Glucose and Non-glucose Predictors of Future Onset of Type 2 Diabetes in Newly Diagnosed Essential Hypertensives

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Background: Baseline fasting plasma glucose (FPG) level predicts the onset of type 2 diabetes mellitus (DM). Other predictors have been less investigated. This study aimed to investigate non-glucose predictors together with FPG for future onset of type 2 DM in fresh essential hypertensives.

Methods: Consecutive nondiabetic patients with newly diagnosed essential hypertension were prospectively evaluated for diurnal blood pressure (BP) change by ambulatory BP monitoring, vascular endothelial function by plethysmography, and biomarkers by blood biochemistry. They were then given guideline-based treatment and followed-up regularly for more than 5 years.

Results: During a mean follow-up period of 5.9 years, 6 of the 106 study patients developed DM. Baseline FPG, alanine aminotransferase (ALT) level, and day-night difference in diastolic BP were related to future onset of DM. FPG > 5.8 mmol/L ($p = 0.034$) and ALT > 31 U/L ($p = 0.048$) independently and day-night difference in diastolic BP $\leq 2.9\%$ potentially predicted new-onset DM ($p = 0.089$). Simultaneously having at least 2 of the indicators mentioned above at baseline is predictive of new-onset DM. Parameters of reactive hyperemia by plethysmography were not relevant.

Conclusion: In addition to FPG, baseline serum ALT level independently and diurnal diastolic BP changes potentially predicted future onset of type 2 DM in newly diagnosed hypertensives. Both glucose and non-glucose indicators could be examined together for early risk stratification of future DM. [J Chin Med Assoc 2009;72(11):564–572]

Key Words: blood pressure, diabetes mellitus, diurnal change, fasting glucose, liver function

Introduction

Type 2 diabetes mellitus (DM) is a disease with multiple complications and premature mortality, and is suggested to be equivalent to myocardial infarction with regard to the significantly increased risk of future or recurrent cardiovascular events.[1] Hypertensive patients frequently have associated insulin resistance and are predisposed to DM with increased cardiovascular risk.[2–4] In treated hypertensive subjects, new-onset DM (which usually takes a considerable duration of time to develop) could be directly associated with cardiovascular events[5] or carry a risk of subsequent cardiovascular disease similar to that in previously known diabetic patients.[6]

In addition to increased body mass index, impaired glucose tolerance (IGT) could be directly related to future onset of type 2 DM.[7] Impaired fasting glucose (IFG), while is more easily and commonly measured, has also been proven to be an important risk factor for the development of type 2 DM in healthy subjects and in hypertensive patients under treatment.[8–10] Nevertheless, not all subjects with increased body mass index, IGT or IFG may go on to develop DM. Comprehensive risk stratification with both glucose and

non-glucose parameters may be required to more efficiently identify the subjects at most risk of developing type 2 DM. It could be particularly important to patients with untreated, newly diagnosed essential hypertension not only due to the potential prognostic impacts[4,6] but also because of concern that some antihypertensive medications may increase the risk of subsequent DM in the future.[11–13]

It has been suggested that some non-glucose indicators may be related to the onset of type 2 DM in specific cohorts.[14–17] The loss of diurnal changes in blood pressure (BP), while being linked to increased cardiovascular risk in common hypertensives,[14,15] is associated with the presence of abnormal glucose metabolism in young essential hypertensives.[16] Elevated alanine aminotransferase (ALT), one of the liver enzymes, was associated with decreased hepatic insulin sensitivity and predicted the development of type 2 DM in Pima Indians.[17] In some other cohorts, endothelial dysfunction may also be detected before the development of type 2 DM.[18–20] However, it is not known whether the above parameters can predict the onset of type 2 DM in untreated, newly diagnosed essential hypertensives. This study was therefore conducted to prospectively evaluate the prognostic impacts of both glucose (fasting plasma glucose [FPG] level) and non-glucose (blood biochemistry, endothelial function, diurnal BP pattern) parameters on the future onset of type 2 DM in a cohort of ethnic Chinese patients with newly diagnosed essential hypertension in Taiwan.

