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Exercise Related Proteinuria in Children

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Transient proteinuria in children can be idiopathic or secondary to exercise or fever. Exercise related proteinuria usually is derived from low renal blood flow to the kidneys. It usually is defined as urinary protein excretion higher than 100-150 mg/m2/day and ends 24 hours after exercise. The intensity of exercise has a main role in the amount of protein excreting in the urine. It usually is transient. However, further assessment is needed to exclude systemic diseases if proteinuria is present besides hematuria, if it does not disappear after 48 hours, or if more than 1 gram of protein is excreted from the urine in a day.

Keywords: Proteinuria; Exercise; Child.

Running Title: Exercise Related Proteinuria

Introduction

Proteinuria is a common laboratory finding in children. It is seen in up to 10% of routine urine samples in school-aged children, although its prevalence decreases to 0.1% with repeated testing [1]. The prevalence of exercise-related proteinuria is 18-100%, depending on the type and intensity of exercise [2]. Totally, it increases with age, peaks during adolescence, and is more common in girls [3].

Definition of Proteinuria

Proteinuria is defined as urinary protein excretion higher than 100-150 mg/m2/day [4, 5]. The urine dipstick test is used for screening of proteinuria. A protein level of more than 30 mg / dl is considered abnormal.

The scale of 1+ (30-100 mg/dl) usually does not reflect a serious underlying disease and is a marker of transient proteinuria while proteinuria ≥2 + (100-300 mg/dl) is considered significant [6].
The 24-hour urine protein excretion method is used to evaluate proteinuria in children. The normal amount is less than 4 mg/m2/hour or 100 mg/m2/day [7].
The single-void urine protein/creatinine ratio (UPr/Cr) is a convenient method for estimating urine protein excretion without a 24-hour urine collection. Multiplying UPr/Cr by 0.63 can give an estimate of the total amount of protein (g/m2/day) in the urine.

UPr/Cr more than 0.2 is considered abnormal [8].

Persistent vs. Transient Proteinuria

Proteinuria may be transient or persistent. Exercise-induced or sport-related proteinuria (SRP) is a type of transient proteinuria. The leading causes of transient proteinuria include idiopathic causes, a medical condition such as fever, or non- medical conditions such as exercise [9]. Exercise-related proteinuria is a transient phenomenon that usually ends 24 hours after exercise [10] and seems to be related to the intensity of exercise rather than its duration [11]. This theory is supported by studies investigating different sports, like a study by Poortmans et al [12] on swimmers that showed post-exercise proteinuria was related to the swimming speed and exercise intensity. The pattern of proteins in this type of proteinuria is different from other types. Post exercise proteinuria is of mixed glomerular-tubular type after a heavy exercise. However, proteinuria after light exercise often has a glomerular type. Clearance of individual plasma proteins suggests an increased glomerular permeability and a partial tubular-reabsorption inhibition of macromolecules [11]. In contact, in sports like American football or boxing, kidney trauma may affect post-exercise proteinuria, too [11].

It is believed that exercise-related proteinuria is partially due to a decline in the renal blood flow (RBF). However, it has been shown in dogs that after 30 minutes of heavy exercise, , urine flow rate is identical but urine protein concentration is significantly elevated compared to the resting state [13]. Regarding the constant RBF in dogs, it is concluded that exercise proteinuria may occur in the absence of RBF changes [13].

Sympathetic excitement and catecholamine release during exercise narrow the renal arteries, which can be a cause of post exercise proteinuria. A decreased renal blood flow reduces the glomerular filtration rate concomitantly that is smaller than renal blood flow reduction and therefore the filtration fraction increases; as a result, high-molecular weight proteins pass through the glomerular membrane more easily than before [14].

