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ORIGINAL RESEARCH

Association of Insulin Resistance, Plasma Glucose Level, and Serum Insulin Level With Hypertension in a Population With Different Stages of Impaired Glucose Metabolism

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BACKGROUND: The interrelationships among the different stages of impaired glucose metabolism, insulin resistance, and hypertension are not fully understood.

METHODS AND RESULTS: We investigated the impact of insulin resistance, plasma glucose, and serum immunoreactive insulin levels on hypertension in 19 166 participants with different stages of impaired glucose metabolism (7114 normal fasting glucose/normal glucose tolerance, 3543 isolated impaired fasting glucose [IFG], 2089 isolated impaired glucose tolerance, 2922 IFG plus impaired glucose tolerance, and 3498 diabetes mellitus]) determined by 75-g oral glucose tolerance tests. Participants were recruited from examinees who finished a general health checkup for atomic bomb survivors between 1982 and 2017. The profiles of plasma glucose and immunoreactive insulin during oral glucose tolerance tests were assessed using the total area under the curve. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance. The rate of hypertension increased from 36.3% in participants with normal fasting glucose/normal glucose tolerance to 50.1%, 50.8%, 58.3%, and 63.8% in participants with isolated IFG, isolated impaired glucose tolerance, IFG plus impaired glucose tolerance, and diabetes mellitus, respectively. Homeostasis model assessment of insulin resistance was associated with hypertension regardless of the presence and the degree of impaired glucose metabolism. Furthermore, fasting plasma glucose and serum immunoreactive insulin levels and areas under the curve for plasma glucose and immunoreactive insulin during oral glucose tolerance tests were associated with hypertension in normal fasting glucose/normal glucose tolerance and isolated IFG, but such a relationship was diminished in other types of prediabetes and diabetes mellitus.

CONCLUSIONS: The prevalence of hypertension increases with worsening stages of impaired glucose metabolism; however, hyperglycemia and hyperinsulinemia are significant contributors to the presence of hypertension only in the early stages of impaired insulin metabolism.

Key Words: diabetes mellitus ■ hyperglycemia ■ hyperinsulinemia ■ hypertension ■ insulin resistance

It is well recognized that diabetes mellitus (DM) and hypertension often coexist,[1–3] and insulin resistance is the key mechanism that connects these conditions.[4–7] Insulin resistance is a condition in blunted response to insulin stimulation of target tissues,[8] and it manifests as hyperglycemia and compensative hyperinsulinemia.[9] Hyperglycemia causes fluid shift from the intracellular to the extracellular compartment, resulting in plasma volume expansion and blood pressure (BP) elevation.[10] Hyperinsulinemia directly increases sodium

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CLINICAL PERSPECTIVE

What Is New?

- The prevalence of hypertension increased with progressing stages of impaired glucose metabolism in the order of isolated impaired fasting glucose or isolated impaired glucose tolerance, which were comparable; impaired fasting glucose and impaired glucose tolerance; and diabetes mellitus.
- Plasma glucose and serum immunoreactive insulin levels were associated with the prevalence of hypertension before the onset of impaired glucose metabolism.
- The associations of hyperglycemia and hyperinsulinemia with hypertension diminished with the progression of impaired glucose metabolism.

What Are the Clinical Implications?

- Impaired fasting glucose and impaired glucose tolerance have additive effects on blood pressure that lead to high prevalence of hypertension in the advanced stage of impaired glucose metabolism.
- Before the onset or early stage, but not advanced stage, of impaired glucose metabolism, plasma glucose level may play a significant role in blood pressure control.