Methods

Patient populations

Between May 1997 and October 2000, a series of 298 consecutive subjects suspected to have hypertension were prospectively investigated for a definite diagnosis of hypertension by a comprehensive protocol at the hypertension clinic of a national medical center in Taipei, Taiwan. In each subject, hypertension was evaluated and diagnosed according to the guidelines in *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Serial work-up was also done to detect the potential presence of secondary hypertension including renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, hyperthyroidism, hypothyroidism, and others. The presence of type 2 DM was determined by FPG level > 7.8 mmol/L in 2 separate tests.

Then, patients with newly diagnosed essential hypertension were prospectively enrolled if they could fulfill the diagnostic criteria and had not taken regular antihypertensive medication prior to the study. Patients were excluded if they had clinical evidence of secondary hypertension, type 1 or 2 DM, significant cardiovascular disease such as coronary artery disease, congenital heart disease, valvular heart disease, congestive heart failure, stroke, peripheral arterial occlusive disease, or other significant systemic diseases including liver dysfunction (elevated value 2-fold above the normal upper limit) and renal impairment (serum creatinine level > 1.7 mg/dL). Since the American Diabetes Association (ADA) criteria for DM were renewed in 2003 (FPG > 7.0 mmol/L in 2 separate tests),[21] the original records were reviewed again in 2005. Patients with initial FPG level > 7.0 mmol/L in 2 separate tests were also retrospectively excluded. The study protocol was approved by the Human Research Committee of the hospital. A written informed consent was obtained from each patient before the study.

BP and heart rate monitoring

All patients received ambulatory BP monitoring for 24 hours by the cuff-oscillometric method with the SpaceLabs 90207 ambulatory BP monitor (SpaceLabs Medical Inc., Redmond, WA, USA). During the procedure, the monitor was programmed to automatically record blood pressure every 20 minutes during the daytime (07:00 A.M. to 10:00 P.M.) and every 30 minutes during the night (10:00 P.M. to 07:00 A.M.). The mean BP at daytime and that at nighttime were calculated individually and analyzed for diurnal variation. In addition, patients were instructed to maintain their regular activities during the day and to follow the sleep schedule at night during the recording period.

Vascular endothelial function evaluation by plethysmography

A mercury-in-silastic strain-gauge venous plethysmograph (Hokanson EC 5R; Hokanson, Bellevue, WA, USA) was used to measure endothelial function of resistance vessels. The method has been described in detail in our previous study.[18] In brief, the patient was lying on a comfortable bed with forearm suspended above the level of the heart. The strain-gauge was placed over the right forearm, and a small cuff was inflated over the right wrist with suprasystolic pressure at 1 minute before and maintained throughout the measurement period. Meanwhile, venous return of forearm was prevented by a rapid-cuff inflator (Hokanson E-20) which afforded 50 mmHg pressure, and forearm blood flow (FBF) was calculated from the increased rate of the volume (mL/100 mL forearm volume per minute). A 7-minute flow recording

was repeated every 15 seconds for 2 minutes. An average of ≥ 3 curves for steady blood flow was used for the mean value of basal FBF. Five minutes after measurement of basal FBF, the upper arm cuff was inflated to a suprasystolic pressure (> 10 mmHg above systolic BP) for 5 minutes, which induced forearm ischemia. Then, the cuff was released and the FBF during reactive hyperemia was recorded every 15 seconds for 2 minutes. Peak value was usually obtained within the initial 30 seconds. The average of the highest 2 of the initial 3 recordings was defined as peak reactive hyperemic blood flow. Finally, to evaluate endothelial-independent vasodilatation effect, nitroglycerin 0.6 mg was administered sublingually after FBF returned to the baseline level. The measurements of BP and FBF were repeated as mentioned above.

Blood sampling

In each patient, a 10-mL blood sample was collected from peripheral vessels in the morning hours after an overnight fast. The blood sample was either analyzed immediately or stored in a −20°C refrigerator until analysis for other biomarkers. Plasma glucose was measured by an automatic chemistry analyzer from PrismaSystems Corp. (Rome, NY, USA). Lipid profiles including total cholesterol (TC), triglyceride (TG), and other biochemical parameters were measured using a Hitachi 7600-310 autoanalyzer (Hitachi, Tokyo, Japan).