Montelpare et al [15] compared the effects of continuous and an intermittent stationary cycling protocol on proteinuria. They showed that intermittent exercise had a greater influence on albuminuria and proteinuria than continuous exercise. They also found that the blood lactate concentration and blood pH were associated with changes in the clearance of urine albumin and protein. Furthermore, the results indicated that the kidney undergoes distinct physiological adjustments during exercise, and that these adjustments are relative to the intensity of the exercise stress.

Recently, a review of 519 abstracts [16] yielded 264 items related to both healthy adults (125 items) and renal disease (139 items) and showed that the prevalence (18-100%) and duration (1-6 days) of exercise proteinuria varied widely, with risks being affected by exercise intensity, posture, age, heat load, altitude, and disease. Moderate training reduced the risk of exercise proteinuria in healthy individuals and in patients suffering from chronic renal disease. They found that factors contributing to exercise proteinuria were hypoxia, lactate accumulation, vascular changes, oxidant stress, hormonal changes, and sepsis [16].

Proteinuria in Children after Acute Aerobic Exercise

The literature is very scarce on this subject. While exercise related proteinuria in adults was first discovered in 1878 in marching soldiers [17], the first report of SRP in children was published by Light et al in 1936 [18]. They assessed proteinuria after strenuous exercise in three school sports: basketball, soccer, and American football. The participants were 29 young healthy boys aged 14-20 years. They reported a fall in urea clearance and increased proteinuria. No correlation was found between the degree of post-exercise proteinuria and changes of urea clearance.

Huttunen et al [19] studied proteinuria in 60 healthy children and adolescents in the age range of 9.2-18.8 years (mean age 14.2 years) after a near-maximal graded exercise test on the cycle ergo meter. The participants were asked to pedal for at least 16 minutes at a cadence of 60-70 with increasing workloads every 4 minutes until the end of exercise. The heart rate at the end of exercise was required to be in the range of 170-200 bpm. Blood pressure was also recorded during the exercise test by an ultrasound device. The children who became exhausted before 16 minutes or their heart rate did not increase to at least 170 bpm were excluded. A post-exercise urine sample was collected after 10 minutes of lying on the bed. The results revealed a significant elevation of urine albumin from baseline that was independent of age or sex. However, urinary albumin excretion decreased in 19 subjects (31.7%). Urinary b2-microglobulin did not change significantly after the exercise. The ratio of urinary albumin to b2-microglobulin increased significantly after exercise. A positive correlation was found between the rate of albumin excretion during exercise and both the physical fitness level of the subjects (estimated by the work load at the heart rate of 170 bpm) and also the maximal systolic blood pressure during the exercise test. Considering no significant change in b2-microglobulin excretion, the authors suggested a glomerular type of proteinuria after exercise in children. They did not report if proteinuria returned to baseline levels afterwards because urine collection was done only once.

On the contrary, some studies have failed to show increased proteinuria after exercise in children. For example, no increase was found in the healthy control group after 30 minutes of light-intensity exercise in a study by Mogensen et al [20] or after 20 minutes exercise on a cycle ergometer in another study [21].

Poortmans et al attributed these contradictory findings to lack of standardization of exercise test protocols among different studies [22]. Further studies are needed to clarify the subject.

Proteinuria in Children after Long-Term Aerobic Exercise

Early animal studies showed positive effects of aerobic training on reducing albuminuria and ultrastructural changes of the glomeruli in diabetes type 2 [23]. More recent evidence suggests that regular exercise decreases resting albuminuria in type 2 diabetic rats [24, 25]. There is also evidence for beneficial effects of regular exercise on type 1 diabetic rats [26].

Cantone et al found that endurance training had no effect on resting levels of urine albumin in young men while it reduced post-exercise albuminuria [27]. They first trained 5 subjects by daily running for 15-30 minutes at top speed in a 50-day training program. Then, a 15-minute treadmill exercise test was performed at a speed of 8 Km/h and a grade of 5%. A urine sample was collected before and 30 minutes after the test. The results showed regular training was associated with lower levels of post-exercise urinary albumin excretion.

