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Hypertension and Diabetes Mellitus: Coprediction and Time Trajectories

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Abstract

Type 2 diabetes mellitus and hypertension overlap in the population. In many subjects, development of diabetes mellitus is characterized by a relatively rapid increase in plasma glucose values. Whether a similar phenomenon occurs during the development of hypertension is not known. We analyzed the pattern of blood pressure (BP) changes during the development of hypertension in patients with or without diabetes mellitus using data from the MCDS and in the FOS during a 7-year follow-up. Diabetes mellitus at baseline was a significant predictor of incident hypertension (in FOS, odds ratio, 3.14; 95% confidence interval, 2.17–4.54) independently of sex, age, body mass index, and familial diabetes mellitus. Conversely, hypertension at baseline was an independent predictor of incident diabetes mellitus. In comparison with the nonconverters group, hypertension and diabetes mellitus converters shared a metabolic syndrome phenotype (hyperinsulinemia, higher body mass index, waist girth, BP, heart rate and pulse pressure, and dyslipidemia). Overall, results were similar in the 2 ethnic groups. We conclude that (1) development of hypertension and diabetes mellitus track each other over time, (2) transition from normotension to hypertension is characterized by a sharp increase in BP values, and (3) insulin resistance is one common feature of both prediabetes and prehypertension and an antecedent of progression to 2 respective disease states.

Keyword: Diabtes mellitus, pre hypertension, pre diabetes, glucose levels

Introduction

Diabetes mellitus and hypertension are among the most common diseases and cardiovascular risk factors, respectively, worldwide, and their frequency increases with increasing age.[1] Elevated blood pressure (BP) values are a common finding in patients with type 2 diabetes mellitus (T2D) and are thought to reflect, at least in part, the impact of the underlying insulin resistance on the vasculature and kidney.[1] On the contrary, accumulating evidence suggests that disturbances in carbohydrate metabolism are more common in hypertensive individuals,[2,3] thereby indicating that the pathogenic relationship between diabetes mellitus and hypertension is actually bidirectional.

The development of hypertension in diabetic individuals not only complicates treatment strategy and increases healthcare costs but also heightens the risk for macrovascular and microvascular complications considerably.[2,4] Although BP lowering is followed by a significant reduction in cardiovascular and microvascular morbidity and mortality,[5,6] a large proportion of diabetic subjects exhibit poorly controlled hypertension. This observation may

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reflect not only delayed recognition of the presence of hypertension, clinical inertia, and poor adherence to the prescribed regimen but also uncertainty regarding the treatment targets and pathogenic correlation.

Methods

Study Populations

The MCDS is a population-based cohort participating in a longitudinal survey of incident diabetes mellitus and cardiovascular risk factors. Low-income neighborhoods in Amabala were identified, and a complete enumeration of these was performed from November 2016 to October 2019. Among the 15532 inhabitants of these neighborhoods, 2280 men and women (aged 35–64 years) were randomly selected from 6 low-income colonias examined between 1990 and 1992 and invited to return for 2 follow-up examinations, the first conducted between 1993 and 1995 and the second between 1997 and 1999. Of the 1770 subjects participating in the first follow-up (at 3.25 years), 1753 returned for the second follow-up (at 7 years). The clinical characteristics of the subjects not returning for the second follow-up were essentially superimposable on those of the subjects who did (data not shown).

Examinations were standardized and included interviews, anthropometry, BP measurements, a fasting blood draw, and a 75-g oral glucose tolerance test. Trained interviewers obtained information on medical history, medication use, and smoking status.

The FOS is a community-based cohort including 3754 men and women who attended the fifth clinic examination of the FHS. Participants were followed up from baseline to the sixth and seventh offspring exams, for an average period of 7 years. We used the exam visit date when a new case of diabetes mellitus or hypertension was identified as the date of diagnosis; otherwise, follow-up was censored at last follow-up (examination 6 or 7) for participants remaining nondiabetic or nonhypertensive.

In both cohorts, hypertension was defined as a systolic BP ≥140 mm Hg or a diastolic BP ≥90 mm Hg or current antihypertensive treatment. In both studies, subjects whose BP was <140/90 mm Hg at baseline and both follow-up visits were classified as normotensives, those whose BP was <140/90 mm Hg at the first visit who became hypertensive at the second or third visit were classified as converters. T2D was classified as a fasting plasma glucose concentration ≥126 mg/dL or a 2-hour plasma glucose concentration ≥200 mg/dL on a standard 75-g oral glucose tolerance test. Subjects who gave a history of diabetes mellitus and who at the time of their clinical examination were taking oral antidiabetic agents were also considered to have T2D regardless of their plasma glucose values. Insulin-taking diabetic subjects whose age of onset was ≥40 years or whose body mass index (BMI) was >30 kg/m^2 were also considered to have T2D. Subjects with type 1 diabetes mellitus were excluded. Subjects who developed diabetes mellitus at the first or second follow-up were denoted as converters. Subjects who tested normal on the oral glucose tolerance test on all 3 examinations were considered to be bona fide nonconverters during the observation period.