Clinical follow-up

All the patients were prospectively followed-up at our hypertension clinics every 1–3 months for at least 5 years. Every patient was treated with at least 1 antihypertensive medication according to the contemporary antihypertensive guidelines (6th and 7th Joint National Committee guidelines or World Health Organization guidelines). In each patient, use of the new antihypertensive drugs such as calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) along with the old drugs including β-adrenergic blockers, α-adrenergic blockers, and diuretics to achieve the goal of guideline-recommended BP (< 140/90 mmHg) was encouraged. The regular antihypertensive medications used for more than 6 months were recorded. During the follow-up period, blood biochemistry studies including FPG, lipid profiles, liver and renal function tests were scheduled every 3–6 months according to the patient's individual condition. Clinical events including death, acute myocardial infarction, stroke, heart failure, coronary artery disease, or other significant systemic diseases were recorded if there were any.

The new onset of type 2 DM was confirmed according to ADA criteria (FPG > 7.0 mmol/L in 2 separate tests).[21] Between February and October 2006, all the patients were interviewed again either at clinics or via telephone. The medical records were also reviewed by an independent investigator blind to their medical history and clinical condition.

Statistical analysis

Data are presented as mean ± standard error of the mean unless otherwise indicated. The numerical variables and frequencies between groups were compared by Student's t test, Mann-Whitney U test, and/or χ^2 test as appropriate. Because of skewed distribution and in order to evaluate the prediction ability of parameters for new-onset DM, quartiles were used for further analysis. The Kaplan-Meier method with log-rank test was performed to assess the difference in the time course of disease-free survival between these groups. Univariate and multivariate Cox proportional hazards regression analyses were used to determine the independent predictors of end point in each group if appropriate. A p value < 0.05 was defined as statistically significant.

Results

Patient characteristics and clinical follow-up

A total of 106 consecutive non-diabetic patients with newly diagnosed essential hypertension were studied. At baseline, their mean age was 55.1 ± 1.0 years and 56% were males. The mean duration of follow-up was 70.6 ± 13.9 months. All the patients survived through the follow-up period. Of them, 6 patients (3 males, 3 females) developed new-onset DM, 1 during the 3rd year and the other 5 during the 5th and 6th years of follow-up. Table 1 shows the baseline clinical characteristics of the 100 patients without and the 6 patients with new-onset DM. Patients with new-onset DM had higher FPG level (p = 0.003) and serum ALT (p = 0.008) at baseline than those without. Eighteen (18.0%) of the patients without new-onset DM and 3 (50.0%) of the patients with new-onset DM had metabolic syndrome (p = 0.056).

During follow-up, most of the patients' systolic BP were kept around 120–150 mmHg and diastolic BP around 60–95 mmHg by various antihypertensive medications (usually calcium channel blockers, β-adrenergic blockers, ACEIs and ARBs, either alone or in combination). However, thiazide diuretics and α-adrenergic blockers were much less used unless in combination with other medications. The initial antihypertensive

Table 1. Baseline characteristics in 6 hypertensive patients with and 100 without new-onset diabetes mellitus*