The results of a large multicenter prospective study of 1390 patients with type 1 diabetes in Finland (the FinnDiane study) were published recently [28]. This was the first large prospective study of the relationship between physical activity and development of diabetic nephropathy in type 1 diabetes. The participants were young to middle aged patients (mean age: 37.0 +/- 12.4 yr) with a diabetes duration of 20.4 +/- 12.3 yr. Their leisure-time physical activity (LTPA) was recorded by a self-reported questionnaire. The results showed both the intensity and the frequency of LTPA were related to the development and progression of nephropathy. The 10-year progression rate for low, moderate and high intensity LTPA was reported to be 24.9%, 13.5%, and 13.1%, respectively. A LPTA frequency of <1, 1-2, and >2 sessions per week was associated with a progression rate of 24.7%, 14.7%, and 12.6%, respectively. Further statistical analyses showed that development of microalbuminuria correlated with the intensity of LTPA, but not with its frequency or duration. A former study by the same authors [29] also proposed that LTPA of low intensity might be followed by microalbuminuria. The authors concluded that physical activity, especially of high intensity, might prevent diabetic nephropathy or slow down its progression.

Considering the findings of this large prospective study, regular aerobic exercise seems to be safe and beneficial in type 1 diabetes, especially at higher intensities. However, further longitudinal studies in children with type 1 diabetes may be more informative and useful for clinical decision making.

Proteinuria after Resistance Exercise

The majority of the previous studies focused on proteinuria after aerobic exercise, and very few studies investigated proteinuria following resistance exercise. The most catastrophic complication of resistance exercise on the renal function is acute renal failure, mainly due to rhabdomyolysis. Other proposed mechanisms include systemic and renal vasoconstriction, oxidative stress, and systemic inflammation [30].

Very few studies have investigated the effect of intense resistance exercise on urinary protein excretion and unfortunately we did not have access to any prospective studies related to the effects of resistance exercise on proteinuria. However, Spada et al [31] recently investigated the effect of high intensity interval resistance training (HIIRT) on urinary protein excretion. They measured urinary albumin and b2-microglobulin in 58 healthy young undergraduate students (range 21-28 years, median: 24 years) before a single session of HIIRT and also 2 and 24 hours after the exercise. The participants, aged >18 years, did not have any history of chronic diseases or drug use and exercised regularly. The exercise intensity was evaluated by the Borg scale or the Rate of Perceived Exertion (RPE) scale. The results showed a significant increase of both urinary proteins 2 hours after exercise in both genders, which returned to baseline levels 24 hours later. Increased urinary excretion of albumin and b2-microglobulin was observed in 87% and 77% of the students, respectively. A positive relation was found between RPE (as an indicator of exercise intensity) and microalbuminuria, but b2-microglobulin excretion was not correlated with RPE. Serum creatinine (sCr) showed a significant increase 24 hours after exercise in 47% of the students. Gender specific analysis revealed no significant increase in sCr in women while the rise of sCr was more than 0.3 mg/dl in 2 men, which was compatible with the diagnostic criteria of "acute kidney injury" (AKI) as defined elsewhere [32]. Increased levels of urinary proteins were observed in both men and women. A significant elevation of serum creatine phosphokinase (CPK) and myoglobin was also reported in both genders 2 and 24 hours post-exercise. CPK rose beyond the reference range limits in 69% of the individuals and was indicative of ER in 19%. As stated by the authors, the elevation of kidney biomarkers in this study was generally below the levels found in AKI and was suggestive of kidney stress or mild kidney injury.

They finally recommended professional supervision and gradual progression of high-intensity resistance training considering the risk factors of kidney injury, especially for the newcomers. It might be better to avoid such training in persons with non-modifiable risk factors. The very short (24 hours) follow-up period of this study limits its clinical usefulness in developing evidence-based recommendations. Future long-term prospective studies are needed to assess the effects of heavy resistance training on individuals who exercise regularly, both in adults and children.