Nonstandard Abbreviations and Acronyms

AUCglu	area under the glucose curve
AUCins	area under the insulin curve
BP	blood pressure
CVD	cardiovascular disease
DM	diabetes mellitus
FPG	fasting plasma glucose
HOMA-IR	homeostasis model assessment of insulin resistance
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IRI	immunoreactive insulin
NFG	normal fasting glucose
NGT	normal glucose tolerance
OGTTs	oral glucose tolerance tests
ORs	odds ratios
SBP	Systolic blood pressure

reabsorption from renal tubules, renin excretion, and sympathetic nervous activity, all of which could lead to BP elevation.[11] Chronically, both insulin resistance and hyperglycemia cause vascular damage through several intermediate pathways, including increased advanced glycation end products, oxidative stress, and inflammation,[12] leading to increased arterial stiffness and BP elevation. Impaired fasting glucose (IFG), a type of prediabetes, is characterized by a marked increase in hepatic insulin resistance and is identified simply by elevated fasting glucose levels. Meanwhile, impaired glucose tolerance (IGT), another type of prediabetes, is characterized by a marked increase in insulin resistance of skeletal muscle and is identified by elevated postprandial glucose levels.[13,14] These distinct pathways within the pathophysiology of prediabetes may have different impacts on resistant vessels and BP. However, the different mechanisms whereby hypertension develops in each type of prediabetes have yet to be well understood. Little is known about whether the impact of insulin resistance, hyperglycemia, and hyperinsulinemia on hypertension changes during the progression of the stages from healthy to prediabetes and DM.

In this study, we investigated the prevalence of hypertension in different stages of impaired glucose metabolism in a large-scale Japanese population, assessing the profiles of glucose metabolism by 75-g oral glucose tolerance tests (OGTTs) with complete data of plasma glucose and serum immunoreactive insulin (IRIS) levels, which reveal all types of prediabetes, including isolated IFG, isolated IGT, and their combination (IFG plus IGT), and DM. Furthermore, we evaluated the homeostasis model assessment of insulin resistance (MOHAIR) as a marker of hepatic insulin resistance[15,16] and the Matsuda index as a marker of whole-body insulin resistance, including skeletal muscle.[17] In the present study, analyzing the complete data set carrying all information on the components of glucose and insulin metabolism, we investigated the association of these insulin resistance indexes, hyperglycemia, and hyperinsulinemia with hypertension in the different stages of impaired glucose metabolism.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Participants

We collected data from Hiroshima GMCVD (Hiroshima Study on Glucose Metabolism and Cardiovascular Diseases), which was a cross-sectional and longitudinal study that examined the interrelationship among impaired glucose metabolism, BP, and cardiovascular outcomes. The participants were recruited from examinees who finished a general

health checkup provided as a governmental service for atomic bomb survivors in Hiroshima City at the Health Management and Promotion Center of the Hiroshima Atomic Bomb Casualty Council between January 1982 and November 2017. Furthermore, the examinees were considered to be eligible to participate in the study if (1) they had no history of antidiabetic medications; (2) they had suspicious impaired glucose metabolism based on the screening of fasting plasma glucose >100 mg/dL, postprandial 1-hour plasma glucose >155 mg/dL, postprandial 2-hour plasma glucose >140 mg/dL, or postprandial 3-hour plasma glucose >120 mg/dL; and (3) they agreed to undergo the 75-g OGTTs. Informed consent forms were obtained from all participants during their health examinations. During the general health checkup, all participants were asked about their regular medications and medical histories, including treatment for hypertension, dyslipidemia, and cardiovascular disease (CVD), and their drinking and smoking habits. Subsequently, each participant underwent 75-g OGTTs within 1 month after the general health checkup. A total of 19 248 participants who had complete data sets of 75-g OGTTs undergone between January 1982 and December 2017 were enrolled in the Hiroshima GMCVD. Among the 19 248 participants, 82 were excluded for lack of serum insulin measurements from the present analysis. Ethics approval for this study was obtained from the Hiroshima Atomic Bomb Casualty Council committee on the ethics of human research. This study was registered under the University Hospital Medical Information Network protocol registration system (ID: UMIN000036648).

Covariate and Outcome Definitions

Hypertension was defined as the use of antihypertensive medications and/or a measured systolic BP (SBP) of ≥140 mm Hg and/or diastolic BP of ≥90 mm Hg.[18] Dyslipidemia was defined as the use of antihyperlipidemic medications. We further explain the selection of this definition of dyslipidemia in Tables S1 and S2. CVD was defined as coronary heart disease or stroke. Regarding the participants' habits, a current smoker was defined as a participant with a current smoking habit, regardless of the number of cigarettes smoked per day, and a habitual drinker was defined as a participant who drank ≥20 g alcohol per day.

