Nonblood/Urine Biomarker of Progression of Kidney Disease in Diabetes Mellitus

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The correlation between autonomic nerve dysfunction and hypertension was described and recognized several centuries ago (1). It is only recently that the nephrology community focused on the effect of sympathetic overactivity on renal function. In the 1980s, abnormalities in the sympathetic nervous system were observed in patients with mild renal failure (2). The concept of the role of the sympathetic nervous system in hypertension and CKD was described and recognized several centuries ago (1). It is only recently that the nephrology community focused on the effect of sympathetic overactivity on renal function. In the 1980s, abnormalities in the sympathetic nervous system in hypertension and CKD were observed. Although compelling evidence has shown that autonomic neuropathy is associated with essential hypertension, insulin resistance, diuretic resistance, and tachycardic arrhythmias (4), the evidence for its role in diabetic kidney disease remains the least recognized and is not completely understood.

There is great variability in timing and severity of diabetic complications. For example, one individual with poorly controlled diabetes for a long time may have much less end organ damage or fewer complications than another individual with shorter duration and relatively controlled diabetes. There is an urgent need to identify reliable biomarkers to predict a more or less progressive course in patients with diabetic nephropathy. Current markers in blood or urine, such as microalbuminuria, turn out to be markers of diabetic kidney disease rather than being predictors of its progression (5).

In this issue of CJASN, Orlov et al. (6) have taken an important step by exploring the potential role of autonomic neuropathy and the progression of renal failure in patients with type 1 diabetes. Orlov et al. (6) undertook a post hoc analysis of 570 participants from the First Joslin Kidney Study of the Natural History of Microalbuminuria whose complete data were available. Cardiac autonomic neuropathy as defined (R-R variation <20) correlated with early GFR loss and incident advanced CKD. After adjusted logistic regression and Cox proportional hazard analysis, Orlov et al. (6) found a higher prevalence of Cardiac Autonomic Neuropathy and GFR loss in patients with microalbuminuria, regardless of the time of onset. Although this study uses data from another study on type 1 diabetes and Orlov et al. (6) performed an excellent analysis to examine their hypothesis, there are some issues that are worth careful attention. The First Joslin Kidney Study of the Natural History of Microalbuminuria used heart rate variability (HRV) to assess autonomic dysfunction. In general, even 24-hour HRV is not a highly sensitive test but has a negative predictive value of 99% (7). However, the reproducibility of this test even in normal subjects is not strong (8). Therefore, only one-time abnormal HRV may not reflect autonomic dysfunction.

Orlov et al. (6) report that patients with autonomic neuropathy were older, had longer uncontrolled diabetes, had higher urinary albumin excretion, and had lower eGFR at baseline. The majority of patients with longstanding diabetes are more likely than their newly diagnosed counterparts to be on a longer list of medications, including α/β-blockers or diuretics, which can potentially impair autonomic nervous system function. Thus, autonomic dysfunction may be a consequence of long-term uncontrolled diabetes or a side effect of some medications. Although their finding is similar to findings of the French Multicenter Study (9), it does not imply a causative relationship.

Recently, in an analysis of the data on the Framingham Heart Study offspring, Wuslin et al. (10) showed that imbalance in the autonomic nervous system predicted cardiovascular event, hypertension, and diabetes. The results from the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (11) and Telmisartan Randomised Assessment Study in Ace Intolerant Subjects with Cardiovascular Disease (Parallel trial) (12) studies showed that, in patients with diabetes ages ≥55 years old with established stable heart disease, those with heart rate >78 versus <58 bpm had a 77% increased risk of cardiovascular disease death and that participants were more likely to be hospitalized. In the Action to Control Cardiovascular Risk in Diabetes Trial, autonomic imbalance predicted sudden death with a hazard ratio of 1.22 (1.01–1.46) (13,14). In the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects Study, presence of autonomic imbalance on top of pain and numbness significantly increased mortality and hazard ratio. Vinik et al. (15) and Maser et al. (16) in meta-analyses of 15 studies showed that, in all but one study, the more abnormalities in autonomic function, the higher the hazard ratio in predicting mortality.

Lieb et al. (17) showed that one of the initial findings in newly diagnosed diabetes was abnormal parasympathetic function, which predicted cardiovascular disease. In addition, this was followed by markers of inflammation, such as IL-6 and TNFα, and a fall in the high molecular

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weight Adiponectin-Leptin ratio (17,18). This may also suggest the mechanism of kidney injury in diabetes. Interestingly, restoration of autonomic balance by using a dopamine agonist, such as bromocriptine, can reduce major adverse cardiovascular events by 52% within 1 year (19).

With regard to the implications for nephropathy, imbalance of the sympathetic and parasympathetic nervous system is able to activate some proinflammatory cascades, leading to progression of renal failure (20); therefore, it is wise to look for autonomic dysfunction early in the course of diabetes.

In the past, many biomarkers from blood or urine were tested to predict the course of diabetic nephropathy with limited success (21). The ideal biomarker should be inexpensive, noninvasive, and easily measured and interpreted. In this line, Sudoscan/EZscan measures electrochemical skin conductance of hands and feet. This is a fast, promising, and sensitive tool to detect neuropathy in patients with diabetes mellitus (22). Two small studies from China and Germany showed that there is a strong correlation between Sudomery score and presence of nephropathy in patients with diabetes (23,24).

The findings in the paper by Orlov et al. (6) are noteworthy and important to both theoretical and clinical nephrology. However, numerous questions still remain unanswered. Why does this proposed correlation not apply to all patients with diabetic nephropathy? Are those patients with autonomic dysfunction the same as patients with salt-sensitive hypertension? What accounts for the great variability in the severity of autonomic dysfunction in patients with diabetic nephropathy? At the moment, the answers to these questions and several others remain uncertain. The strength of the study by Orlov et al. (6) is that it introduces a pathophysiologic concept for future clinical experiments. This study suggests a need for well designed clinical trials to examine the role of autonomic dysfunction in diabetic nephropathy, especially when the evidence of sympathetic overflow in hypertension and insulin resistance is strong (6).

In conclusion, the pathogenesis of diabetic kidney disease is multifactorial, and autonomic neuropathy is just one of the players in this context. It took centuries to understand the role of the autonomic nervous system in healthy populations. Assessment of autonomic nervous system function might prove to be a good biomarker for the prediction of progression of diabetic kidney disease, offering the potential for a novel therapeutic approach through restoration of autonomic balance, but it is still in an early phase of development.

Disclosures
None.

References


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See related article, “Cardiac Autonomic Neuropathy and Early Progressive Renal Decline in Patients with Nonmacuroalbuminuric Type 1 Diabetes,” on pages 1136–1144.