

Impact of obesity on childhood kidney

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Abstract

Obese patients are known to have greater risks to develop hypertension, coronary vascular disease, and insulin resistance, and more attention has been recently paid to the impact of obesity on kidney. This study was conducted to investigate whether obese children have higher risk of renal injury as well as adults. Eighteen hundred and thirty school children aged 6-14 years with abnormal urinary findings on thrice occasions detected by the screening program for renal disease in Japan were enrolled. Of them, 27 children with nephritis or suspected nephritis diagnosed by persistent proteinuria with hematuria were compared to 588 without urinary abnormalities regarding their body mass index (BMI), blood pressure (BP), and serum level of total cholesterol. BMI and systolic BP (mmHg) were significantly higher in the former than in the latter. As a result, obesity may be associated with the development of renal injury even in childhood.

Introduction

It is well documented that obese patients are at greater risks to develop hypertension, coronary vascular disease, and insulin resistance, and more attention has been paid to the impact of obesity on kidney, recently.¹⁻³ Since the first description regarding the relationship between massive obesity and proteinuria in 1974,⁴ increased evidence demonstrated that obesity-related glomerulopathy (ORG) should be identified as an isolated complication of obesity in adults.^{1,2} It is, however, unclear whether this condition exists even in children with obesity.³

As the prevalence of obesity has been also rising in children in developed countries including Japan,^{3,5} this study was conducted to investigate whether obese children have higher risk of renal injury indicating nephritis.

Materials and Methods

In Japan, the annual urinary screening for renal disease of elementary and junior high-school students has been mandatory since 1974 when the Ministry of Education revised the school health law to identify children at risk of renal failure in adulthood. According to this law, detailed urinalysis is performed for all elementary and junior high-school students living in Japan. The program is described in detail previously.⁶ Briefly, patients positive for protein and/or occult blood on two serial occasions are subjected to a 3rd examination: these patients are asked to attend a medical center for a detailed examination consisting of urinalysis, medical history, physical examination including measurements of weight and height, and laboratory studies, performed by pediatricians. This approach aims to detect any clinical, hematological, or serological abnormalities associated with renal disease. After the 3rd examination, presumptive diagnoses⁶ are made based and grouped into 6 categories as shown in the Table 1.

As a result, eighteen hundred and thirty children aged 6-14 years with abnormal urinary findings detected by the screening program in part of Tokyo in 2007 were enrolled in this study. For comparison of the nutritional status among the categorized subjects, body mass index (BMI) was applied.

For statistical analysis, analysis of variance (ANOVA) and Dunnett's test were used among the 6 groups. P value less than 0.05 was considered significant. All numerical data were expressed as mean and standard deviation.

Results

Eighteen hundred and thirty subjects were classified into 6 categories (Table 1): 588 in A, 112 in B, 278 in C, 570 in D, 255 in E and 27 in F. As shown in the Table 2, the BMI was significantly higher only in F (nephritis/suspected nephritis) than in groups A (no kidney disease: P=0.039).

We further analyzed the difference in blood pressure and serum levels of total cholesterol between the category A and category F because obesity is known to influence these parameters: significant difference was found in mean systolic blood pressure between the group A and group F (P = 0.011) in addition to BMI (Table 2).

Discussion

It is estimated that 7% of children in the world are obese.⁷ The national surveys from the USA found that since 1980 the number of

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overweight children has doubled, and the number of overweight adolescents has tripled.⁸ As several lines of evidence demonstrated that ORG should be identified as an isolated complication of obesity in adults, attention has been recently paid to the impact of obesity not only on hypertension, coronary vascular disease, and insulin resistance but also on kidney.¹⁻³ In fact, obese subjects, even in the absence of diabetes, can have glomerulomegaly, thickening of glomerular basement membranes, proliferation of mesangial matrix, focal segmental glomerulosclerosis (FSGS) and increased microralbuminuria called ORG, both in normotensive and hypertensive subjects.³ Kambham *et al.* brought to our attention a tenfold increase in the prevalence of ORG,¹ from 0.2% in 1986-1990 to 2% in 1996-2000 in obese subjects (BMI >30 kg/m²).

These findings prompted us to investigate whether overweight children have an independent risk of developing to kidney disease as well as in adult. As a result, we firstly demonstrated that children having both proteinuria and hematuria are more obese than those without urine abnormalities. This suggests that ORG may develop even in childhood.

