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Prevalence of Proteinuria in School-Aged Turkish Children, and Its Association with Obesity and Hypertension

Okul Çağı Türk Çocuklarında Proteinüri Sıklığı ve Obezite ve Hipertansiyonla İlişkisi

Ali Gül[1], Samet Özer[1], Resul Yılmaz[1], Ergün Sönmezgöz[1], Tuba Kasap[1], Şahin Takçı[1], Nafia Özlem Kazancı[2], Şeyma Ünüvar[1], Yalçın Önder[3], Rıza Çıtıl[3], İlknur Bütün[4]

[1]*Gaziosmanpaşa University Faculty of Medicine, Department of Pediatrics, Tokat, Turkey*
[2]*Başkent University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Nephrology, Ankara, Turkey*
[3]*Gaziosmanpaşa University Faculty of Medicine, Department of Public Health, Tokat, Turkey*
[4]*Gaziosmanpaşa University Faculty of Medicine, Department of Biochemistry, Tokat, Turkey*

ABSTRACT

Aim: In kidney diseases, renal damage may be mild and initially asymptomatic. Proteinuria, a marker of kidney injury, directly contributes to chronic tubulointerstitial damage. We investigated the prevalence of proteinuria (POP) in school-aged children in Turkey.

Materials and Methods: The cluster sampling method was used to calculate the required size of the study group for this cross-sectional study. Urine samples were randomly obtained to determine urinary protein/creatinine ratio (Upr/Ucr) from 1374 children aged 6 to 18 years. POP was also specifically assessed in hypertensive and obese children.

Results: The mean age of the subjects was 11.68±3.43 years. The children were from rural (23.9%) and urban (76.1%) regions of Tokat, Turkey. Upr/Ucr ≥0.20 was detected in 92 children, corresponding to a POP rate of 6.7%, without any statistically significant difference between girls and boys. Among 141 obese children, 16 (11.3%) and 76 of 1233 non-obese children (6.2%) had proteinuria ($p<0.05$). Children with hypertension had a POP of 7.5% compared to the 6.7% of those without hypertension ($p>0.05$).

Conclusion: Among school-aged Turkish children POP was 6.7%. POP was higher in obese than in non-obese children. But there was no association between POP and hypertension. While screening programs allow the early detection of renal disease, further cohort studies are required to be able to suggest urinary screening programs.

Keywords: Proteinuria, children, obesity, protein creatinine ratio, hypertension

ÖZ

Amaç: Böbrek hastalıklarında renal hasar başlangıçta asemptomatik ve hafif olabilir. Böbrek hasarının bir belirteci olan proteinüri, kronik tübülointerstisyel hasara doğrudan katkıda bulunur. Okul çağındaki çocuklarda proteinüri prevalansını (PP) araştırdık.

Gereç ve Yöntemler: Bu kesitsel çalışma için çalışma grubunun gerekli boyutunu hesaplamak için küme örnekleme yöntemi kullanıldı. Altı-on sekiz yaş arasındaki 1374 çocuğun idrar protein/kreatinin oranını (Upr/Ucr) belirlemek için idrar numuneleri rastgele elde edildi. PP hipertansif ve obez çocuklarda ayrıca hesaplandı.

Bulgular: Olguların yaş ortalaması 11,68±3,43 yıl idi. Olguların %23,9'u kırsal alanlardan ve %76,1'i kentsel bölgeden alındı. Kız ile erkek çocuklar arasında istatistiksel olarak anlamlı farklılık olmaksızın, 92 çocukta Upr/Ucr ≥0,20 saptandı, PP %6,7'ye karşılık geldi. Yüz kırk bir obez çocuktan 16'sında (%11,3) proteinüri vardı; obez olmayan 1233 çocuğun 76'sında (%6,2) proteinüri vardı ($p<0,05$). Hipertansiyonlu çocuklarda proteinüri %7,5 iken hipertansif olmayanlardaki prevalans oranı %6,7 idi ($p>0,05$).