Exercise Related Proteinuria in Diabetic Children

A classic study by Mogensen and Vittinghus in 1975 suggested that exercise test might induce albuminuria in young diabetic adults (all cases were over 21 year old) without proteinuria at rest (defined by negative Albustix test), while it had no significant effect on urinary albumin excretion in healthy controls; therefore, exercise test might be useful as a provocative test [20]. The authors selected the intensity of exercise in their study based on preliminary experiments indicating that specific intensity probably would only cause increased albuminuria in diabetics (and not in controls). Nonetheless, this aspect of their study might be considered a major methodological flaw because they used an identical absolute work load for all the subjects, which would mean different relative workloads for different individuals. This is especially true in children and adolescents as they may be very different in physical fitness, body weight and height, and puberty stage. They concluded that exercise test might be used as a provocative test for detection of early changes in the renal function. A similar study confirmed these findings later [21].

Following the interest in exercise testing, some investigators tried to assess it in diabetic children. After publishing the results of the their research into exercise-induced proteinuria in healthy children [19], Huttunen et al reported similar results in a study with a similar design in 64 children and adolescents (mean age: 13.7 years) with type 1 diabetes mellitus [33]. At baseline, 13 diabetic patients (20%) reported occasionally positive dipstick tests for urinary albumin, but none of them had persistent proteinuria. The duration of diabetes ranged from 1 week to 15.1 years (mean: 6 years). Post-exercise albuminuria was significantly greater in diabetics compared to the healthy control group (mean age: 13.9) and was weakly correlated with the duration of exercise. The diabetic participants with occasional proteinuria at rest had greater post-exercise albuminuria in this study. A stronger correlation was found for HbA1 which indicated poorer metabolic control of diabetes was associated with higher levels of post-exercise proteinuria. This finding was compatible with the results of another study [34] that showed improved metabolic control after 2 weeks of continuous subcutaneous infusion of insulin may reduce or even correct post-exercise proteinuria in young men aged 19-40 years. This positive effect of improved metabolic control was later observed in teenagers as well [35]. The precise protocol of exercise testing in this study was not clear, but the target heart rates mentioned suggest a moderate intensity of exercise, which is different from the high intensity exercise test in diabetic children and adolescents in the study by Huttunen et al [33].

Dahlquist et al [35] used a standardized exercise test in 19 type 1 diabetic teenagers and young adults for evaluating post-exercise proteinuria after moderate-intensity exercise and assessed the outcomes of better metabolic control on the results of exercise test. The patients had no signs of nephropathy and were Albustix negative. The duration of diabetes varied from 3 to 16.8 years and the degree of metabolic control was poor (HbA1c> 13.5% in all cases). The subjects first underwent a maximal exercise test using a cycle ergo meter to determine their Vo2 max. On the next day, each patient was tested again at a workload of about 60% of their Vo2 max for 30 minutes and a urine sample was taken 30 minutes after the end of the exercise test. Then, on the second visit, the patients underwent a 6-8 week treatment aiming at improving glycemic control during which they had multiple self-measurements of blood glucose and increased dosage of insulin. Measuring HbA1c after this period showed improved metabolic control in diabetic subjects. Then, a maximal exercise test (the first day) and a submaximal exercise test at 60% of Vo2 max (the second day) were taken again. The results showed higher baseline albumin excretion in diabetics (compared to controls) on both visits. After the exercise, diabetics had higher levels of albuminuria on both visits while no increase in albumin excretion was observed in controls. Exercise-induced albuminuria was not correlated with blood or urinary glucose levels on the first visit, but it was significantly lower on the second visit compared to the first. This finding regarding the effect of improved metabolic control was consistent with the results of an earlier study in young adults [34]. In patients who had diabetes for less than 5 years, the rate of post-exercise albuminuria was not different from controls on either visits. The duration of diabetes showed a positive correlation with exercise-induced albuminuria (on the second visit). This finding was interpreted by the authors to be the result of irreversible structural changes of the glomeruli that was related to the duration of diabetes. B2-microglobulin, which was only measured in diabetics, did not show any post-exercise increase on either visit, which was consistent with previous studies [21, 33].