	No DM (n = 100)	New-onset DM (n = 6)	p†
Men/Women	56/44	3/3	0.774
Age (yr)	54.9 ± 1.1	57.5 ± 4.6	0.613
BMI (kg/m²)	26.3 ± 0.3	26.2 ± 0.8	0.827
Waist circumference (cm)	86.3 ± 11.2	88.4 ± 12.9	0.657
Hip circumference (cm)	100.3 ± 8.9	101.5 ± 8.3	0.578
Metabolic syndrome	18 (18.0)	3 (50.0)	0.056
Blood chemistry			
Total cholesterol (mg/dL)	202.2 ± 4.1	230.0 ± 21.2	0.196
Triglyceride (mg/dL)	133.2 ± 7.2	143.2 ± 13.1	0.286
FPG (mmol/L)	5.3 ± 0.1	6.2 ± 0.2	0.005†
ALT (U/L)	28.4 ± 3.7	39.1 ± 4.9	0.010†
AST (U/L)	23.8 ± 1.2	28.5 ± 3.7	0.082
BUN (mg/dL)	14.9 ± 0.4	18.2 ± 2.5	0.224
Creatinine (mg/dL)	1.1 ± 0.1	1.0 ± 0.0	0.728
24-hour BP recording			
Daytime (07:00 A.M. to 10:00 P.M.)			
Systolic BP (mmHg)	150.9 ± 9.6	151.8 ± 8.2	0.853
Diastolic BP (mmHg)	100.4 ± 6.7	98.5 ± 4.3	0.253
Mean BP (mmHg)	116.7 ± 7.2	114.7 ± 5.3	0.632
Pulse pressure (mmHg)	50.2 ± 0.8	55.2 ± 2.1	0.043†
Heart rate (beat/min)	73.1 ± 5.4	74.4 ± 5.7	0.283
Nighttime (10:00 P.M. to 07:00 A.M.)			
Systolic BP (mmHg)	141.7 ± 8.3	145.4 ± 7.5	0.246
Diastolic BP (mmHg)	91.2 ± 4.5	97.6 ± 4.6	0.373
Mean BP (mmHg)	105.7 ± 6.4	112.7 ± 5.1	0.272
Pulse pressure (mmHg)	49.1 ± 0.9	51.0 ± 2.4	0.347
Heart rate (beat/min)	67.3 ± 4.4	68.5 ± 5.5	0.284
Day-night BP difference (%)			
Systolic BP	5.9 ± 0.7	3.4 ± 1.5	0.235
Diastolic BP	7.9 ± 0.8	0.7 ± 1.4	0.006†
Mean BP	6.9 ± 0.7	1.4 ± 1.4	0.019†
FBF by plethysmography (mL/100 mL/min)			
Baseline	4.6 ± 0.2	3.8 ± 0.5	0.534
At peak reactive hyperemia	15.6 ± 0.4	13.6 ± 0.9	0.240
After sublingual NTG	4.6 ± 0.2	3.6 ± 0.3	0.247

*Data presented as n or mean ± standard deviation or n (%); †Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables; ‡p < 0.05. DM = diabetes mellitus; BMI = body mass index; FPG = fasting plasma glucose; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; BP = blood pressure; FBF = forearm blood flow; NTG = nitroglycerin.

medications and the number of drugs used were similar between the 6 patients with and the 100 without new-onset DM.

Through the follow-up period, there were 8 patients with cardiovascular events, including 3 strokes, 1 acute myocardial infarction, 1 hospitalization for congestive heart failure, and another 3 with stable coronary artery disease proven by coronary angiography during the follow-up period. Among the 6 patients with new-onset DM, 1 experienced stroke, 1 had acute myocardial infarction, and another 1 had stable coronary artery disease following the onset of DM. These patients did not have the history of hepatitis during the follow-up period. The incidence of hard cardiovascular events including death, acute myocardial infarction and stroke was 4% in patients without and 33% in those with new-onset type 2 DM (p < 0.05).

24-hour ambulatory blood pressure monitoring

The differences in BP levels between daytime and nighttime (day-night difference) are also presented in Table 1. The difference was calculated by daytime BP minus nighttime BP then divided by daytime BP. Baseline day-night difference in diastolic BP (p = 0.004)

Table 2. Predictors for new-onset diabetes mellitus in hypertensive patients

	RR (95% CI)	p
Univariate Cox proportional hazards regression		
FPG > 5.8 mmol/L	15.01 (1.75–128.81)	0.014*
Day-night difference in diastolic BP ≤ 2.9%	6.99 (1.27–38.46)	0.025*
ALT > 31 U/L	6.06 (1.11–33.13)	0.038*
Multivariate Cox proportional hazards regression		
FPG > 5.8 mmol/L	10.47 (1.20–91.28)	0.034*
Day-night difference in diastolic BP ≤ 2.9%	4.44 (0.80–25)	0.089
ALT > 31 U/L	5.39 (0.98–29.62)	0.048*

*$p < 0.05$. RR = relative risk; CI = confidence interval; FPG = fasting plasma glucose; BP = blood pressure; ALT = alanine aminotransferase.

and that in mean BP ($p = 0.016$) but not systolic BP were significantly reduced in patients with new-onset DM compared to the patients without. Daytime pulse pressure was also increased in the former compared with the latter group. There were no differences in baseline heart rate, either in daytime or nighttime, between the 2 groups.

