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Narisa Futrakul, Papada Chaisuriya, Kavi Ratanabanangkoon & Prasit Futrakul

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LETTER TO THE EDITOR

Microvascular dysfunction in normotensive, normoalbuminuric, normo- or hyperfiltrate type 2 diabetes

Due to the present therapeutic failure in restoring renal perfusion and function in diabetes under current practice, which is usually initiated at a rather late stage of diabetic kidney disease (DKD) associated with an impaired renal function,[1] an alternative conceptual view of therapeutic strategy is to recognize the DKD at an early stage and to implement the treatment as a primary prevention at this early reversible stage aiming to restore the renal perfusion and function.[2] This conceptual view has recently been supported by several studies that demonstrate the beneficial effect of vasodilator(s) angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) in enhancing the renal perfusion and restoring the creatinine clearance in normotensive, normoalbuminuric type 2 diabetes with a mildly impaired renal function.[3,4] In this regard, a concern has been raised whether vasodilator(s) play an important role in treating the diabetics associated with normotension. There is crucial evidence to respond to this issue. First, it has been documented that there is a disassociation between systemic pressure and renal microvascular resistance in this early stage of DKD patients; meaning that despite the patients are normotensive but the renal arteriolar resistance has already been elevated as well as the reduction in renal plasma flow and peritubular capillary flow – an indication of renal ischemia in normotensive normoalbuminuric patients.[3] Second, evidence of an early renal function impairment is documented as compared to the healthy subject.[4] Third, there is an abnormally elevated value of fractional excretion of magnesium (FE Mg) in these patients which implies the presence of tubulointerstitial fibrosis, since FE Mg has been demonstrated earlier to correlate with the magnitude of tubulointerstitial fibrosis.[5] Therefore, the preceding evidence-based informations render support to the therapeutic implementation with vasodilator(s) in normotensive, normoalbuminuric patients.

In addition to the above conceptual view concerning the therapeutic strategy in DKD patients associated with an impaired renal function, there has been evidence to support the presence of renal microvascular dysfunction in the earlier stage of DKD associated with normo- or hyperfiltration (a normal or increased creatinine clearance). In this regard, we have recently studied the vascular biomarkers such as nitric oxide (NO), endothelin 1 (ET-1), angiotensin converting enzyme (ACE), and an antiangiogenic factor; endostatin in this particular group of patients (number 40), which revealed significant alterations in ACE and ET-1 indicating a vasomotor disturbance (Tables 1 and 2). Increased value of nitric oxide, ACE and ET-1 in this study and others[6–8] would likely represent the compensatory state of microvascular dysfunction in this earlier stage of DKD (renal hyperfiltration). A sustained glomerular hyperfiltration would lead to progressive DKD. This view is supported by a progressive rising of

Table 2. Demonstrated vascular biomarkers in normotensive, normoalbuminuric, normo- or hyperfiltrate type 2 diabetes.

	NO (μmol/L)	ET-1 (pg/mL)	ACE (ng/mL)	Endostatin (ng/mL)
I. Control	27 ± 12	0.85 ± 0.14	107 ± 30	101 ± 19
p Value (I:II)	0.08	<0.05	0.001	0.05
II. Normoalb DKD	40 ± 20	1.6 ± 0.6	149 ± 37	115 ± 24
p Value (I:III)	<0.05	<0.05	<0.001	<0.05
III. Microalb DKD	52 ± 21	1.8 ± 0.8	153 ± 26	142 ± 32

Table 1. Demonstrated renal function blood chemistry in normotensive, normoalbuminuric, normo- or hyperfiltrate type 2 diabetes.

	SCr (mg)/dL	CCr (mL/min/1.73 m^2)	eGFR (mL/min/1.73 m^2)	MA/Cr (mg/g)	FE Mg (%)	HbA_{1C} (%)
I. Control	0.6 ± 0.5	107 ± 16	101 ± 12	7 ± 5	1.2 ± 0.6	5.6 ± 0.2
p Value (I:II)	NS	<0.05	NS	NS	0.05	0.05
II. Normoalb DKD	0.68 ± 0.1	122 ± 25	109 ± 24	7.8 ± 12	2.6 ± 0.7	6.7 ± 1
p Value (I:III)	0.08	<0.05	<0.05	<0.001	<0.05	0.09
III. Microalb DKD	1 ± 0.3	95 ± 49	87 ± 23	108 ± 77	3.6 ± 12	7.6 ± 1.7

Notes: SCr = serum creatinine, CCr = creatinine clearance, eGFR = estimated GFR, MA/Cr = microalbumin:creatinine ratio, FE Mg = fractional excretion of magnesium, HbA_{1C} = hemoglobin A_{1C}.

endostatin which correlates with the renal disease severity.[9] The glomerular hyperfiltration would be ameliorated by glycemic control as well as a low dose of renin angiotensin system blockade.[10]

The preceding information renders support to the conceptual view that there would be never too early to treat DKD.[11]

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Narisa Futrakul
Renal Microvascular Research Group,
King Chulalongkorn Memorial Hospital,
Chulalongkorn University, Bangkok, Thailand
E-mail: fmednft@yahoo.com

Papada Chaisuriya and Kavi Ratanabanangkoon
Princess Chulabhorn Research Institute,
Bangkok, Thailand

Prasit Futrakul
Bhumirajanagarindra Kidney Institute and
Academy of Science, The Royal Institute of Thailand,
Bangkok, Thailand

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