Sonuç: Okul çağındaki Türk çocuklarında PP %6,7 idi. PP, obezlerde obez olmayan çocuklardan daha yüksekti. Ancak, PP ve hipertansiyon arasında herhangi bir ilişki mevcut değildi. Tarama programları, böbrek hastalığını erken tespitte yardımcı olsa da üriner tarama programlarının önerilmesi için daha fazla kohort araştırmaları gereklidir.

Anahtar Kelimeler: Proteinüri, çocuklar, obezite, protein kreatinin oranı, hipertansiyon

Address for Correspondence/Yazışma Adresi
Ali Gül MD, Gaziosmanpaşa University Faculty of Medicine, Department of Pediatrics, Tokat, Turkey
Phone: +90 505 347 29 61 E-mail: draligul@yahoo.com ORCID ID: orcid.org/0000-0001-5350-2192
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Introduction

Chronic kidney disease (CKD), characterized by the irreversible deterioration of kidney function, leads to end-stage renal disease (ESRD), which is a major and growing public health problem (1,2). The early detection of kidney disease based on the determination of proteinuria and the identification of its cause are important for early treatment to prevent CKD, and therefore, ESRD development (1). Almost all of the proteins filtered by the kidney glomeruli are reabsorbed in the proximal tubule by endocytosis at the luminal membrane. Significant proteinuria occurs when this energy-requiring mechanism is saturated and it can thus be measured by determining the amounts of protein (mg) and creatinine (mg) in a random urinary sample, expressed as the urinary protein/creatinine ratio (Upr/Ucr) (3). In children <2 years of age the normal upper limit of the Upr/Ucr is 0.50; in children >2 years of age, it is 0.20 (4,5). The Upr/Ucr correlates well with 24 h urine protein excretion (3).

In kidney diseases, renal damage may be mild and initially asymptomatic. If proteinuria is detected before nephrotic involvement, the progression of renal injury to ESRD can be prevented or delayed. A failure to promptly refer patients with early kidney disease to a nephrologist may result in the need for renal replacement therapy (6). Because proteinuria is a significant symptom of renal injury, it is also a stronger marker of CKD progression; if the loss of function is minimal there will be little or no proteinuria (7). Moreover, while proteinuria was previously considered a marker of the severity of the underlying disease, it is now clear that proteins filtered through the glomerular capillaries have an intrinsic renal toxicity that contributes to disease progression (8). This finding has highlighted the importance of the early detection of proteinuria to prevent CKD, and its progression to ESRD (9). The worldwide prevalence of childhood obesity has increased greatly over the past three decades (10). This led to an increase in CKD prevalence in the last decade of the century. It has been recently emphasized that obesity is an independent risk factor for CKD (11). The initial body mass index (BMI) is recommended as an independent predictor of the progression of CKD (12).

We investigated the prevalence of proteinuria (POP) as a benign symptom or a sign of CKD in the province of Tokat in northern Turkey by measuring protein levels in random urine samples collected from a pediatric population. Also in this study, we aimed to determine the effect of obesity and hypertension on POP in school aged-children.

Materials and Methods

The number of students to be surveyed and the number of clusters to be surveyed from each school were determined by multi-layered proportional cluster sampling method considering the number of students in primary, secondary and high schools in the province center and districts according to the 2013-2014 academic year records of the provincial national education directorate sex and age groups. The potential study population consisted of 108.514 school children between the ages of 6 and 18 years. The cluster sampling method was used to calculate the number of participants needed to power the study according to an expected (p) POP of 50% and a deviation (d) of 0.05 based on the 97% confidence interval. Thus, in this cross-sectional study the required size of the study group was 1584 children. However, 210 children were excluded from the study due to inadequate or inappropriate sampling. The remaining 1374 children were enrolled. Although first morning and two urine samples were suggested including the first urine in the morning, we used only one randomized urine sample in the day time in favor of usability. Urinary samples were randomly obtained from the children in the schools between April 2014 and June 2014.