Basal and hyperemic FBF

As shown in Table 1, basal FBF was similar between patients with and without new-onset DM ($p = 0.356$). FBF significantly increased during reactive hyperemia in both groups ($p < 0.001$, respectively). There was no difference in FBF either during peak reactive hyperemia or after sublingual nitroglycerin administration between the 2 groups.

Antihypertensive medications during the follow-up period

All patients were treated according to the guidelines from *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* or guidelines from the World Health Organization. At final follow-up, the morning office BP was < 160/100 mmHg in all patients, < 140/90 mmHg in 90 patients (85%) and < 130/80 mmHg in 62 patients (58%). There were no differences in the final office BP and in the antihypertensive medications prescribed between patients with and those without new-onset DM during the follow-up period. The average number of antihypertensive medications was 2.2 in patients with new-onset DM and 2.3 in those without. Among the 6 patients with new-onset DM, 33% were treated with thiazide diuretics, 33% with β-adrenergic blockers, 33% with α-adrenergic blockers, 50% with ACEIs or ARBs, and 67% with calcium channel blockers before the onset of DM. The medications were similar in patients without new-onset DM (28% treated with thiazide diuretics, 40% with β-adrenergic blockers, 35% with α-adrenergic blockers, 52% with ACEIs or ARBs, and 72% with calcium channel blockers).

Predictors for new-onset diabetes by Cox proportional hazards analysis

In order to determine the predictors for new-onset DM in patients with essential hypertension, the optimal cutoff value of each potential parameter was constructed by quartiles because of the skewed distribution. Patients with FPG, ALT, or daytime pulse pressure in the highest quartile were compared with those in the quartiles below. On the other hand, patients with the day-night difference in diastolic or mean BP in the lowest quartile were compared with those in the quartiles above.

Table 2 shows the potential predictors for new-onset DM at follow-up. In univariate Cox proportional hazards analysis, FPG > 5.8 mmol/L (104 mg/dL) ($p = 0.014$), day-night difference in diastolic BP ≤ 2.9% ($p = 0.025$), and ALT > 31 U/L ($p = 0.038$) were associated with increased risk of new-onset DM. By multivariate Cox proportional hazards analysis, both FPG > 5.8 mmol/L (relative risk, 10.47; 95% confidence interval, 1.20–91.28; $p = 0.034$) and ALT > 31 U/L ($p = 0.048$) were independent predictors of new-onset DM in hypertensive patients. Day-night difference in diastolic BP ≤ 2.9% ($p = 0.089$) was borderline significant as an independent predictor for new-onset DM.

