Microalbuminuria is a marker for both hypertension and diabetic complications, and the association between elevated blood pressure (BP) and diabetic complications is well known. Until recently, focus has been directed toward increments in diastolic rather than systolic BP. Systolic BP often rises with age, whereas diastolic BP remains unchanged or declines, resulting in a widening of the pulse pressure (PP). These hemodynamic changes, thought to be because of the development of arteriosclerosis-induced stiffness of the arteries, were until recently thought to be physiological and benign in nature. However, several randomized trials have shown substantial benefits of treating isolated systolic hypertension in elderly patients, and several studies have shown that PP is a major, independent predictor of cardiovascular events in nondiabetic subjects. Moreover, studies have shown that PP is a major, independent predictor of cardiovascular events in nondiabetic subjects and type 2 diabetic patients, elevated PP and isolated systolic hypertension have been shown to be associated with microalbuminuria.

We have demonstrated previously a strong association between ambulatory PP and microvascular and macrovascular complications in a group of middle-aged Danish type 2 diabetic subjects, and, in particular, the association between PP and albuminuria was very strong. We suggested that PP could be a risk factor for the progression of albuminuria in this patient group, although the cross-sectional nature of the study did not allow for any firm conclusions regarding causality.

However, in this issue of Hypertension, Palmas et al present prospective data on this subject originating from the Informatics for Diabetes Education and Telemedicine (IDEATel) Study, a large prospective study evaluating telemedicine as a means of managing the care of older (age ≥55 years) Medicare beneficiaries with diabetes residing in New York state. Ambulatory BP, urinary albumin/creatinine ratio (ACR), hemoglobin A1c, blood lipids, and so forth were assessed at baseline. As one would expect, greater severity of albuminuria was associated with traditional risk factors for cardiovascular disease (higher office and ambulatory BP, nondipping, unfavorable lipid profile, and smoking).

A 1- and/or 2-year follow-up ACR was available on 1040 of 1665 included subjects. In a repeated-measures mixed linear model adjusting for baseline ACR and multiple other covariates, both ambulatory and office PP were strongly and independently associated with follow-up ACR. Cox proportional hazards regression was used to test whether office and ambulatory PP were independent predictors of progression of albuminuria in the 164 of 954 subjects without macroalbuminuria at baseline who progressed ≥1 level from normoalbuminuria or microalbuminuria to microalbuminuria or macroalbuminuria. After adjustment for other clinical covariates, ambulatory PP, age, glycemic control, number of antihypertensive medications, and smoking were, whereas office PP was not, independently associated with progression of albuminuria. The authors suggest that ambulatory PP may predict the progression of albuminuria, above and beyond office BP, in elderly subjects with type 2 diabetes.

The results of the present study raise several questions. First, does calculation of PP add to the predictive value of BP measurement in these subjects? Numerous studies have emphasized the importance of systolic rather than diastolic BP for the development and progression of diabetic complications, but whether PP is superior to systolic BP as a predictor of diabetic complications is not yet fully elucidated. The solution of this issue is impeded by the collinearity between these 2 variables. In fact, in the present study, PP was also strongly correlated with the other BP parameters, for which reason they were not included in the analyses to avoid excessive multicollinearity, and, therefore, the present study does not address this question. In the Hypertension Optimal Treatment (HOT) Study, a low BP goal was associated with a better outcome but only in diabetic subjects; however, at this point no study has been specifically designed to examine whether antihypertensive intervention directed against elevations of PP provides a more favorable outcome than interventions directed at other BP components.

Second, is ambulatory PP superior to office PP in the prediction of progression of diabetic kidney disease? Compared with office BP measurements, ambulatory BP monitoring offers several advantages, including multiple measurements that improve reproducibility and a much better correlation with hypertensive organ damage, for example, left ventricular hypertrophy. Furthermore, numerous studies have shown that ambulatory BP variables are better predictors than office BP variables for the development of cardiovascular disease in nondiabetic and diabetic subjects and for the progression of albuminuria in diabetic subjects. The present study adds the novel information that ambulatory PP
predicts the progression of albuminuria in elderly type 2 diabetic subjects, above and beyond office PP.

Third, what is the pathophysiological background for the association between an elevated PP and microvascular complications in type 2 diabetic patients? An augmented PP might to some extent be an epiphenomenon, reflecting a decreased elasticity of large and middle-sized arteries. One might imagine that the capability of these vessels to absorb changes in BP is decreased, and consequently, these vessels would be more likely to allow the propagation of an increased BP to the microcirculation. The resulting increased BP amplitude imposes a steep rise in shear stress on the microvasculature, especially if resistance vessel innervation and autoregulation is impaired (eg, because of neuropathy), resulting in capillary/glomerular hypertension and subsequent development of microvascular damage. In the kidney, an elevated systemic BP leads to hyperperfusion, glomerular hypertension, and subsequent glomerular leakage of plasma proteins, thus forming the basis for the increase in albuminuria.

In recent cross-sectional studies, elevations in PP have been associated with endothelial dysfunction as assessed by acetylcholine-stimulated vasodilation and systemic inflammation as measured by serum levels of C-reactive protein. If an increased PP promotes endothelial dysfunction and inflammation via the above-described microvascular shear stress, these well-established cardiovascular risk factors could represent a link between PP and vascular damage. However, the causal nature of these associations cannot be determined because of the cross-sectional design of the studies; thus, endothelial dysfunction and inflammation may as well accelerate the process of atherosclerosis, causing a stiffening of the arteries and subsequently leading to a widening of the PP. Hence, prospective studies are needed to clarify these associations.

In summary, the data from the present study provide further evidence of the importance of rigorous BP control for the prevention of diabetic kidney disease, and they highlight the superiority of ambulatory BP monitoring compared with office BP measurement in the individual risk evaluation. Ambulatory PP was a very strong predictor of the progression of albuminuria in elderly diabetic subjects, and this parameter could be important in the future risk assessment in diabetic subjects. However, whether PP is superior to systolic BP in this respect remains to be clarified. Moreover, intervention studies are needed to evaluate whether antihypertensive treatment should be initiated on the basis of PP rather than systolic BP values in this patient category.

Disclosures

None.

References

Ambulatory Pulse Pressure and Progression of Albuminuria in Type 2 Diabetes: Evidence Provided, New Questions Emerge

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