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CLINICAL STUDY

Preliminary Study of Renal Hemodynamic Alteration in Early Childhood Diabetes Mellitus

Suttipong Wacharasindhu[1], Rottanat Rugpolmuang[1], Thapana Roonghiranwat[1], Vichit Supornsilchai[1], Taninee Sahakitrungruang[1], Suphab Aroonparkmongkol[1] and Tawatchai Chaiwatanarat[2]

[1]*Department of Pediatrics, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand;* [2]*Department of Radiology, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand*

Abstract

Renal hemodynamic study was performed in eight patients associated with type 1, early childhood diabetes mellitus (DM) and seven patients associated with type 2, early childhood DM. The results in both types of DM revealed a significant reduction in peritubular capillary flow and a high value of glomerular filtration rate (GFR) in the presence of reduced renal perfusion characteristic of glomerular hyperfiltration. These findings imply that renal ischemia has already developed in both types of early stage childhood DM and GFR is overestimated in DM, which may mislead to improper interpretation of renal function.

Keywords: renal hemodynamics, glomerular hyperfiltration, fractional excretion of magnesium, diabetic nephropathy, renal microvascular disease

INTRODUCTION

Diabetes mellitus (DM) has been considered to be associated with an inflammatory process of vascular disease.[1] Such vascular disease is the product of a variety of circulating toxins, namely oxidative stress, cytokines, and metabolic products such as sugar, lipid, and glycation end products, which induce both macrovascular and microvascular diseases.[2] In this regard, renal microvascular disease has been substantially confirmed in both type 1 and type 2 adult diabetic nephropathy (DN). Clinically, this is reflected by the altered intrarenal hemodynamics, which reveals a reduction in renal plasma flow (RPF) or peritubular capillary flow (PTCF).[3,4] Therefore, the purpose of this study is to assess renal hemodynamics in early childhood DM patients associated with normal serum creatinine concentration and normoalbuminuria.

MATERIAL AND METHODS

Eight patients with type 1 DM and seven patients with type 2 DM were recruited in this study. All of them had no clinical evidences of microvascular complications such as diabetic retinopathy or microalbuminuria (20 μg/mg creatinine). Five healthy subjects were recruited as a control group.

Blood specimen was collected in the early morning after 10 h fasting for the measurement of fasting plasma glucose (FPG), blood urea nitrogen, creatinine, cholesterol, hemoglobin A1C (HbA1c), and magnesium simultaneously with the measurement of urine creatinine and urine magnesium levels in all diabetic children and control.

The intrarenal hemodynamic study by simultaneous assessments of effective RPF using ^{131}I-labeled orthoiodohippuric acid (hippuran) and of glomerular filtration rate (GFR) using ^{99m}Tc-labeled diethylenetriaminepentaacetic acid (DTPA) was determined by the previously described method.[5] Fractional excretion of magnesium (FE Mg), which indirectly reflects tubulointerstitial fibrosis, was derived from the following formula:

$$\text{FE Mg} = \frac{\text{Urine magnesium}}{\text{Plasma magnesium}} \times \frac{\text{Plasma creatinine}}{\text{Urine creatinine}} \times 100\%^{6}$$

Address correspondence to Suttipong Wacharasindhu, Department of Pediatrics, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: Wacharasindhu@yahoo.com

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This study has been approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

RESULTS

Baseline clinical data of all patients are demonstrated in Table 1. Children with type 1 DM have been suffered from diseases for a longer period of time than those with type 2 DM. In addition, a poorer control of diabetes was demonstrated in children with type 1 DM who showed higher FPG and HbA1c levels.

As indicated in Table 2, the serum creatinine values of both type 1 and type 2 DM were not significantly different from the healthy subjects. FE Mg values were abnormally elevated in type 1 DM, but the difference did not reach the level of statistic significance. Creatinine clearance was relatively high in both types of DM. The intrarenal hemodynamics revealed a significant reduction in PTCF in both types of DM.