Mostafa et al [36] studied 50 children and adolescents (range: 8-17 yr, mean age: 13 yr) with type 1 diabetes for at least 5 years (range: 5-14 yr, mean duration: 7 yr). None of the patients were albuminuric and 54% had a poor metabolic control (HbA1c > 7.6%). They performed a 20-minute submaximal standardized treadmill exercise test at a moderate intensity of 50% of their hear rate reserve (HRR) immediately after which a urine sample was taken. Post-exercise urine samples showed increased albumin excretion compared to baseline in both diabetics and healthy controls. Post-exercise albuminuria was significantly higher in diabetics (compared to controls); 60% of the diabetics developed microalbuminuria and 6% became macroalbuminuric. Post-exercise microalbuminuria was observed in 33% of controls of whom one had macroalbuminuria. The authors proposed exercise testing to detect covert albuminuria in type 1 diabetes.

On the other hand, some studies failed to show the provocative effect of exercise testing in diabetic adolescents. Poortmans et al [37] studied 21 male adolescents and young adults aged 13-25 years with type 1 diabetes for 3-14 years (mean: 8.2 yr). None of the patients had albuminuria at rest using the Albustix and their metabolic control was estimated to be good or fair (although HbA1c was not measured). The subjects underwent a 30-minute maximal stress test on a cycle ergometer with increasing a workload of 25 Watts every 5 minutes until exhaustion. Urine samples were taken before and also 5 and 30 minutes after the exercise. Four urine variables were reported: total protein, albumin, b2-microglobulin, and albumin: b2-microglobulin ratio. At baseline, all protein measurements were higher in diabetics compared to healthy controls, except the albumin: b2-microglobulin ratio that was not significantly different. Then, 30 minutes after the exercise, the diabetics showed increased excretion of b2-microglobulin and decreased albumin: b2-microglobulin ratio compared to the controls. Urinary albumin or total proteins were not significantly different between diabetics and healthy controls 30 minutes after the exercise. Intra-group analysis revealed a significant increase in post-exercise urinary albumin and total proteins with no changes in b2-microglobulin in controls while no significant changes were observed in the 4 variables in diabetics. This finding was in contrast to some previous studies [20, 21]. The reason for the difference might be different exercise intensities or the populations of these studies. The authors finally concluded that a maximal exercise test would not help detect incipient albuminuria in diabetic adolescents [37].

Another study by Hermansson & Ludvigsson [38] showed similar results earlier. They studied 55 children and adolescents (age: 8-20.5 years, mean: 14.3 years) with type 1 diabetes (duration: 9 months to 17.5 years, mean: 7.6 years). The patients had regular physical activity and none of them had a positive Albustix test for albuminuria at rest. Their metabolic control ranged from poor to very good, but most of them had rather good control. The exercise test on a cycle ergometer consisted of three stages (6 minutes each) with a target final heart rate of 170 bpm or less. Absolute workloads were different for each patient and selected based on individual characteristics like age, sex, weight, and physical fitness. At baseline, albumin excretion was not significantly different between diabetics and controls, but b2-microglobulin excretion was higher in diabetics. After the exercise test, albumin excretion did not differ significantly between patients and controls while b2-microglobulin excretion was higher in diabetics. A greater post-exercise increase in both urinary albumin and b2-microglobulin in diabetics compared to controls was only observed in the age group 16-20 years. Comparison of post-exercise results with baseline values in diabetics revealed no increase in albumin excretion in patients with diabetes duration of less than 2 years. The authors concluded that provocative exercise test might be of value only in adolescents aged 16-20 years, although this finding might be due to methodological problems.