Measurements

After an overnight fast, the 75-g OGTT was conducted in the morning. For measurements of plasma glucose and serum IRI levels, the samples were drawn just before and 30, 60, and 120 minutes after glucose ingestion. Plasma glucose was measured in all participants using the hexokinase/glucose-6-phosphate dehydrogenase method at our institution. Serum IRI concentrations were measured using a radioimmunoassay at the SRL Laboratories (SRL Inc., Tokyo, Japan) between January 1982 and March 2003 and using a chemiluminescent immunoassay and the Beckman Coulter Unicell DXI at our institution between April 2003 and December 2017. In this study, we further analyzed insulin resistance, including the HOMA-IR and the Matsuda index, only in 12 378 participants who underwent serum IRI assessment using the radioimmunoassay (Table 1) because we found significant differences in the serum IRI values produced by the 2 methods. We present the serum IRI values, total areas under the insulin curves, and insulin resistance indexes assessed using chemiluminescent enzyme immunoassays between April 2003 and December 2017 in Table S3. We divided the participants into 5 groups according to their glycemic status, as defined by the American Diabetes Association criteria[19]: (1) normal fasting glucose (NFG)/normal glucose tolerance (NGT), defined as fasting plasma glucose (FPG) <100 mg/dL and 2-hour postload glucose <140 mg/dL; (2) isolated IFG, defined as FPG 100 to 125 mg/dL and 2-hour postload glucose <140 mg/dL; (3) isolated IGT, defined as FPG <100 mg/dL and 2-hour postload glucose 140 to 199 mg/dL; (4) IFG plus IGT, defined as FPG 100 to 125 mg/dL and 2-hour postload glucose 140 to 199 mg/dL; and (5) DM, defined as FPG ≥126 mg/dL and/or 2-hour postload glucose ≥200 mg/dL.

We also assessed insulin resistance as following 2 parameters: (1) HOMA-IR, which was calculated as insulin (mIU/L) times glucose (mg/dL) divided by 405,[15] and (2) the Matsuda index as a measure of whole-body insulin resistance, which was calculated as 10 000 divided by the square root of FPG×fasting IRI×2-hour postload glucose×2-hour postload IRI.[17,20] Post–glucose-load insulin secretion and plasma glucose level were estimated through total area under the insulin curve (AUCins) and the total area under the glucose curve (AUCglu) during 0 to 120 minutes of the 75-g OGTTs, respectively. The trapezoidal method was used to calculate AUCins and AUCglu during the OGTT. Insulin resistance and the plasma glucose and serum IRI levels are closely linked to worsening of glucose metabolism, and stages of impaired glucose metabolism are distinguished by marked differences in these parameters. Consequently, to investigate the impact of insulin resistance on hypertension in participants at different stages of impaired glucose metabolism, we defined high HOMA-IR as a value above the median and a low Matsuda index as a value below the median in each category of impaired glucose metabolism. Similarly, we defined high FPG, high AUCglu, high

fasting IRI, and high AUCins as a value above the median in each category of impaired glucose metabolism.

BP was measured with participants seated in a chair with back support and their arm supported at heart level after a >5-minute rest when they received health examinations. A mercury sphygmomanometer was used for BP measurements before 2012, and a digital automatic BP-measuring instrument was used after 2013.

Statistical Analysis

Continuous variables are expressed as mean±SD, and normality of continuous variables was examined using the Kolmogorov–Smirnov test. The differences among the 5 groups (ie, NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM) were analyzed using the Kruskal–Wallis test, and the Steel–Dwass post hoc test was used for multiple-comparison testing. Categorical variables were summarized as percentages and were analyzed using the χ^2 test. Moreover, the significance of trends in the proportion of hypertension in the order of participants with NFG/NGT, with isolated IFG, with isolated IGT, with IFG plus IGT, and with DM was examined using the Cochran–Armitage trend test. The unadjusted and adjusted odds ratios (ORs) of hypertension based on the impaired glucose metabolism

Table 1. Clinical Characteristics of Participants With Impaired Glucose Metabolism