Total protein and creatinine levels were measured using a Cobas 6000 auto analyzer and commercial kits (Roche Diagnostics, USA). The urine samples were denatured with benzethonium chloride before measuring the amount of protein using the turbidimetric method, and the amount of creatinine using the Jaffe colorimetric method. The results were expressed as mg/dL. The Upr/Ucr (mg/mg) was also calculated from the samples. The cut-off value for proteinuria to determine POP was 0.20.

Age, sex, weight, height, BMI, body temperature, and systolic and diastolic blood pressure (BP) were recorded, as was a history of drug use or chronic disease of any kind. Since five children to be enrolled to the study had been diagnosed with epilepsy, five with Familial Mediterranean Fever, one child with atypical autism, and one with celiac disease, a total of twelve children from the substitute list were recruited in their place. Weights were measured using a digital scale (Seca Corp., Chino, California, USA). The measurements were taken while the patients were barefoot and wearing light clothing. Height was measured using a portable stadiometer (Seca) together with weight. BMI was calculated as weight in kg divided by the square meter of the height (kg/m^2). The subjects were diagnosed as obese according to BMI >95 percentile, considering the sex-and age-specific growth curves and cut-off levels for Turkish children. BPs were measured by using a digital sphygmomanometer (Omron 705IT, Omron Healthcare Co., Kyoto, Japan), and if the measured BP was high according to age, sex and height, the mean of the two measurements were noted. Hypertension has been defined as BP ≥95th percentile according to age and sex, and height (13). The relationships between obesity and proteinuria and between hypertension and proteinuria were investigated by determining the POP value in subgroups of the participants. In addition, for POP and Upr/Ucr determinations, the children were divided into three age-based groups: 6-9 years, 10-13 years, and 14-18 years.

The study protocol was in accordance with the Helsinki Declaration of the World Medical Association, and ethical standards. Gaziosmanpaşa University Ethics Committee

approval was received for this study (approval number: 14-KAEK-035). Informed consent was obtained from, and the questionnaires used to gather information about the children were answered by the parents and families.

Statistical Analysis

Quantitative data are expressed as the arithmetic mean and standard deviation. An independent sample t test or one-way analysis of variance was used to compare continuous normal data between the groups. A χ^2 test or the Yates correction χ^2 test was used to compare categorical data. Categorical variables were expressed as counts and percentages. A multivariate logistic regression model was implemented to determine the relation between selected variables and proteinuria. A p value <0.05 was considered to indicate statistical significance. The statistical analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., and Somers, New York).

Results

Urine samples were collected from 1374 children, 683 (49.7%) females and 691 (50.3%) males. Their mean age was 11.68±3.43 years (6-18 years). The mean ages of girls and boys (11.70±3.46 years and 11.66±3.41 years respectively) were similar. The children resided in rural (n=329, 23.9%) and urban (n=1045; 76.1%) regions. The characteristics of the study group are provided in Table I.

A Upr/Ucr ≥0.20 was determined in 92 children, corresponding to a POP of 6.7%. POP was 5.8% in the girls and 7.6% in the boys; the difference was not statistically significant (p>0.05).

Among 141 obese children, 16 (11.3%) had proteinuria, whereas in 1233 non-obese children proteinuria was measured in 76 (6.2%); the difference was statistically significant (p<0.05). Children with hypertension had a POP of 7.5% compared to the 6.7% of those without hypertension but the difference was not statistically significant (p>0.05). POP in children living in urban areas was 7.6%, and those in rural areas had a POP of 4%; the difference was statistically significant (p<0.05).

POP was 0.5%, 3.0%, and 16.7% in the age groups 6-9 years, 10-13 years, and 14-18 years respectively. A statistically significant difference was observed when age increased (p<0.001, Table I).

An association between the risk of proteinuria and obesity, age group and settlement was estimated using multivariate logistic regression. In multivariate analysis, proteinuria as the dependent variable was entered into a multiple logistic regression model with adjustment variables, age group, obesity and settlement as independent predictor variables. Both the 10-13 years and 14-18 years groups, obese, and urbans showed a significantly increased risk for proteinuria. Table II shows the results of the logistic regression model for proteinuria.

