophysiology, treatment (e.g., medication), hypo-activity, and deconditioning.[5,11,12]

Patients with uveitis have decreased muscle strength that is possibly caused by the same combination of mechanisms that are responsible for the reduced exercise capacity.

From the literature it is known that low exercise capacity, decreased muscle strength, the inflammation itself, circulating cytokines and the use of systemic corticosteroids are correlated with an increased risk of cardiovascular diseases.[11,12,55,56] In children with uveitis, these factors are present. Therefore, physicians should be alert and try to eliminate extra cardiovascular risk factors.

Our patients report 32 minutes of moderate-to-vigorous physical activity (MVPA) per day which is considerably less than the 60 minutes of daily MVPA as recommended by the WHO and the MVPA of the reference group.[46,57] Similar results have been found for adolescents with JIA.[8,9] Hypoactive children are often at greater risk of preventable health problems, such as obesity and cardio-metabolic diseases.[5,52] Cardiovascular health in children can be improved by sufficient physical activity (PA) and physical fitness,[58] whereas PA also has a beneficial effect on HR-QoL.[4] In several auto-immune diseases, PA has been shown to be safe, to improve HR-QoL and to reduce fatigue.[4]

The parents of our patients score a lower quality of life and higher levels of fatigue for their children than parents of healthy children, whereas the children themselves report outcomes comparable to those of their healthy peers on both questionnaires. This difference is probably due the proxy-problem, a known variation in patient and parent-report.[59] In the measurement of quality of life, parents tend to score a lower quality of life for their chronically ill children than the children themselves. This is possibly due to the differences in adaptation to a chronic disease in child and parent. Parents are possibly more aware of the health risks and have a broader perspective than children.[59,60] Also, it is likely that the parent- reported HR-QoL and fatigue are influenced by their frequent visits to the hospital and their efforts associated with the medical treatment of their child.

The positive correlations in our study between exercise capacity, muscle strength and BMI are not supported in the literature.[61] Also, the reported loss of HR-QoL[49,62] and increase in fatigue in children with overweight is not found in our results. We cannot explain these findings. Perhaps the significantly lower PA combined with adaptation in coping strategies by the children are responsible for these contradictory results. We did not investigate body composition, so we cannot comment on the influence of differences between

Table 3. Correlations.

	VO_2peak*		HDD*		HR-QoL child		HR-QoL parent	
	P	P	r	p	r	p	r	p
Gender	−0.15	0.51	−0.13	0.55	−0.25	0.25	−0.06	0.79
Age	0.37	0.09	0.51	**0.01**	0.40	0.06	0.30	0.17
Duration of active disease	−0.28	0.19	−0.12	0.59	−0.16	0.47	−0.63	**0.001**
systemic medication	−0.28	0.20	−0.05	0.81	−0.07	0.75	−0.21	0.33
Previous systemic CS	−0.20	0.37	0.17	0.43	−0.10	0.96	0.30	0.18
BMI*	0.30	0.17	0.69	**< 0.001**	0.38	0.08	−0.11	0.63
HDD*	0.53	**0.01**			0.55	**0.01**	0.19	0.38
VO2peak*			0.53	**0.01**	0.35	0.10	0.26	0.24
MVPA	0.05	0.85	−0.08	0.74	0.04	0.86	0.24	0.32
DI					−0.64	**0.001**	−0.10	0.64
HR-QoL child	0.35	0.10					0.06	0.78
HR-QoL parent	0.26	0.24			0.06	0.78		
Fatigue child	0.36	0.09	0.46	**0.03**	0.83	**< 0.001**	−0.21	0.34
Fatigue parent	0.33	0.12	0.21	0.33	−0.04	0.85	0.73	**< 0.001**

Values presented as Spearman correlation (P) or Pearson correlation (r) and statistical significance (p). * Z-scores. Abbreviations: CS = corticosteroids, BMI = body mass index, HDD = hand-held dynamometry measurements for muscle strength, VO_2peak = peak oxygen consumption (l/min), MVPA = moderate-to-vigorous physical activity, DI = disability index, HR-QoL = health related quality of life.

muscle and fat mass on measured BMI in relation the muscle strength and exercise capacity. The negative correlations between lower HR-QoL (reported by children) and loss of functional ability and between lower HR-QoL (reported by parents) and longer disease duration are in line with the literature.[48–51,63,64]

Limitations of the study

We performed this study as a pilot with a small number of patients. Next to that, the study-design is cross sectional, data was collected retrospectively and most patients had a long disease duration and had disease control for a relatively long time. Patients in other phases of the disease may have different results. A prospective case-control study with a group of healthy children from the same region as controls would have improved the power and interpretation of the results. Also, there is an unknown selection bias, because - for unknown reasons - not all eligible patients participated. Furthermore, visual field examination was not possible in all patients. Therefore, we could not investigate nor comment on the likely impact of visual field loss on the level of activity, functioning and HR-QoL. Measurements of physical activity by the accelerometer where verified by filling in a diary which is subject to interpretation and therefore a possible cause of bias.[65]

Conclusion

This pilot-study investigated the physical and psychosocial consequences of uveitis in childhood. We showed that patients with noninfectious uveitis are at risk of developing cardiovascular risk factors early in life. Children with uveitis have a higher BMI, lower cardio-respiratory fitness and are less physically active when compared to healthy peers. Furthermore, their parents report a lower quality of life and more fatigue for their children compared to the parents of healthy children. To optimize the treatment for children with uveitis, treatment should be aimed at improving the physical and psychosocial health and reducing cardiovascular risk factors in addition to maintaining and preserving vision. Therefore, clinicians should discuss the importance of sufficient levels of physical fitness and PA with patients and their parents during outpatient visits. Also, close monitoring of body weight should be performed and the prevention of overweight should be a treatment goal.

Authors contributions

WW and RB designed the study, recruited the patients, performed patients testing, performed statistical analysis and wrote the manuscript. LL designed the study and was major contributor in writing the manuscript. OL designed the study, performed patients testing and was major contributor in writing the manuscript. WA designed the study, performed patients testing and was major contributor in writing the manuscript. All authors have read the manuscript, have approved the paper and agree to it being submitted for publication. All authors meet the Uniform Requirements for Manuscripts Submitted to Biomedical Journals criteria for authorship.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent for publication

Written consent was collected from parents and patients to collect data including permission to publish the results.

Disclosure of potential conflicts of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The Medical Ethical Committee of the University Medical Center of Groningen (UMCG) approved the conduction of the study. Consent to participate was obtained from the parents and from the child if the child was ≥ 12 years old.

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