Diurnal blood pressure profile, autonomic neuropathy and nephropathy in diabetes

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Given the crucial role of elevated blood pressure (BP) in the progression of diabetic nephropathy, the study of the diurnal variation in BP in diabetes is a surprisingly late phenomenon. It is well documented that the normal night-time drop in BP is reduced in patients with increased urinary albumin excretion (UAE) and in patients with autonomic neuropathy (1). Several recent studies have demonstrated an association between autonomic neuropathy, reduced night-time fall in BP and elevated UAE (2, 3).

The question of a possible causative role of autonomic neuropathy in the development of diabetic nephropathy has naturally arisen (2, 3) and was actually coined 10 years ago (4, 5). The proposed pathogenic link is a higher BP burden at night which is more readily transmitted to glomeruli because of renal vasodilation. If true, ambulatory BP monitoring could identify normoalbuminuric patients at risk of progressing to microalbuminuria as those with a disturbed diurnal BP variation. In support of the theory it has been reported that even in normoalbuminuric patients a proportion present abnormal regulation of BP (6). However, we do not know how many of these patients ultimately develop microalbuminuria. The night/day ratio of BP in patients who progress during a 3-year follow-up study overlaps with the values for the non-progressors (7). Diabetes duration is an important confounder, since the night/day ratio of BP is elevated in very long-term normoalbuminuric patients, who *a priori* are expected to have a favourable prognosis (1, 7). Against the theory is the fact that a substantial number of patients with microalbuminuria show a night/day ratio which is considered normal. Thus a disturbed diurnal BP regulation cannot be decisive for progression to microalbuminuria (8). Furthermore, it should be recognized that the night/day ratio of BP is not a very reproducible parameter and this problem cannot be overcome by remeasurement as easily as for UAE. Therefore it is not plausible that ambulatory BP monitoring will become a sensitive instrument for detecting normoalbuminuric patients at risk of progressing.

Alternatively, autonomic neuropathy and blunted diurnal variation of BP could merely be cofactors. According to this view autonomic neuropathy has no independent role in the development of diabetic renal disease (but may promote progression of nephropathy when established). The coexistence of autonomic neuropathy and nephropathy might be explained by the effects of poor metabolic control on a background of unknown genetic factors. Obviously there is a need for longitudinal studies in normoalbuminuric patients: this should combine information about the evolution of UAE, ambulatory BP and autonomic neuropathy.

The discussion of the role of very early autonomic neuropathy in insulin-dependent diabetes mellitus (IDDM) patients closely mimics the classical controversy about the temporal relationship between UAE and BP in incipient diabetic nephropathy (i.e. which is the first to rise?). Our understanding of this relationship has been affected by the methodology for studying BP. Originally it was thought that a rise in (clinical) BP appeared rather late after patients had become microalbuminuric. After the measurement of ambulatory BP a parallel rise of BP and UAE has been observed from normoalbuminuria to even low microalbuminuric levels (7). If the diagnosis of autonomic neuropathy is based on a standard battery of bed-side tests, this complication is mainly seen in patients with overt nephropathy. It is conceivable that the relationship between UAE and autonomic neuropathy can be expanded if autonomic neuropathy is evaluated by a more refined test such as analysis of 24 h heart rate variability (9).

The exact pathogenic mechanism explaining the impaired reduction of night-time BP in diabetes is not known. Autonomic neuropathy and unopposed nocturnal sympathetic cardiovascular stimulation are probably of primary importance, but the accumulation of sodium and water with a nocturnal shift to the intravascular space also seems to be involved in patients with diabetic nephropathy and markedly reduced glomerular filtration rate (10). In non-insulin-dependent diabetes mellitus patients with high night-time BP and autonomic neuropathy, the nocturnal level of atrial natriuretic peptide has been reported to be higher, and the level of plasma renin activity and aldosterone to be lower than in patients with a normal reduction of night-time BP (11). This observation may be explained as a defence against volume expansion. The significance of volume expansion has recently been challenged in a study which found no association between extracellular volume and reduction of night-time BP in IDDM patients with nephropathy (12).
If elevated night-time BP accelerates the decline of renal function in diabetic nephropathy, it is logical to attempt to restore a normal circadian variation in BP. This might be accomplished by a shift from a morning to an evening dose of some anti-hypertensive drugs (13), but this has not been reported in diabetic patients and the effects are not known. It has long been recognized that reduced heart rate variability in post-myocardial infarction patients heralds a poor prognosis. Administration of lipophilic beta blockers as secondary prophylaxis is of particular value in diabetic patients. Beta blockers improve some of the parameters indicative of autonomic dysfunction in (non-diabetic) post-myocardial infarction patients. It can therefore be hypothesized that cardioselective and lipophilic beta blockers might modulate the effects of autonomic dysfunction in diabetes either peripherally by opposing the sympathetic stimulus or by central acting mechanisms (9, 14).

We have seen the introduction of a new instrument with which to study IDDM patients with nephropathy (ambulatory BP monitoring) and the discovery of a new abnormality (elevated night-time BP), which add to the existing long list of abnormalities in these patients. However, it is far from proven that elevated night-time BP and autonomic neuropathy represent a causative factor. The only established risk factors for transition from normo- to microalbuminuria are still high normal values of the indicator itself (UA), poor glycaemic control and cigarette smoking.

**References**


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