Discussion

Among school-aged children in Tokat province, located in northern Turkey, POP was 6.7%. Asymptomatic POP in school-aged children in other regions of Turkey has been reported to be 1.81% in Trabzon (14), 2.7% in Ankara (15), 8.7% in Isparta (16), and 4.06% in Kayseri (17). A POP of 0.12% in primary school children has been reported in Malaysia (18) and a 2.7% POP has been reported in children of ages 2 to 5 years in Nigeria (14). In those studies, however, the urine dipstick method was used, which is not as sensitive a method as Upr/Ucr determination because of the high false-negative rate (19). Nonetheless, while the Upr/Ucr is recommended for the determination of proteinuria in a single random urine sample or a limited number of samples, the dipstick method is more practical for mass screening programs (9,20,21). In fact, there are few studies in which the Upr/Ucr was used to identify POP (22,23).

Like other childhood diseases, kidney disease can be

Table I. Demographic and clinical characters of the subjects

Variables		Total n=1374	Proteinuria		p
			No 1282 (93.3)	Yes 92 (6.7)	
Gender	Female	683 (49.7)	631 (92.4)	52 (7.6)	0.176
	Male	691 (50.3)	651 (94.2)	40 (5.8)	
Obesity	Obese	141 (10.3)	125 (88.7)	16 (11.3)	0.020
	Nonobese	1233 (89.7)	1157 (93.8)	76 (6.2)	
Age group	6-9 ages[a]	417 (30.3)	415 (99.5)	2 (0.5)	<0.001
	10-13 ages[b]	508 (36.9)	493 (97.0)	15 (3.0)	
	14-18 ages[c]	449 (32.7)	374 (83.3)	75 (16.7)	
Settlement	Urban	1045 (76.1)	966 (92.4)	79 (7.6)	0.022
	Rural	329 (23.9)	316 (96.0)	13 (4.0)	
Hypertension	Yes	67 (4.9)	62 (92.5)	5 (7.5)	0.797
	No	1307 (95.1)	1220 (93.3)	87 (6.7)	

[a,b,c]Different superscripts indicate statistical significant difference
Data are shown as n (%)

Table II. Odds ratios for the combined (multivariate, including age group, obesity, and settlement) effects of variables on proteinuria risk

Variables	β	p	OR	95% CI
10-13 years group	1.837	0.015	6.277	1.425-27.648
14-18 years group	3.780	<0.001	43.826	10.661-180.157
Obese	0.874	0.006	2.397	1.289-4.456
Urban	0.654	0.039	1.923	1.034-3.578

Reference categories are non-obese for obese variable, 6-9 years group for age group variable, rural for settlement variable
OR: Odds ratio, CI: Confidence interval

initially asymptomatic, which has led to the assessment of screening programs and prevalence research (14,20,24). Mass urinalysis screening in children has been implemented since 1973 in Japan (20) and since 1998 in Korea (25).

A comparison of Japan with its mandatory urinary screening program in school children, and the USA, which lacks a similar program, showed that when adjusted for the population, the rate of ESRD based on new cases annually is about 4-fold higher in America than in Japan (20,26). Dipstick-based screening programs were previously carried out in the USA, and in 2000 the American Academy of Pediatrics suggested urine screening in preschool children and in adolescents. However, subsequent studies have confirmed that dipstick-based urinary screening is not suitable because it is not cost effective (21,27). Similarly, there are no mass screening programs in Europe.

We found that POP was higher in obese than in non-obese children. Csernus et al. (28) reported a positive association between proteinuria and adult obesity, consistent with the identification of obesity as an independent risk factor for proteinuria. However, in other studies, either proteinuria was not related to obesity (29) or obese children had higher albuminuria than the control group (28).

In our study population, there was no association between proteinuria and hypertension. While this finding is in agreement with some studies (24,28), it conflicts with another, which found a positive correlation (30).