Predictors for new-onset diabetes by Kaplan-Meier analysis

Kaplan-Meier analysis was also done to further elucidate the relationship between the time course of new-onset DM and the potential parameters (Figure 1). Patients with baseline FPG > 5.8 mmol/L ($p = 0.001$) (Figure 1A), day-night difference in diastolic BP ≤ 2.9% ($p = 0.009$) (Figure 1B) or ALT > 31 U/L ($p = 0.018$) (Figure 1C) had significantly more new-onset DM
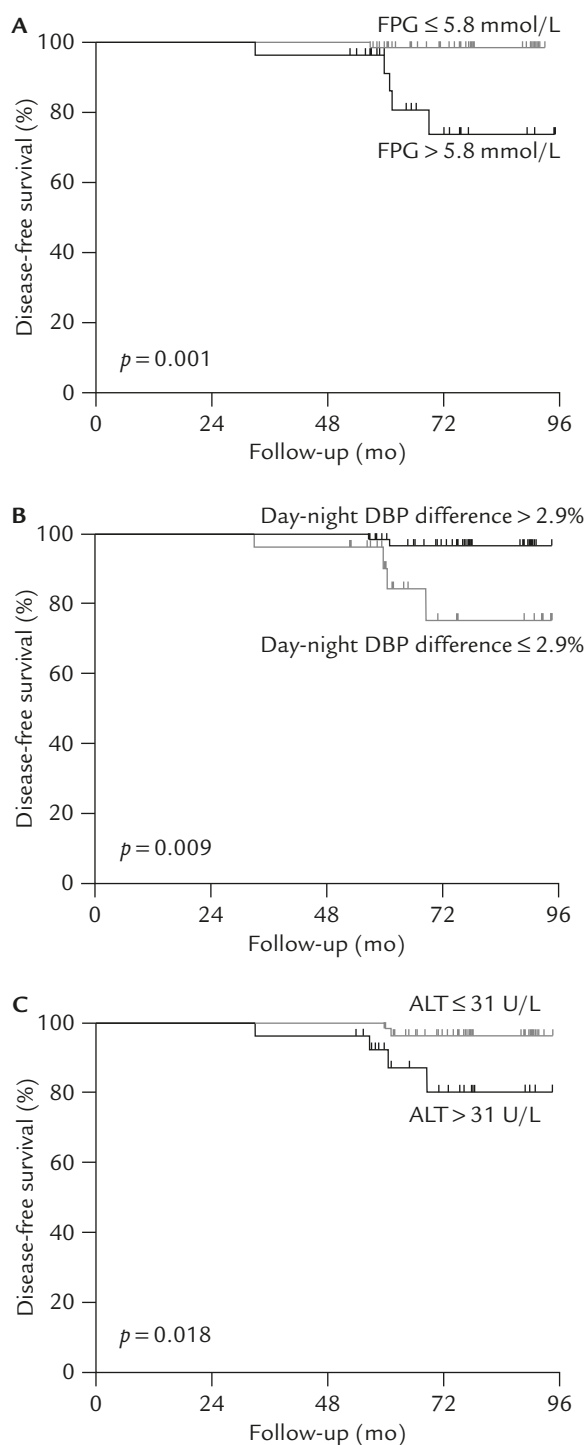
Figure 1. Kaplan-Meier estimation of survival free of new-onset diabetes mellitus for: (A) fasting plasma glucose (FPG); (B) day-night diastolic blood pressure (DBP) difference; and (C) serum alanine aminotransferase (ALT) level. The rate of new-onset diabetes was significantly increased in patients with baseline FPG > 5.8 mmol/L (the highest quartile) ($p = 0.001$ by log-rank test), day-night DBP difference ≤ 2.9% (the lowest quartile) ($p = 0.009$ by log-rank test), or ALT > 31 U/L (the highest quartile) ($p = 0.018$ by log-rank test).

than those without, respectively. In addition, patients with metabolic syndrome had more new-onset DM than patients without metabolic syndrome ($p = 0.019$). However, metabolic syndrome is complex and heterogeneous. Thus, only the individual components of metabolic syndrome were evaluated.

Approach with multiple risk factors for new-onset diabetes in fresh hypertensive patients

Further analysis showed that among the 6 patients with new-onset DM, 1 had baseline FPG ≤ 5.8 mmol/L, 1 had baseline ALT ≤ 31 U/L, and another 1 had day-night difference in diastolic BP > 2.9%. Only 3 of the 6 patients had all of the 3 indicators mentioned above at baseline. The other 3 patients had only 2 indicators at baseline. Accordingly, no single indicator could predict new-onset DM in all patients. At least 2 of the 3 indicators were required to predict future onset of type 2 DM in newly diagnosed hypertensive patients.

Discussion

It was shown in this study that in addition to FPG, serum ALT level independently predicted the onset of type 2 DM in a cohort of originally non-diabetic, untreated, newly diagnosed hypertensive patients. Baseline 24-hour BP parameter such as decreased diurnal change in diastolic BP was also related to the onset of DM. These findings could be of clinical significance since the development of type 2 DM in the current study was in conjunction with contemporary antihypertensive treatments used in the real world. However, no single indicator mentioned above could predict new-onset DM in all patients. At least 2 of the 3 indicators were required simultaneously for final risk stratification. Thus, a comprehensive strategy with both glucose and non-glucose indicators may be justified to identify patients at risk of future frank DM even before the guideline-oriented antihypertensive treatment is given. In concordance with the findings of a previous study,[5] the incidence of hard cardiovascular events was significantly higher in hypertensive patients with new-onset DM than in those patients without, suggesting the clinical impact of early risk stratification for future DM in fresh hypertensives. In this study, type 2 DM usually developed 2–5 years after the diagnosis of hypertension. It should be possible to prevent the onset of DM in individual hypertensive patients via early risk stratification and identification followed by a tailored interventional strategy in the future.