Variables	NFG/NGT	Isolated IFG	Isolated IGT	IFG Plus IGT	Diabetes Mellitus	*P* Value
n	7114	3543	2089	2922	3498	
Age, y, mean±SD	66.8±8.0	66.0±8.4	67.7±7.7	66.3±8.3	64.8±8.7	<0.001
Female, n (%)	4109 (58)	1644 (46)	1039 (50)	1337 (46)	1637 (47)	<0.001
BMI, kg/m^2, mean±SD	22.3±2.9	23.2±3.1	23.2±3.2	24.0±3.2	24.4±3.4	<0.001
Smoker, n (%)						<0.001
Never	4881 (69)	2224 (63)	1327 (64)	1823 (62)	2138 (61)	
Current	1163 (16)	652 (18)	368 (18)	542 (19)	833 (24)	
Former	1070 (15)	667 (19)	394 (19)	557 (19)	527 (15)	
Habitual drinker, n (%)	1253 (18)	899 (25)	446 (21)	745 (26)	823 (20)	<0.001
Dyslipidemia, n (%)	1237 (17)	526 (15)	388 (19)	510 (17)	466 (13)	<0.001
History of CVD, n (%)	715 (10)	368 (10)	264 (13)	331 (11)	430 (12)	<0.001
Plasma glucose, mg/dL, mean±SD						
0 min	91.7±5.2	106.3±5.7*†	93.2±5.7*	108.8±6.6*†‡	132.8±29.2*†‡§	<0.001
30 min	146.8±27.2	173.5±29.2	163.1±23.3	184.8±26.1	223.5±42.5	<0.001
60 min	137.8±36.6	168.8±41.4	177.4±36.7	203.1±39.5	268.4±55.7	<0.001
120 min	106.8±20.0	112.4±19.3	159.6±15.5	165.1±17.0	257.1±71.7	<0.001
AUCglu, mg/dL·h	253.1±41.5	296.1±44.3*	317.7±38.8*‡	354.5±43.2*†‡	474.8±95.8*†‡§	<0.001
SBP, mm Hg	129±17	135±18*	135±18*	137±18*†‡	141±19*†‡§	<0.001
DBP, mm Hg	75±10	78±11*	77±10*	79±11*†‡	81±11*†‡§	<0.001
Antihypertensive medication, n (%)	1023 (14)	735 (21)	482 (23)	761 (26)	933 (27)	<0.001
Serum IRI, μU/mL, mean±SD						
n	3878	2285	1267	2021	2927	
0 min	5.9±3.3	7.4±4.0*†	6.7±3.5*	8.4±4.6*†‡	10.0±6.2*†‡§	<0.001
30 min	38.8±27.8	38.8±27.3	35.9±24.6	36.0±24.4	27.7±19.5	<0.001
60 min	46.4±35.8	59.2±43.1	46.5±32.4	54.3±38.0	45.1±33.4	<0.001
120 min	32.0±22.2	38.7±27.3	58.1±39.5	62.5±43.1	57.5±42.4	<0.001
AUCins, μU/mL·h	71.7±43.3	85.0±50.7*	83.6±51.5*	92.1±56.4*†‡	78.9±52.1†‡§	<0.001
HOMA-IR	1.33±0.75	1.96±1.09*†	1.54±0.81*	2.28±1.27*†‡	3.41±2.40*†‡§	<0.001
Matsuda index	9.98±5.97	7.33±4.36*†	5.48±2.79*	4.29±2.21*†‡	3.23±2.01*†‡§	<0.001

Serum IRI levels were obtained from the participants between January 1982 and March 2003. *P* values were calculated using the Kruskal–Wallis or χ^2 test. The Steel–Dwass post hoc test was used for multiple comparison testing. AUCglu indicates total area under the glucose curve; AUCins, total area under the insulin curve; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; NFG, normal fasting glucose; NGT, normal glucose tolerance; and SBP, systolic blood pressure.

$^{*}P<0.001$ vs NFG/NGT.

$^{\dagger}P<0.001$ vs isolated IGT.

$^{\ddagger}P<0.001$ vs isolated IFG.

