

## Pediatric nephrology patients are overweight: 20 years' experience in a single Canadian tertiary pediatric nephrology clinic

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### Abstract

**Background** Obesity is an independent risk factor for chronic kidney disease (CKD). We compared the body composition of pediatric nephrology patients with that of the general child population over 2 decades.

**Methods** About 4,959 patients above 2 years of age (mean:  $9.6 \pm 4.5$ ) were referred to a tertiary pediatric nephrology clinic from 1985 to 2006. In 3,422

patients (69.0% with the same mean age) there were sufficient data to analyze body composition, expressed as body mass index (BMI) Z-score and calculated on the basis of normal data taken from the National (USA) Center for Health Statistics (2000). **Results** Hematuria (21.68%), recurrent urinary tract infections (16.09%), proteinuria (13.95%) and hypertension (8.27%) were the most common referral diagnoses. Mean BMI Z-score of the pediatric nephrology patients increased significantly from  $0.29 \pm 1.07$  during the years 1985–1991 to  $0.44 \pm 1.27$  in 1992–1999 and  $0.87 \pm 1.70$  in 2000–2006 ( $P < 0.0001$ , ANOVA). Whereas the rate of the increase in BMI Z-score was not statistically different from that seen in the normal population, the young nephrology patients had over the entire time consistently significantly higher BMI Z-scores (average +0.72) than the comparable normal USA data. Several disease groups with potential for development of CKD had higher BMI Z-scores than found in the age- and sex-adjusted control data.

**Conclusions** The increased rate of obesity in our studied population suggests that pediatric nephrology patients are at even greater risk for developing CKD later in life than could be predicted from their renal disease only. We recommend therapeutic intervention to address this potentially modifiable risk factor.

**Keywords** Body mass index (BMI) · Childhood · Chronic kidney disease (CKD) · Obesity · Z-score

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## Introduction

In a previous long-term follow-up of pediatric nephrology patients, we reported on the changing pattern of pediatric renal disease over time [1]. In that paper we identified a high prevalence of obesity in our young renal patient population and commented on this finding as a co-morbid factor. The present paper concentrates and expands specifically on body composition [measured as body mass index (BMI) Z-score because of the age and sex dependency of BMI] in pediatric nephrology patients with BMI Z-scores obtained from a comparable, age- and sex-adjusted healthy general pediatric population.

The problems related to obesity are of paramount importance for all children and especially for those already suffering from or prone to renal disease. For instance, a low congenital endowment of nephrons due to impaired intrauterine nephrogenesis irrespective of its etiology, prematurity, intrauterine malnutrition or toxic influences, has been associated with an increased incidence CKD, hypertension, diabetes and obesity in later life [2]. A recent publication by Hsu et al. [3] showed that a high baseline BMI in young adulthood is an independent risk factor for the development of end-stage renal disease (ESRD), even after adjustment for hypertension and diabetes. Several other reports have indicated that obesity contributes to the pandemic increase of CKD in adults [4, 5], whereas similar associations have been suggested in pediatric studies [6, 7].

These observations are worrisome in the light of an unprecedented increase in bodyweight during childhood, which, as we know, is predictive of adult obesity. Pediatric male BMI increased from an average of 18.6 in the years 1976–1980 to 19.3 and 19.9 for the time periods of 1988–1994 and 1999–2002, respectively [8–10].

In the tertiary pediatric nephrology service at the CHEO in Ottawa, Canada, data on a significant number of young renal patients have been compiled during a follow-up of more than 20 years. These data enabled us to evaluate whether the observed increase in mean BMI Z-score in children with renal disease paralleled or deviated from that seen in the general pediatric population. Being overweight is a potentially modifiable risk factor, and it is therefore important to determine and treat such a tendency as early as possible.

## Methods

All outpatients ( $n = 7,926$ ) referred during the period from April 1985 to June 2006 to the pediatric nephrology services of the Children's Hospital of Eastern Ontario (CHEO) were included in the study. Since no reference data for BMI Z-scores were available for children under 2 years of age, 1,351 patients were excluded. Patients with isolated primary enuresis were also excluded ( $n = 1,616$ ), as enuresis is generally not a renal disease. After these deductions, 4,959 patients (mean age of  $9.6 \pm 4.5$  years) remained of which 3,422 (69.0%) had sufficient data to calculate the BMI Z-scores. These remaining 3,422 patients (mean age of  $9.6 \pm 4.3$  years) were mostly Caucasians and 1,856 (54.24%) were female. The data collected included age at first clinic visit, height, weight and reason for referral. CHEO's ethics board gave full approval for the study.