DISCUSSION

The renal hemodynamics was performed in early childhood DM, which is reflected by a normal serum creatinine concentration, and the value of microalbumin/creatinine ratio was in the normal range (20 μg/mg creatinine). The result of this study in both types of DM revealed a tendency for reductions in RPF and PTCF. However, a significant reduction was observed only in PTCF, which directly supplies the tubulointerstitial structure. This study implies that renal ischemia has already developed in this very early stage of childhood DM. The reduction in PTCF documented in this study is similar to that observed in adult type 2 DM associated with normoalbuminuria and normal serum creatinine concentration.[4,5] The difference is that such magnitude of renal ischemia in adult type is usually associated with evidence of tubulointerstitial injury indirectly reflected by the abnormally elevated value of fractional excretion of magnesium (FE Mg).[6] FE Mg, which has previously been shown to correlate directly with the degree of tubulointerstitial fibrosis,[6–8] was higher in type 1 DM (2.9 ± 0.5%) than in control group (2 ± 0.5%). However, the difference does not reach the level of statistic significance. This is probably due to a limited number of subjects in this study.

In addition to the reduction in renal perfusion, the GFR was relatively high in the presence of the state of renal hypoperfusion. This is a characteristic of glomerular hyperfiltration phenomenon reflected by a high value of filtration fraction. In fact, this is an overestimation of the GFR and may mislead to wrong interpretation of the status of renal function in these patients. In this regard, creatinine clearance is likely to be overestimated, and diagnostic markers such as serum creatinine determination or microalbuminuria cannot differentiate early childhood DM from normal healthy subject. The duration of DM and level of plasma glucose had no correlation with renal hemodynamic study in this study, and this may be due to insufficient subjects. However, the renal hemodynamic alteration such as a reduction in PTCF and the abnormal elevation of FE Mg[9] would be recognized in an early stage of childhood diabetes.

Recognition of early childhood diabetes is essentially relevant to preventive strategy of renal disease since treatment at early stage of diabetes is vulnerable to the restoration of renal function due to the adequacy of the mechanism of vascular repair associated with nitric oxide production documented in the early stage of DN.[2] Treatment at this early stage with appropriate vasodilators would be able to enhance the PTCF, thereby correct the renal ischemia that determines the renal disease progression, and eventually restores the renal function. In contrast, treatment with vasodilators under common practice can neither correct the renal ischemia nor restore renal function due to the delay of treatment at

Table 1. Baseline clinical data of children with diabetes and control.

	Type 1 DM ($n = 8$)	Type 2 DM ($n = 7$)	Control ($n = 5$)
Sex (male, female)	5, 3	4, 3	4, 1
Age (year)	14.4 ± 2.8	15.4 ± 2.0	16 ± 1.2
Duration of DM (year)	5.5 ± 1.9	3.6 ± 1.8	–
BMI (kg/m^2)	18.7 ± 1.0	30.1 ± 7.2	20.1 ± 2.7
FPG (mg/dL)	206.1 ± 106.3	127.6 ± 57.3	81.9 ± 8.0
HbA1c (%)	9.1 ± 1.3	6.8 ± 0.7	5.3 ± 0.4
Cholesterol (mg/dL)	183.1 ± 32.2	183.9 ± 15.4	166.5 ± 23.0

Notes: DM, diabetes mellitus; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1C.

Table 2. Demonstrated the studies of renal function an intrarenal hemodynamics in early childhood DM.

	Controls	*p*-Value CVSDM1	Type 1 DM	*p*-Value CVSDM2	Type 2 DM
1. Serum creatinine (mg/dL)	0.5 ± 0.1	NS	0.5 ± 0.1	NS	0.6 ± 0.1
2. FE Mg (%)	2 ± 0.5	NS	2.9 ± 0.6	NS	2 ± 2
3. Creatinine clearance (mL/min/1.73 m^2)	119 ± 42	NS	137 ± 91	NS	167 ± 69
4. GFR (mL/min/1.73 m^2)	133 ± 30	NS	144 ± 28	NS	138 ± 40
5. RPF (mL/min/1.73 m$^{2)}$	601 ± 93	NS	503 ± 138	NS	432 ± 97
6. PTCF (mL/min/1.73 m^2)	484 ± 81	0.05	359 ± 134	0.01	314 ± 94
7. Filtration fraction (%)	0.2 ± 0.05	0.09	0.3 ± 0.1	0.1	0.29 ± 0.01

Notes: DM, diabetes mellitus; GFR, glomerular filtration rate; RPF, renal plasma flow; PTCF, peritubular capillary flow.

the late stage associated with altered vascular homeostasis and an impaired nitric oxide production.

In conclusion, this study is in favor of an implementation of vasodilator treatment in early childhood DM during an environment favorable for vascular angiogenesis and renal regeneration.

***Declaration of interest*:** We declare no conflict of interest. We are responsible for the writing and the detailed issue in this article.

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