Johnnason et al [39] used a standardized submaximal exercise test to investigate post-exercise proteinuria in a group of 7 physically active children and adolescents (age: 10-17, mean: 14.5 years) with type 1 diabetes for 2-6 years (mean: 3.9). The mean HbA1c was 12.1% (range: 10.3% - 13.8%). All patients were Albustix negative. The controls in this study were children with a history of minimal change disease who were in remission for 1-4 years (mean: 2.8). The subjects first underwent a maximal cycle ergometer test in which the load increased for 10W/min until exhaustion. On the second day, a submaximal test at 70% of the maximal load was performed for 20 minutes after which urine samples were collected. The results showed no significant difference in post-exercise albuminuria between the patients and controls. This was in contrast to a study by Dahlquist et al [35] that also used a submaximal exercise test. The reason for the difference might be better metabolic control and shorter duration of diabetes in the study conducted by Johannson et al [39]. The fact that no difference was found in post-exercise albuminuria between the shorter duration subgroup of patients (<5 yr) and controls in the study by Dahlquist et al [35] confirms this hypothesis.

Proteinuria and Exercise Intensity

Some researchers have studied the effect of exercise intensity on urine albumin in diabetic adolescents. Most early studies have used either maximal exercise test until exhaustion [37] or identical absolute workloads [20, 21]. Hermansson et al used individual submaximal workloads and found no relationship between diabetes and post-exercise proteinuria, except in adolescents older than 16 years.

According to a study by Lane et al [40], it seems that exercise may be safe in normo-albuminuric patients with type 1 diabetes. They studied the effects of moderate and intense aerobic exercise in 18 young adult males with type 1 diabetes. The patients (age: 29 +/- 2 yr, duration of diabetes 14 +/- yr) were normo-albmunric and normotensive with a good metabolic control (HbA1c: 7.0 +/- 0.2%) and did not take ACE-Is or ARBs (as these drugs have been shown to decrease albumin excretion). The subjects underwent twotreadmill exercise tests of 30 minutes: one at moderate intensity (as defined by 50% of their hear rate reserve [HRR]) and the other (being performed within 3 months of the first test) at high intensity (75% of HRR). After each exercise test, urine samples were collected at timely intervals of 4 hours within the next 24 hours. The patients were also asked to collect 24-hour urine samples the days before and after the exercise. The results revealed no increase in albumin excretion beyond the normal limit after moderate exercise, with a non-significant elevation of albumin in the first 4 hours. Intense exercise was associated with significantly higher albuminuria during the first 4 hours after the exercise. The authors concluded that 30 minutes of either moderate or intensive exercise did not cause abnormal levels of albuminuria in the subjects. They also emphasized that these results could not be generalized to the diabetic patients who were already albuminuric or took ACEI/ARB medications, as previous studies in young adults showed greater elevations of urinary albumin in micro-albuminuric patients compared to normo-albuminurics [41].

Kornhause et al [42] found a relationship between exercise intensity and post-exercise albuminuria in adolescents with type 1 diabetes mellitus. Ten diabetics aged 10-18 years with disease duration of less than 10 years who had a normal renal function and were normo-albuminuric were enrolled in the study. A good metabolic control was found in only 4 patients (as indicated by HbA1c <8%) and they were not regular exercisers. Initially, the patients underwent a maximal stress test on treadmill to determine their VO2 max. One week later, they were tested again by running for 20 minutes at an exercise intensity of 60% of their maximal heart rate. A third exercise test was performed 1 week later at an intensity of 80% of the maximal heart rate. After each of the 3 exercise tests, urine samples were collected 30 minutes after the exercise and tested for albumin. The results showed abnormal post-exercise albuminuria in three patients at an intensity of 60%, in seven at an intensity of 80%, and in nine patients at an intensity of 100%. The rate of post-exercise albuminuria was higher in girls in all three exercise intensities. No association was found between post-exercise albuminuria with either duration of diabetes or its metabolic control, which was in contrast to many previous investigations [35, 39]. Based on this study, Chimen et al [43] recommended that caution should be taken for higher intensity exercises in a recent review article. However, due to the small size of this uncontrolled study, the clinical utility of its findings remains doubtful.