Impacts of FPG on new-onset diabetes mellitus in hypertensives

It has been suggested that the higher the level of FPG, the higher the risk of progressing to diabetes, which might be true even when FPG is < 5.6 mmol/L.[9,22] However, in the present study, the risk of new-onset DM was significantly increased in those patients with baseline FPG > 5.8 mmol/L. Thus, the correlations between FPG and the future risk of frank DM are not always constant and linear across different populations. An artificial threshold of FPG may be required for highest predictive value for future DM according to individual clinical condition. Recently, the criteria of the ADA for IFG that was previously defined as 6.1 mmol/L was further lowered to 5.6 mmol/L.[21] However, a more recent study indicated that the lower cutoff for IFG (ADA 2003 criteria) may result in a category of IFG that no longer represents a high-risk state of cardiovascular disease, and that only subjects who convert from IFG to diabetes have a high risk of cardiovascular mortality.[5] Thus, our findings may have impacts specific to patients with newly diagnosed hypertension, in whom a baseline FPG level >5.8 mmol/L could be associated with a more than 10 times increase in the risk of new-onset DM in the next 6 years compared to a baseline FPG level ≤5.8 mmol/L. This baseline FPG level (5.8 mmol/L) might be a good cut-off value to identify the risk of future DM. Given the association between the onset of DM and cardiovascular events, future prospective follow-up studies are indicated to determine whether this baseline FPG level is highly correlated with long-term prognosis in patients with fresh hypertension.

Impacts of elevated liver enzyme on new-onset DM in hypertensives

In this study, baseline ALT level, in addition to FPG level, was another independent predictor of future onset of type 2 DM in newly diagnosed hypertensive patients. Though similar findings had been reported in young healthy subjects as well as in older men,[17,23] they were for the first time demonstrated in patients with fresh hypertension.

It has been suggested that elevated ALT level, even within normal range, could be associated with decreased hepatic insulin sensitivity and predict the development of type 2 DM in originally non-DM subjects.[17] Elevated ALT level may be correlated with fatty liver and represent visceral fat disposition as a hallmark of metabolic syndrome.[17,23,24] Further, subjects with metabolic syndrome may have a more than 4-fold increase in the risk of future onset of type 2 DM, which might be explained, at least partially, by

elevated ALT due to increased visceral fat disposition.[23] However, another line of evidence indicates that elevated serum levels of ALT and γ-glutamyl-transferase may be only markers of inflammation and oxidative stress independent of the metabolic syndrome.[25,26] In the present study, hypertensive patients with baseline ALT level > 31 U/L had a more than 5-fold increase in the future risk of new-onset DM. It is not known whether these patients may have fatty liver and/or increased oxidative stress since abdominal sonogram and associated examinations were not performed. However, most of them did not meet the definition of metabolic syndrome. It seems that elevated ALT level, regardless of fatty liver, rather than the presence of metabolic syndrome, is a sensitive early indicator for the consequent development of type 2 DM in hypertensive patients. Further large-scale study may need to confirm this issue.

Potential impacts of reduced baseline diurnal BP changes to new-onset DM in hypertensives

Another interesting finding of this study is the potential association between reduced diurnal diastolic BP changes at baseline and future onset of type 2 DM. Compared to the others, those patients with nocturnal reduction in diastolic BP ≤2.9% had a more than 4 times increase in the risk of new-onset DM in the next 6 years. It has been recognized that normal diurnal changes in BP consist of a significant, ≥10%, reduction during nighttime. We had previously shown the presence of glucose intolerance and pancreatic β-cell dysfunction in young hypertensive subjects with < 10% nocturnal reduction in daytime BP.[15] In these patients, autonomic dysfunction including sympathetic overactivity and/or parasympathetic withdrawal can also be found,[15,27] which may not only increase insulin resistance but also attenuate the release of insulin as well as increase hepatic glucose production.[28] However, in the present study, baseline heart rate was similar between patients with and those without new-onset DM. Therefore, there is doubt as to whether there is a connection between the pre-existing autonomic dysfunction and the late onset of DM in this study.