Our age-based analysis showed that the POP increased with age. In Korea, the POP in elementary and junior high school children is 0.34% and 0.48% (25) respectively; in Japan, the corresponding rates are 0.06% and 0.32% (20). However, it has also been proposed that the increased physical activity of older children results in transient proteinuria, due to orthostatic or exercise-induced proteinuria, resulting in a higher rate of POP to be recorded. So, the higher POP in the older age group may be a reflection of orthostatic proteinuria.

Finally, we found that POP was also higher in urban than in rural areas. While we were unable to find similar studies in the literature, we can suggest that in densely populated areas such as cities and towns, infections and therefore fever are more common. Because fever causes transient proteinuria, this scenario may explain the higher rate of POP in urban children. However, this hypothesis remains to be confirmed in further studies.

Study Limitations

Since this is a prevalence study, investigation of individuals in whom renal disease was detected requires a cohort study. So, it is beyond the scope of this study. The first morning and two urine samples have been suggested, but we used only one randomized urine sample in the day. These were the limitations of our study.

Conclusion

Proteinuria in children may be the first indicator of CKD. However, the early diagnosis of renal disease in asymptomatic individuals can prevent or slow its eventual progression to CKD, and thus the development of ESRD. Among school-aged Turkish children POP was 6.7%. POP was higher in obese than in non-obese children, but there was no association between POP and hypertension. Although screening programs allow the early detection of renal disease, further cohort studies are required to suggest urinary screening programs.

Ethics

Ethics Committee Approval: The study was approved by the Gaziosmanpaşa University Local Ethics Committee (approval number: 14-KAEK-035).

Informed Consent: Inscriptive informed consent was obtained from parents who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.G., S.Ö., R.Y., N.Ö.K., Ş.Ü., E.S., Concept: A.G., S.Ö., R.Y., Design: R.Y., S.Ö., E.S. Data Collection or Processing: Ş.T., Y.Ö., R.Ç., İ.B., Analysis or Interpretation: A.G., S.Ö., Ş.T., Literature Search: A.G., R.Y., Ş.T., T.K., Writing: A.G., R.Y., S.Ö., T.K.

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References

1. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int 2003;63:1468-74.
2. Soylemezoglu O, Duzova A, Yalçınkaya F, Arinsoy T, Süleymanlar G. Chronic renal disease in children aged 5-18 years: a population-based survey in Turkey, the CREDIT-C study. Nephrol Dial Transplant 2012;27(Suppl 3):146-51.
3. Guignard JP, Santos F. Laboratory investigations. In: Avner ED, Harmon WE, Niaudet P, (eds). Pediatric nephrology. 5th ed. Lippincott Williams & Wilkins, 2004;399-424.
4. Wong CS, Pierce CB, Cole SR, et al. Association of proteinuria with race, cause of chronic kidney disease, and glomerular filtration rate in the chronic kidney disease in children study. Clin J Am Soc Nephrol 2009;4:812-9.
5. Pais P, Avner ED. Introduction to the Child with Proteinuria. In: Kliegman RM, Stanton B, Geme JS, Schor NF, Behrman RE, (eds). Nelson textbook of pediatrics. 20th ed. Elsevier Health Sciences, 2015:2517-8.
6. Jungers P, Massy ZA, Nguyen-Khoa T, et al. Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. Nephrol Dial Transplant 2001;16:2357-64.