In conclusion, the degree of post-exercise albuminuria in diabetic adolescents is affected by different factors such as age, gender, duration of diabetes, metabolic control, basal albumin excretion, and exercise intensity [42]. Due to the small size of previous studies, their short follow-ups, and different populations and methodologies, no evidence-based recommendation could be made about the safe intensity or duration of exercise in diabetic children and adolescents. There is currently no evidence that exercise can induce diabetic nephropathy or speed up its progression [44]. Further longitudinal studies with larger sample sizes are needed to better elucidate exercise-related proteinuria in diabetic children.

Exercise Related Proteinuria as a Prognostic Factor

A Long-term study with a follow-up period of 29 ± 3 years by Dahlquist el al [45] found that microalbuminuria (defined by urinary albumin excretion > 15 mg/min) was a strong predictor of developing persistent albuminuria later in life in type 1 diabetes (positive predictive value: 93%).

Meanwhile, some studies have proposed that exercise-related proteinuria might be an early sign of impaired renal function in normo-albuminuric diabetes [20, 21, 46, 47] while there is contradictory evidence from other studies [37]. Hence, some studies evaluated the relationship between post-exercise albuminuria and the development of microalbuminuria at rest in diabetic children. No relationship was found in a prospective study of 66 type 1 diabetic children and adolescents by Bognetti et al [48]. The mean age of the children was 15.3 ± 3.1 years with a mean diabetes duration of 8.9 ± 3.0 years. The patients were followed for 6.2 ± 1.7 years. Urinary albumin was measured after a treadmill exercise test of 15 minutes walking at a speed of 5 Km/h. The mentioned intensity of the exercise test was moderate; however, it was in fact considered a low intensity for some patients. It is difficult to compare these results with pervious investigations that mainly used moderate-to-vigorous intensity exercise. The results showed that among 8 patients with microalbominuria, post exercise albuminuria was observed only in the 3 patients. Post-exercise albumin excretion was not significantly different between 3 patients with and 5 patients without microalbuminuria. Of 58 patients who did not develop microalbuminuria, 12 patients (20.7%) had abnormal post-exercise albuminuria but they had no significant difference in resting albuminuria during follow-up. The authors concluded that post-exercise albuminuria after a moderate-intensity exercise test could not predict the development of microalbuminuria at rest. However, their conclusion should be interpreted cautiously, as the intensity of exercise test in their study might have been light (not moderate). They did not measure urinary b2-microglobulin.

Another study by Elving et al [49] in young adults and adolescents with type 1 diabetes showed that 30% of normo-albuminuric patients developed abnormally high excretion of albumin following a standardized test, which could not predict resting microalbuminuria after a 5-year follow-up.

By contrast, a study by Garg et al [46] in 187 young adults (mostly 18-22 years) with a 4-year follow-up proposed that higher levels of post-exercise albuminuria indicated a transition from normo-albuminuria to abnormal overnight albumin excretion. They also suggested a “window period” is present during which improving glycemic control may correct increased post-exercise proteinuria, and that progression to resting albuminuria is likely without appropriate treatment.