$^{\S}P<0.001$ vs IFG plus IGT.

categories (NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM) were also evaluated using univariate and multivariate logistic regression analyses with the following 2 models: model 1 included age and sex, and model 2 also included body mass index (kg/m^2), smoking (never smoker, current smoker, or former smoker), habitual drinking (yes or no), presence of dyslipidemia (yes or no), and history of CVD (yes or no). Next, we stratified the participants into NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM, and we evaluated the association of insulin resistance (high HOMA-IR and low Matsuda index), plasma glucose level (high FPG and high AUCglu), and serum IRI level (high-fasting IRI and high AUCins) with hypertension in each category using univariate and multivariate logistic regression analyses. Similarly, we investigated the associations of insulin resistance, plasma glucose level, and serum IRI level with high BP (defined as SBP ≥140 mm Hg). For balancing the sample size and variables between the NFG/NGT and DM groups, we built a propensity score–matching model using multivariate logistic regression, including age, sex, body mass index, smoking, drinking, dyslipidemia, and history of CVD. Thereafter, we investigated the associations of insulin resistance, plasma glucose level, and serum IRI level with high BP and hypertension in the propensity score–matched NFG/NGT and DM groups. To exclude the influence of a change in BP measurement, we also performed univariate and multivariate logistic regression analyses to evaluate the unadjusted and adjusted ORs of hypertension based on the categories of impaired glucose metabolism only in participants who underwent BP assessment using a mercury sphygmomanometer between January 1982 and December 2012. We considered $P<0.05$ as statistically significant. All statistical analyses were performed using the JMP 14.2 statistical software (SAS Institute).

RESULTS

A total of 19 166 participants (9400 men and 9766 women) with a mean age of 66.3±8.2 years and mean body mass index of 23.2±3.2 were enrolled in the present analysis. Of these participants, 9355 (49%) had hypertension, 3107 (16%) had dyslipidemia, and 2108 (11%) had a history of CVD. Moreover, 3558 (19%) were current smokers, 3215 (17%) were former smokers, and 12 393 (64%) were never smokers, whereas 4166 (22%) were habitual drinkers. Table 1 summarizes the clinical characteristics and the results of OGTTs in the participants with NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM. Both FPG and fasting IRI levels increased in the order of NFG/NGT, isolated IGT, isolated IFG, IFG plus IGT, and DM. AUCglu increased in the order of NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM. AUCins increased in isolated IFG and isolated IGT to a similar extent compared with NFG/NGT and further increased in IFG plus IGT compared with the isolated IFG and isolated IGT; however, AUCins decreased in DM to the level of NFG/NGT. The HOMA-IR increased in the order of NFG/NGT, isolated IGT, isolated IFG, IFG plus IGT, and DM, whereas the Matsuda index decreased in the order of NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM. Both SBP and diastolic BP measured during the patients'