BMI was calculated from the ratio of weight (kg) and the square of the height (cm). BMI is age and gender dependent. Therefore age-independent BMI Z-scores were calculated using the formula:  $Z = [X - \mu] / \sigma$ ;  $X$  is the BMI measured in the patient, whereas  $\mu$  and  $\sigma$  represent the mean and the standard deviation for age and gender-matched controls taken from the National Center for Health Statistics (USA). The most recent National Health and Nutrition Examination Survey (NHANES) III database (1999–2002) was used for all patients [11]. In order to determine the slope of the development of BMI Z-scores over time, we also used earlier surveys. The NHANES II data were collected between 1976 and 1980, and the first set of the NHANES III data were gathered during the years 1988–1994, and the latest NHANES III data set were collected from 1999 until 2002. As the average BMI Z-score increased over the time periods of each study, the respective middle of each time period was chosen to determine the x-coordinates for the healthy population, namely 1978, 1991 and 2001 for estimation of the regression line. We then calculated the three control BMI Z-scores of the averages for all ages (2–19 years) using the BMI reference data from the most recent NHANES III data [11] and determined the slope by regression analysis. For the comparison of the BMI Z-scores of the patients with those of the normal population, the slopes and the elevations of the regression lines were compared using analysis of

covariance to test the null hypothesis that the slopes of the regression lines were different.

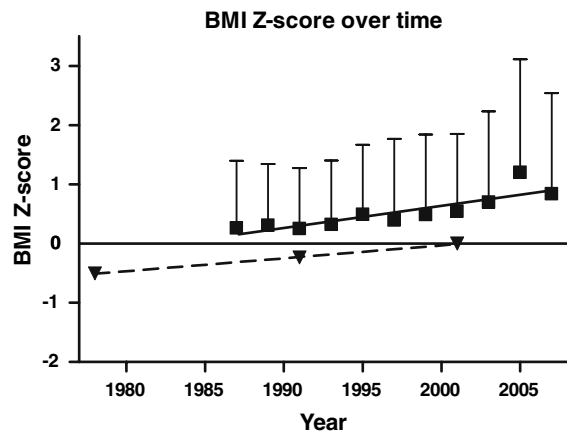
Statistical analysis was performed with the GraphPad Prism version 4.02 for Windows (GraphPad Software, San Diego, CA). Contiguous data were analyzed for normal distribution with the D'Agostini Pearson omnibus test. Mean and standard deviation were reported for normally distributed data; otherwise, median and range were given. Simple descriptive tests were employed, using appropriate parametric tests for normally distributed data and non-parametric tests otherwise. Contingency tables were analyzed by the chi square test. A *P*-value of  $<0.05$  was considered statistically significant. Associations between variables (e.g., date of presentation and BMI Z-score) were assessed with standard regression analysis.

## Results

The most common referral diagnoses were hematuria (21.68%), recurrent urinary tract infections (16.09%), proteinuria (13.95%) and hypertension (8.27%). In 3,422 of the 4,959 patients (69.0%, 54.24% female), sufficient data were available for the calculation of BMI Z-scores. The proportion of patients with referral diagnoses that were associated with significantly elevated BMI Z-scores did not differ between the 69% who had sufficient data to calculate the BMI Z-score and the 31% that had insufficient data ( $P = 0.10$ , chi-square test). The mean BMI Z-score in females was  $+0.47 \pm 1.28$ , which was not statistically different from males  $+0.61 \pm 1.46$ ,  $P = 0.28$ , unpaired *t*-test).

The average body mass index Z-score for both patients, presented for each 2-year interval, and controls increased significantly over time (Fig. 1). The slope of the regression line of the patients' BMI Z-score was not significantly different from the increase in the BMI Z-score in the general population ( $P = 0.20$ ), but the elevations of the regression lines were very different ( $F = 25.97$ ,  $P = 0.00034$ ).