Anthropometric Measurements

Diabetes mellitus in at least one parent or sibling was coded as a positive family history of diabetes mellitus. Before examinations, all participants were asked to fast for at least 12 hours. Height, weight, waist and hip circumferences, and systolic and diastolic BP were measured; pulse pressure was calculated as the difference between systolic and diastolic BP and mean BP as the sum of diastolic BP and one third of pulse pressure.

Biochemical Measurements

Blood samples were obtained in the fasting state and 2 hours after a standard 75-g oral glucose load. Serum samples were centrifuged, divided into aliquots, and stored at −70°C until assayed. Fasting concentrations of serum insulin, proinsulin, plasma glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and plasma glucose and insulin concentrations 2 hours after an oral glucose load were determined as described elsewhere[7] at baseline and at follow-up.

Results

Development of Hypertension

At the 3 examinations, 16% to 46% of the study subjects were hypertensive; among them, the prevalence of diabetes mellitus (20%–39%) was significantly

higher than that among normotensive subjects (P<0.0001 for all 3 data sets_. Among subjects who were normotensive at baseline (n=1876), 108 became hypertensive at 3.25 years; another 107 subjects who were normotensive at both baseline and 3.25 years were found to be hypertensive at 7 years, and 28 other subjects who were normotensive at baseline and missed examination 2 were hypertensive at examination 3. Thus, a total of 243 subjects converted to hypertension during the 7-year follow-up, yielding a crude conversion rate of ≈2% per year.

In comparison with subjects who were seen and found to be normotensive at all 3 examinations (nonconverters), converters to hypertension were older, heavier with a more central fat distribution, and had higher systolic and diastolic BP values and higher pulse rate at baseline regardless of their time of conversion. Diabetes mellitus was more prevalent among either group of converters than in nonconverters. Moreover, among normotensive individuals, diabetes mellitus at baseline was a significant predictor of incident hypertension independently of age, BMI, and family history of diabetes mellitus. Of note, when the baseline mean BP was included in the model, the predictive value of diabetes mellitus was attenuated and became nonsignificant .

All subject groups exhibited weight gain during the observation period independently of the conversion status or the time of conversion. In MCDS, the increase in BMI was a significant independent predictor of incident hypertension (the hazard ratio for 1 SD change in BMI was 1.31; 95% CI, 1.12–1.55 and in the same model, the corresponding hazard ratio for the presence of diabetes mellitus at baseline was 1.79; 95% CI, 1.14–2.77). On conversion, both systolic and diastolic BP values rose markedly and similarly in both groups of hypertension converters .Using only the data of MCDS subjects not receiving antihypertensive treatment, the rise in systolic BP was 19 (14) mm Hg in subjects converting at examination 2 (n=65) and 19 (17) mm Hg in those (n=60) converting at examination 3. Values higher than the 90th percentile of the changes in systolic BP observed in nonconverters were found in 70% of the subjects converting at examination 2 and in 58% of those converting at examination 3. Similar changes were observed in the converters of FOS. The presence of diabetes mellitus did not consistently affect the pattern of BP change in patients developing hypertension during the follow-up. Thus, in MCDS patients not receiving antihypertensive medications, the increase in systolic BP in those converting to hypertension at examination 2 was 18 mm Hg if nondiabetic and 20 mm Hg if diabetic. On the contrary, the corresponding changes in systolic BP for patients converting at examination 3 were 27 mm Hg in diabetic versus 17 mm Hg in nondiabetic patients (P<0.05)..