Recent data showed that inhibition of the renin-angiotensin system may potentially result in a significant reduction in the incidence of type 2 DM in patients with arterial hypertension.[29,30] The HOPE (Heart Outcomes Prevention Evaluation) study included 5,720 patients without known DM (2,837 on ramipril and 2,883 on placebo).[31] The diagnosis of type 2 DM determined from self-report at follow-up visits every 6 months during a mean period of 4.5 years was compared between the 2 groups.

One hundred and two individuals (3.6%) in the ramipril group developed type 2 DM compared with 155 (5.4%) in the placebo group (odds ratio, 0.66; 95% confidence interval, 0.51–0.85; $p < 0.001$). The LIFE (Losartan Intervention For Endpoint reduction in hypertension) study was a double-masked, randomized, parallel-group trial in 9,193 participants aged 55–80 years with essential hypertension (sitting blood pressure 160–200/95–115 mmHg) and left ventricular hypertrophy.[32] There was a 25% lower incidence of new-onset type 2 DM in the losartan group than in the atenolol group. Among the 6 patients with new-onset DM in our study, 50% were taking ACEIs or ARBs before the onset of DM. The medications were similar in patients without new-onset DM (52% with ACEIs or ARBs). We do not know whether ACEIs or ARBs lowered the incidence of new-onset DM in our current study.

There are several issues that need to be further addressed. First, since this study's main aim was to evaluate the potential predictors of new-onset DM, the detailed pathological mechanisms were not elucidated. We did not include parameters such as inflammatory markers or family history in our study. Further large-scale studies are indicated to clarify these issues. Second, in this study, the presence of DM was determined mainly by the level of FPG according to ADA criteria.[21] It was then impossible to evaluate the presence of postprandial hyperglycemia or IGT in our patients. However, plasma value of hemoglobin A1C was used to confirm the presence of DM once the FPG level was > 7.0 mmol/L and also to exclude the presence of DM when FPG > 6.4 mmol/L in 2 separate tests. Third, endothelial function assessed by plethysmography could not predict new-onset DM in our patients. Whether this was due to the limited sample size, the lack of close causal relationship or the difference in study methodology is not known. Further study with different methodology may be considered. Fourth, it has been suggested that some antihypertensive medications including diuretics and β-blockers might variably increase the risk of subsequent DM in hypertensive patients.[10–13,30] However, in this study, antihypertensive medications were similarly given in patients with and without new-onset DM. Fifth, it should be noted that the findings of this study were derived mainly from a primary-prevention cohort of hypertensive patients with relatively low cardiovascular risk. There were only 3 strokes and 1 acute myocardial infarction during the whole follow-up period, giving a < 1% annual incidence of hard adverse events. It is then impossible to evaluate the individual impacts of each indicator on long-term prognosis. However,

in patients with new-onset DM, 2 (33%) developed hard events including stroke and myocardial infarction whereas only 2 (2%) of the patients without DM had stroke at follow-up. These results are compatible with the previous suggestion that new-onset DM, though usually taking a considerable duration of time to develop, could be directly associated with cardiovascular events.[5] Finally, and perhaps most importantly, the relatively small sample size makes this study a pilot study only. Further large-scale studies are indicated to confirm the current findings.

In conclusion, in addition to elevated FPG, elevated baseline serum ALT and reduced diurnal diastolic BP changes can also predict the development of type 2 DM in originally non-diabetic, newly diagnosed hypertensive patients. Our findings may provide a rationale for comprehensive risk stratification using both glucose and non-glucose parameters to identify, early on, those hypertensive patients at a particular risk of future DM. In these high-risk patients, regular metabolic follow-up is essential, and both aggressive lifestyle modifications and evidence-based pharmacological interventions may be required to prevent the onset of type 2 DM and associated cardiovascular events.[33–35] Future community-based studies are indicated to validate the feasibility of such comprehensive risk stratification in different ethnic cohorts with different patterns of hypertension.

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