O’Brien et al [47] found that exercise test was a predictor of microalbuminuria in type 1 diabetes in young adults after a 10 year follow-up. They prospectively studied 32 young adults (age: 28.7 ± 9.75 years) with a diabetes duration of 15.5 ± 9.82 years who were normo-albuminuric. A treadmill exercise test was taken for 20 minutes at an intensity causing the heart rate to reach twice the person’s resting heart rate. The ratio of urinary albumin to creatinine (UA/UC) was measured before and after the exercise. UA/UC ratio more than 30 mg/gr was considered as a positive exercise test.. The subjects were followed for 10 years and then the UA/UC ratio at rest was compared with the baseline values. The results showed 4 out of 4 patients who developed persistent microalbuminuria (as defined by UA/UC> 15 mcg/min) had a positive exercise test after 10 years. The reported sensitivity and specificity of the exercise test for microalbuminuria was 80% and 92.3%, respectively. Only post-exercise UA/UC was correlated with a change in UA/UC after 10 years (not the resting UA/UC). The authors suggested a single exercise test instead of repeated spot urine tests for screening microalbuminuria.

Dash et al [50] conducted a well-designed study in young adult males with type 1 diabetes to predict nephropathy by 2 different methods of exercise testing. The patients once underwent a cycle ergo meter exercise test at a fixed workload (150 W) and once they were tested at a fixed heart rate (145-165 bpm). Follow-up of the patients for 13.1 ± 3.2 years showed that patients who developed microalbuminuria had higher levels of post-exercise albuminuria only during the fixed heart rate exercise test. The authors concluded that the type of exercise test would determine its usefulness to predict diabetic nephropathy. To the best of our knowledge, no study has compared different types of exercise test for predicting diabetic nephropathy or microalbuminuria in diabetic children.

In conclusion, due to the lack of large prospective studies, it is not yet certain whether or not exercise-related proteinuria predicts progressive impairment of renal function. It is better to investigate the effects of exercise in different stages of nephropathy in future studies, similar to a study by Koh et al who evaluated three groups of diabetic adults with normo-albuminuria, micro-albuminuria, or overt albuminuria [51].

Proteinuria in High Altitude Exercising

Proteinuria is also seen in high altitudes (above 2500 meters). The suggested mechanisms for high-altitude proteinuria may be increased glomerular permeability to protein, reduced tubular protein reabsorption, or both, in response to hypoxic injury. A study found that post exercise urinary total protein, albumin, and β2- microglobulin increased significantly after 2 sets of 30- minute exercise at 70% of the maximal heart rate compared to baseline values, while no significant difference was found in these parameters between hypoxia and normoxia conditions. However, there was a significant difference in β2-microglobulinuria between normoxia and the simulated 2750-m altitude (P = .007), which disappeared at higher elevations [52].

Exercise Proteinuria and Gender

The results of a study showed that the effect of exercise increased with age [53]. In particular, the excretion of macromolecules increased between 6 and 9 year of age in boys while no increase was seen by maximal exercise in girls. There was a direct relationship between absolute intensity of the exercise and protein excretion rates of all protein components. Moreover, high- and low-molecular weight protein excretion increased in boys and girls aged 9 to 18 years.

Management of Exercise Induced Proteinuria

Proteinuria detected within 24-48 hours after a vigorous exercise in healthy children and adolescents can be considered harmless provided that it disappears completely after 48 hours [54].+ Further assessment is needed to exclude systemic diseases if proteinuria is present besides hematuria, if it does not disappear after 48 hours, or if more than 1 gram of protein is excreted from the urine in a day [54]. Moreover, long-standing hematuria, flank pain, presence of urinary casts, positive urine cultures, and oliguria 12 hours after a vigorous exercise should be viewed as alarming signs of renal problems and additional investigation is required [55].

Due to possible miss-interpretation of exercise induced proteinuria with other causes of proteinuria, many authors recommend that all athletes undertake a routine dipstick test prior to vigorous physical activity [54,56]. It is important to consider that exercise-induced proteinuria is asymptomatic and is only identified with a dipstick test.

Conclusion

Exercise induced proteinuria is a common finding among the children. It is detected within 24-48 hours after a vigorous exercise. It usually is transient but further assessment is needed to exclude systemic diseases if proteinuria is present besides hematuria, if it does not disappear after 48 hours, or if more than 1 gram of protein is excreted from the urine in a day.

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