In addition to BMI, there was a significant difference only in systolic blood pressure between group A and group F, while there were no significant differences among group A, B, C, D, and group E as shown in the Table 2. Recent observations revealed that systolic blood pressure correlates well with BMI than diastolic blood pressure.⁹ Furthermore, a meta-analysis indicated that the change in blood pressure associated with body weight is more pronounced in systolic blood pressure than in diastolic blood pressure.¹⁰ These factors might

Table 1. Criteria of diagnoses in the urinary screening program in Japan.

Findings	Presumptive diagnosis	Category
No abnormal findings on urinalysis, medical history, physical examination, and laboratory studies	No kidney disease	A
Significant proteinuria (>20 mg/dL) in the random urine samples but not in the first voided urine sample in the morning	Orthostatic proteinuria	B
Significant proteinuria (>20 mg/dL) without abnormal findings in medical history, physical examination, and laboratory studies	Asymptomatic proteinuria	C
Significant hematuria (6-20 RBC/HPF) without abnormal findings in medical history, physical examination, and laboratory studies	Minimal hematuria	D
Significant hematuria (>20 RBC/HPF) without abnormal findings in medical history, physical examination, and laboratory studies	Hematuria	E
Both proteinuria and hematuria positive cases with or without abnormal findings in medical history, physical examination, and laboratory studies	Nephritis/ suspected nephritis	F

HPF, high power field; RBC, red blood cells.

Table 2. Body mass index, blood pressure and serum cholesterol in the subjects.

	Category A	Category B	Category C	Category D	Category E	Category F
Number	588	112	278	570	255	27
BMI	18.57±3.06	18.07±2.80	18.43±3.46	17.45±3.06	17.73±3.22	20.07±5.67*
Systolic blood pressure (mmHg)	102.29±11.81	103.45±11.31	103.48±11.92	97.82±11.73	98.75±11.19	109.00±15.56*
Diastolic blood pressure (mmHg)	61.01±9.83	60.17±9.18	60.55±9.18	57.53±9.67	58.37±8.71	60.54±9.00
Total cholesterol (mg/dL)	164.61±26.49	162.66±28.01	159.50±23.90	164.21±27.36	165.14±26.07	171.00±26.87

BMI, body mass index; *P<0.05 compared to group A (children with no kidney diseases: controls).

lead to the finding that there was only significant difference in systolic blood pressure but not in diastolic blood pressure.

The pathogenic mechanism responsible for proteinuria in obese subjects is speculated to be from glomerular hyperfiltration based on direct observation of increased glomerular filtration rate in obese individuals, and indirectly from similarity in clinical course between ORG and renal diseases characterized by glomerular hyperfiltration, such as secondary FSGS.^{11,12} In addition, recent study revealed that adipose tissue plays a pivotal role in the development of renal injury. Adipose tissue is recognized as a source of inflammatory cytokines such as tumor necrosis factor- α (TNF α), interleukin-6 (IL-6) and C-reactive protein (CRP)¹³ and CRP is higher in men and women with an elevated body mass index.¹⁴ Thus, obesity is associated with a state of low-grade systemic inflammation, which may contribute to renal injury and cardiovascular disease. In fact, recent observation confirmed this finding demonstrating the increased gene expression of inflammatory cytokines, such as TNF α or IL-6 RNA in patients with ORG.¹⁵

Taken these findings into consideration, we speculate that intra-glomerular hyperfiltration and inflammatory cytokines play important roles in development of proteinuria and hematuria in obese children, respectively. Another result in the present study that systolic blood pressure is higher in children having proteinuria with hematuria than those without abnormal urinary findings lends support to this

speculation because hypertension can be caused by increased inflammatory cytokines, such as TNF α or IL-6.¹⁶

There is some limitation in this study: because of the screening-urinalysis based study, patients positive for protein and/or occult blood on three serial occasions are recommended to refer a pediatric nephrologists freely, who make a decision for further examinations including renal biopsy. Therefore, the pathological findings of the children with hematuria and proteinuria cannot be available. The lack of pathological information offers a hindrance to investigate the histopathology of ORG in children.

In conclusion, although the further study is clearly needed, obesity can be associated with the development of renal injury characterized by proteinuria and hematuria even in childhood and early intervention to lose weight should be mandatory, as the benefit of weight loss in ORG in adult is reported to be limited.

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