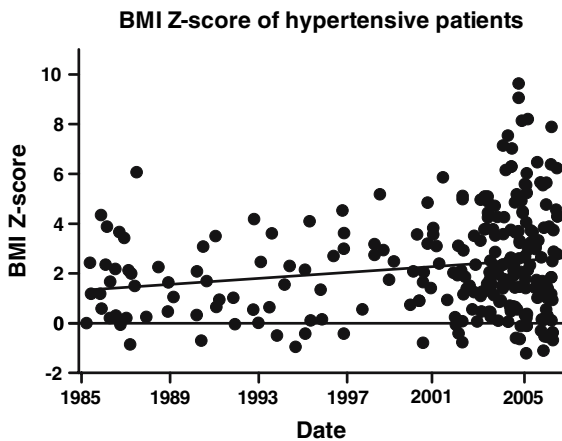
The BMI Z-scores were also calculated according to referral diagnoses. One would expect that patients with orthostatic proteinuria, generally a benign renal condition, would have a BMI Z-score close to that of normal controls. That was indeed the case since their average BMI Z-score of  $-0.17$  did not differ



**Fig. 1** Average BMI Z-score for each 2-year period over the 20 years of the study (solid line), given as mean  $\pm$  1 SD. The method for the determination of the line for the development of the BMI Z-score for the general pediatric population (dotted line) is discussed in the Methods section. The normal average (BMI Z-score of zero) is given as a straight line for orientation

significantly from zero. By contrast, several groups of patients with referral diagnoses that are commonly associated with the risk for progression to CKD exhibited significantly elevated BMI Z-scores. Not unexpectedly, patients with the referral diagnosis of hypertension exhibited the highest BMI Z-score ( $+2.28$ ). Hypertension was the referral diagnosis in 410 patients. Their mean age was  $12.5 \pm 4.0$  years, which was significantly higher than for the patient group as a whole ( $P < 0.001$ , unpaired *t*-test). There was a significant increase of referrals for hypertension over the 20-year study ( $P < 0.001$ ), and a weak but significant positive correlation between the year of presentation with hypertension and the BMI Z-score (Pearson correlation coefficient 0.18,  $P = 0.004$ , Fig. 2). The mean BMI Z-score of the hypertensive patients was  $2.28 \pm 2.07$ ; however, the data were not normally distributed. The median BMI Z-score was  $+1.97$ , range  $-1.23$  to  $+9.61$ , with a 25th percentile of  $+0.618$  and a 75th percentile of  $+3.61$ . Figure 2 illustrates the BMI Z-scores of the 261 hypertensive patients, plotted versus the year of presentation.

We also found increased BMI Z-scores for certain other diagnoses that may be associated with decreased physical activity such as neurogenic bladder, commonly associated with spina bifida (average BMI Z-score  $+0.35$ ), nephrogenic diabetes insipidus (average BMI Z-score  $+0.57$ ) and hypophosphatemic rickets (average BMI Z-score  $+1.47$ ). Patients with



**Fig. 2** The relationship between BMI Z-score at the time of first visit for patients with the referral diagnosis of hypertension. The slope of the regression line was significantly non-zero, but not significantly different from the normal population. The normal average (BMI Z-score of zero) is given as a straight line for orientation

hypophosphatemic rickets have a known association with obesity because of reduced physical activity owing to chronic bone pain. The high BMI Z-score of patients with nephrotic syndrome (+1.10) could possibly be explained by water and salt retention due to the underlying disease or to corticosteroid therapy. Similarly, in patients with the referral diagnosis of proteinuria, the significantly elevated BMI Z-score could theoretically be due to edema. We are unaware of any previously published associations of obesity with hypercalciuria (BMI Z-score of +0.89) or nephrolithiasis and nephrocalcinosis (+0.51). Patients with a solitary kidney presumably have reduced nephron endowment, and their average BMI Z score of +0.95 is worrisome.

## Discussion

This paper analyzes the changes in bodyweight, expressed as the BMI Z-score, of a large pediatric nephrology patient population over 2 decades. We observed a steady increase in the BMI Z-scores of our young patients with renal disease paralleling the normal, healthy pediatric population. The increase in overweight children in North America and Europe is well recognized [7, 11–13]. An imbalance between caloric intake and energy expenditure is responsible for becoming overweight. Several recent epidemiologic

studies have shown that obesity and the metabolic syndrome are independent predictors of CKD [3, 4]. In addition to diabetes and hypertension, several other mechanisms have been postulated to initiate and maintain kidney injury in patients with obesity and the metabolic syndrome. There are a number of potential mechanisms of renal injury in the setting of obesity, with a focus on the role of inflammation, hyperlipidemia and hemodynamic factors that may account for this association [14].

In this context, it is extremely worrisome that throughout the study period the (Canadian) pediatric nephrology patients were identified to be heavier than the average (USA) child population. This finding is novel and deserves further consideration.