Development of Diabetes Mellitus

Among subjects who were nondiabetic at baseline (n=1966), 89 had developed diabetes mellitus by 3.25 years; another 71 subjects who were nondiabetic at both baseline and 3.25 years were found to be diabetic at 7 years, and 10 other subjects who were nondiabetic at baseline and missed examination 2 were diabetic at examination 3. Thus, a total of 170 subjects converted to diabetes mellitus during the 7-year follow-up, yielding a crude conversion rate of 1.2% per year. Among nondiabetic individuals, hypertension at baseline was more prevalent among diabetes mellitus converters than nonconverters (25% versus 15%; P=0.001) and was a significant predictor of incident diabetes mellitus (in FOS, OR, 3.33; 95% CI, 2.50–4.44) independently of sex, age, BMI, and familial diabetes mellitus .Again, the increase in BMI during the observation period was a significant predictor of incident diabetes mellitus (in MCDS, the hazard ratio for 1 SD change in BMI was 1.36; 95% CI, 1.16–1.60 and the corresponding hazard ratio for presence of hypertension at baseline in the same model was 1.80; 95% CI, 1.03–3.04). Among the 1656 participants who were normotensive and nondiabetic at baseline, 104 had converted to diabetes mellitus at 7 years, 165 to hypertension, and 24 to both diabetes mellitus and hypertension. In comparison with the nonconverters group, hypertension and diabetes mellitus converters shared most phenotypic traits, namely, higher BMI, waist girth, BP, heart rate and pulse pressure values, serum triglycerides, and plasma insulin concentrations .

Discussion

The first main finding of the present study is that not only does the presence of hypertension predict future diabetes mellitus, in agreement with earlier epidemiological observations,[2,3,8,9] but also the incidence of hypertension increases significantly in the presence of diabetes mellitus. During the 7 years

of follow-up, BP behaved as a tracking variable as individuals who converted to hypertension (at the first or second follow-up visit) had increased baseline BP values compared with nonconverters, although still within the normal range.[10] Indeed, baseline BP was the strongest predictor of incident hypertension, and its inclusion in the statistical model significantly attenuated the predictive value of diabetes mellitus. More strikingly, hypertension and diabetes mellitus tracked each other consistently .Thus, the general population contains a pool of individuals with the phenotype of the metabolic (or insulin resistance) syndrome from which new hypertension or diabetes mellitus (or both) emerge over time. Importantly, weight gain may be one factor that contributes to the development of both hypertension and diabetes mellitus. Parenthetically, the increased incidence of hypertension in patients with diabetes mellitus may also reflect the closer surveillance of these individuals (ie, a small detection bias). The second, and possibly the most important, finding of this study is that the progression from normotension to hypertension in individuals destined to become hypertensive is marked by a steep increase in BP values averaging 20 mm Hg for systolic BP within 3.5 years. In >60% of the converters, the increase in BP values during the period that preceded conversion was greater than the 90th percentile of the changes in systolic BP observed in nonconverters. This biphasic BP pattern is similar to that previously described for blood glucose values in MCDS individuals developing diabetes mellitus.[7] Finally, both the coprediction of hypertension and diabetes mellitus and this biphasic pattern of progression are not unique to Hispanic individuals because essentially the same findings were observed in the non-Hispanic white population of FOS.

One potential factor responsible for the covariance of diabetes mellitus and hypertension is insulin resistance. Of note, in a subcohort of FOS with a shorter follow-up, an inverse association between incident hypertension (or BP progression) and a proxy of insulin resistance was seen principally in younger people.[10] Here, however, both fasting plasma insulin (a typical proxy for insulin resistance in epidemiological studies) and plasma insulin concentrations 2 hours after glucose ingestion were consistently higher at baseline in both hypertension and diabetes mellitus converters. Furthermore, baseline insulin levels copredicted both hypertension and diabetes mellitus after controlling for age and BMI and also for baseline BP and plasma glucose values .This pattern of results lends support to the notion that insulin resistance is one common feature of both prediabetes and prehypertension, and one antecedent of progression to the 2 respective disease states.

Apart from the detrimental effects that disturbed insulin signaling exerts on carbohydrate metabolism, the hyperinsulinemia that characterizes insulin resistance states leads to vascular smooth muscle cell proliferation and increased vascular stiffness, which predispose to the development of hypertension. Additionally, insulin may directly or indirectly impair vasodilation and increase oxidative stress and the inflammatory process in the vascular wall. The sum of these effects is the impaired autoregulation of vascular tone, increased vascular resistance, and BP elevation. Finally, the antinatriuretic properties of insulin increase renal retention of sodium and water leading to volume overload, thereby predisposing to the development of hypertension.

Conclusion

In line with these suggestions, in our population, BMI values at baseline and weight gain during the observation period were significant predictors of both incident hypertension and diabetes mellitus, whereas heart rate and pulse pressure, both raw indices of sympathetic nervous system activity, were found to be elevated in patients who converted to hypertension. Finally, obese individuals with or without diabetes mellitus have been shown to have reduced concentrations of circulating natriuretic peptides. Because these molecules favorably affect intravascular volume status and vascular tone, this mechanism may be involved in the pathogenesis of hypertension in patients with diabetes mellitus.

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