7. Neild GH. What do we know about chronic renal failure in young adults? II. Adult outcome of pediatric renal disease. Pediatr Nephrol 2009;24:1921-8.
8. Hebert LA, Wilmer WA, Falkenhain ME, Ladson-Wofford SE, Nahman NS Jr, Rovin BH. Renoprotection: one or many therapies? Kidney Int 2001;59:1211-26.
9. Yap H, Quek C, Shen Q, Joshi V, Chia KS. Role of urinary screening programmes in children in the prevention of chronic kidney disease. Ann Acad Med Singapore 2005;34:3-7.
10. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet 2010;375:1737-48.
11. Ross WR, McGill JB. Epidemiology of obesity and chronic kidney disease. Adv Chronic Kidney Dis 2006;13:325-35.
12. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. Kidney Int 2008;73:19-33.
13. Tümer N, Yalçinkaya F, Ince E, et al. Blood pressure nomograms for children and adolescents in Turkey. Pediatr Nephrol 1999;13:438-43.
14. Mocan H, Ökten A, Gedik Y, Erduran E, Akyazıcı P. Trabzon il merkezi ilkokul çocuklarında preteinüri hematüri ve hipertansiyon prevalansı. Türk Nefroloji Dializ ve Transplantasyon Dergisi 1992;1:15-8.
15. Piyal B, Selma A, ARISOY M, Yaman LS. Ankara'nın dört merkez ilköğretim okulu'nun ikinci ve altıncı sınıf öğrencilerinde glukozüri ve proteinürü görülme sıklığı. Ankara Üniversitesi Tıp Fakültesi Mecmuası 1998;51:191-5.
16. Tunç B, Akdoğan M, Serel TA, Aydemir M, Yorgancıgil B, Tahan V. İlkokul Çocuklarında Asemptomatik Piyüri, Bakteriüri ve Proteinüri Prevalansı. SDÜ Tıp Fakültesi Dergisi 1995;2:21-4.
17. Düşünsel R, Hasanoğlu E. Kayseri il merkezi ilkokul çocuklarında proteinüri-hematüri prevalansı. Çocuk Sağlığı ve Hastalıkları Dergisi 1988;31:117-24.
18. Zainal D, Baba A, Mustaffa BE. Screening proteinuria and hematuria in Malaysian children. Southeast Asian J Trop Med Public Health 1995;26:785-8.
19. Rumley A. Urine dipstick testing: comparison of results obtained by visual reading and with the Bayer CLINITEK 50. Ann Clin Biochem 2000;37:220-1.
20. Murakami M, Hayakawa M, Yanagihara T, Hukunaga Y. Proteinuria screening for children. Kidney Int Suppl 2005:23-7.
21. Sekhar DL, Wang L, Hollenbeak CS, Widome MD, Paul IM. A cost-effectiveness analysis of screening urine dipsticks in well-child care. Pediatrics 2010;125:660-3.
22. Ferris M, Hogan SL, Chin H, et al. Obesity, albuminuria, and urinalysis findings in US young adults from the Add Health Wave III study. Clin J Am Soc Nephrol 2007;2:1207-14.
23. Chavers BM, Rheault MN, Foley RN. Kidney function reference values in US adolescents: national health and nutrition examination survey 1999-2008. Clin J Am Soc Nephrol 2011;6:1956-62.
24. Odetunde OI, Odetunde OA, Neboh EE, Okafor HU, Njeze NR, Azubuike JC. Urinary screening for asymptomatic renal disorders in pre-school children in Enugu metropolis, South-east Nigeria: Useful or useless. Saudi J Kidney Dis Transpl 2015;26:1241-5.
25. Park YH, Choi JY, Chung HS, et al. Hematuria and proteinuria in a mass school urine screening test. Pediatr Nephrol 2005;20:1126-30.
26. Hattori S, Yosioka K, Honda M, Ito H; Japanese Society for Pediatric Nephrology. The 1998 report of the Japanese National Registry data on pediatric end-stage renal disease patients. Pediatr Nephrol 2002;17:456-61.
27. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA 2003;290:3101-14.
28. Csernus K, Lanyi E, Erhardt E, Molnar D. Effect of childhood obesity and obesity-related cardiovascular risk factors on glomerular and tubular protein excretion. Eur J Pediatr 2005;164:44-9.
29. Cındık N, Baskın E, Ağras PI, ve ark. Sağlıklı şişman okul çocuklarında böbrek fonksiyonları ve enflamasyon belirteçleri. Çocuk Sağlığı ve Hastalıkları Dergisi 2006;49:24-9.
30. Boulatov VA, Stenehjem A, Os I. Association between albumin: creatinine ratio and 24-hour ambulatory blood pressure in essential hypertension. Am J Hypertens 2001;14:338-44.