What could be the explanation for our findings? First, a referral bias has to be considered. This possibility is unlikely on the basis of the Canadian public health care system [1]. The geographical isolation and CHEO's role as the compulsory pediatric tertiary referral center for approximately 250,000 children in Eastern Ontario and parts of Western Quebec make referral bias unlikely. While there are clearly regional differences in the prevalence of overweight children in Canada, with the lowest likelihood in the Western provinces and the highest prevalence of overweight children in the Atlantic provinces of Canada, childhood body composition in Ontario is close to the national average [12]. It is possible that the socio-economic status of the families may impact the rate of overweight youth, and the capital region may in this respect differ from the average in the country [13]. A recent study demonstrated that children in high-income neighborhoods were half as likely to be obese as their peers living in low-income neighborhoods [15]. Thus children in the capital region should be leaner than the national average, as the average annual income per family in the capital region is higher (\$69,518) when compared to the rest of the provincial (\$61,024) and the national median (\$55,016) [16]. It is also unlikely that our population differed from the reference population. The prevalence of a BMI value at or above the 95th percentile (overweight) among children and adolescents in the United States based on the 1999–2002 NHANES III database was 16.5% [17], which compares to a prevalence of 15% overweight children in Ontario [18]. It is therefore unlikely that children in Ontario are different from

the NHANES III study population and certainly not heavier than children in the USA.

Because of the possible influence of the changing incidence of renal disease in the pediatric population [1], we separately analyzed two disease entities known to be associated with increased bodyweight: nephrotic syndrome, which is associated with edema and/or corticosteroid therapy [19], and hypertension [20–22]. The vast majority of patients with nephrotic syndrome were seen at initial diagnoses prior to initiation of steroid therapy [23]. While an edematous state would contribute to an elevated BMI Z-score, the overall effect would be negligible due to the small number of children with nephrotic syndrome in our study cohort (1.4%). Many of the other referral groups that clearly are associated with an increased risk for CKD also exhibited increased average BMI Z-scores. There was certainly an increase in the referral pattern of children with hypertension over time, as observed by others [24]. As the percentage of other referral diagnoses such as enuresis or proteinuria did not increase (data not shown), we hypothesize that we observed a true increase of children with hypertension, probably owing to the increase of weight, and our observation was not due to a selection bias. In total, these patients comprised 7.63% of our study population, and their mean BMI Z-score was rather high at +2.28. Some other diagnoses such as hypophosphatemic rickets do not exhibit a nephrological explanation for their obesity, but rather immobility owing to their chronic disease. The association of nephrogenic diabetes insipidus with obesity is unusual, as intuitively these children would demonstrate a tendency towards dehydration. We wonder whether consumption of high-caloric drinks may explain the obesity in this patient cohort. Regardless, patients with hypophosphatemic rickets have a risk for CKD secondary to treatment-induced nephrocalcinosis, and nephrogenic diabetes insipidus patients can develop CKD secondary to the development of neurogenic bladder and increased bladder capacity. Therefore control of body weight is an important task in these patients.

In adult patients, CKD has been linked to obesity, generally in diabetics [4, 25]. This probably also holds true for CKD secondary to diabetic nephropathy in children [26]. The proportion of referrals for diabetic nephropathy was insignificant (0.50%) and would also not have influenced the mean reported

BMI Z-scores for the entire study population. Possible confounding factors include parents' BMI, exercise and lifestyle, all of which were unavailable for the current study. The patient age at referral increased significantly over the 2 decades of the study.

The make-up of pediatric nephrology patients is changing, and we nowadays encounter a more adult-like pattern of lifestyle-related problems such as obesity-related hypertension.

The most important next step is to confirm the findings of this study in other pediatric nephrology populations. If indeed confirmed, the recently demonstrated link between a high BMI in child- and early adulthood and the risk for developing CKD later in life gives rise to significant concern. The data of the present study point to a major threat to the future health of pediatric nephrology patients with further aggravation of the already alarming increase of CKD. A large proportion of our young renal patients was seen for conditions such as proteinuria, hypertension, hematuria, etc., all of which are clearly associated with a higher risk of CKD. Assuming that obesity is causative for the increase of CKD, weight would be a modifiable risk factor, and substantial resources should be devoted towards prevention and treatment of childhood obesity.

This study demonstrates that Canadian (Ontario) pediatric nephrology patients have a higher BMI than the average US childhood population, while the rate of increase is similar to that in the general population. The lack of a local or Canadian control group forms a major limitation. We are currently repeating the study in another center where we have access to a very sizeable control group. The limited literature suggests that the prevalence of unhealthy weights in Canadian children and youth is comparable to that of the US. We were unable to explain this finding by specific confounding factors such as hypertension and edema. Adolescents were more affected than younger children. This implies that these patients are at even greater risk for development of CKD later in life. We therefore strongly recommend therapeutic intervention to address this potentially modifiable risk factor.

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