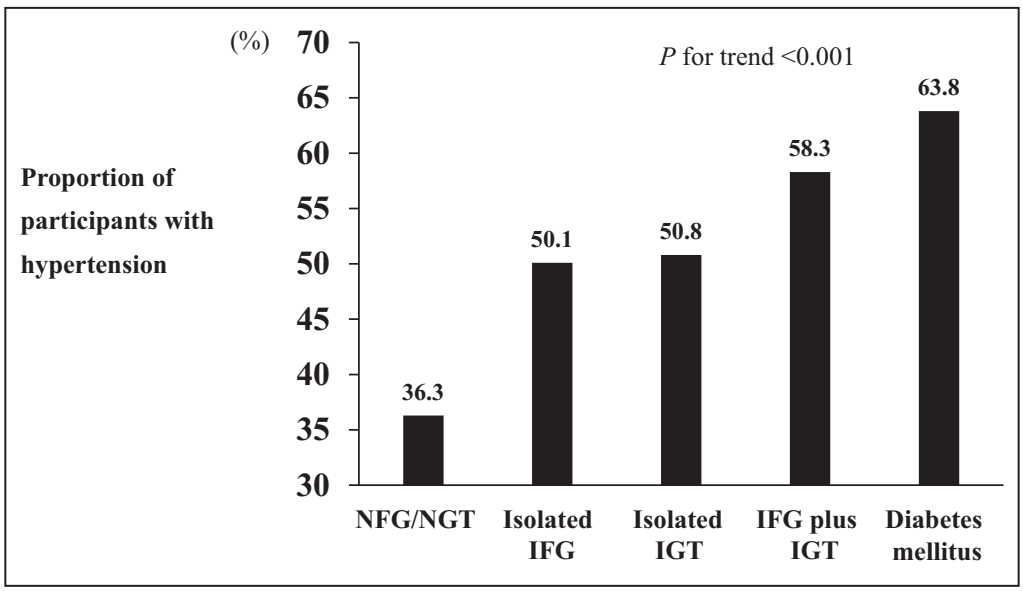

Figure. Proportion of participants with hypertension in normal fasting glucose/normal glucose tolerance (NFG/NGT), isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), IFG plus IGT, and diabetes mellitus.

Table 2. Univariate and Multivariate Logistic Regression Analyses for Hypertension (n=19 166)

Variables	Univariate			Model 1			Model 2		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
NFG/NGT	1			1			1		
Isolated IFG	1.76	1.62–1.91	<0.001	1.74	1.60–1.89	<0.001	1.61	1.48–1.75	<0.001
Isolated IGT	1.81	1.64–2.00	<0.001	1.74	1.58–1.92	<0.001	1.62	1.46–1.79	<0.001
IFG plus IGT	2.45	2.24–2.67	<0.001	2.40	2.20–2.63	<0.001	2.08	1.90–2.28	<0.001
Diabetes mellitus	3.09	2.85–3.37	<0.001	3.17	2.91–3.46	<0.0001	2.66	2.44–2.91	<0.001

Model 1 included age and sex. Model 2 included age, sex, body mass index, smoking, drinking, dyslipidemia, and cardiovascular disease. Hypertension was defined as taking antihypertensive medications and/or having systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. IFG indicates impaired fasting glucose; IGT, impaired glucose tolerance; NFG, normal fasting glucose; NGT, normal glucose tolerance; and OR odds ratio.

health checkups were lowest in NFG/NGT, elevated in isolated IFG and isolated IGT to a similar extent, and elevated further in IFG plus IGT and DM, in this order. The proportion of participants taking antihypertensive medications increased in the order of NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM.

Figure shows the proportion of participants having hypertension in NFG/NGT, isolated IFG, isolated IGT, IFG plus IGT, and DM. The rate of hypertension was significantly increased in the order of NFG/NGT (n=2584, 36.3%), isolated IFG (n=1775, 50.1%), isolated IGT (n=1061, 50.8%), IFG plus IGT (n=1702, 58.3%), and DM (n=2233, 63.8%; *P*<0.001 for trend).

Table 2 shows the unadjusted and adjusted ORs for the presence of hypertension in the category groups of impaired glucose metabolism. The presence of hypertension was significantly associated with the presence of isolated IFG (OR: 1.76; 95% CI, 1.62–1.91; *P*<0.001), isolated IGT (OR: 1.81; 95% CI, 1.64–2.00; *P*<0.001), IFG plus IGT (OR: 2.45; 95% CI, 2.24–2.67; *P*<0.001), and DM (OR: 3.09; 95% CI, 2.85–3.37; *P*<0.001). After adjusting for age, sex, body mass index smoking, drinking, dyslipidemia, and CVD, the significant association between the presence of hypertension and the presence of impaired glucose metabolism in any category persisted. Similar results were obtained from an analysis that included only participants who underwent BP assessment using a mercury sphygmomanometer (Table S4).

Table 3 summarizes the results of univariate and multivariate logistic regression analyses to determine the contribution of insulin resistance, plasma glucose level, and insulin secretion to hypertension in all category groups of impaired glucose metabolism. After adjusting for confounding factors, high HOMA-IR was significantly associated with hypertension in all categories from NFG/NGT (OR: 1.27; 95% CI, 1.10–1.47; *P*<0.001) to DM (OR: 1.25; 95% CI, 1.06–1.48; *P*=0.008). The Matsuda index was significantly associated with hypertension in NFG/NGT, isolated IFG, and DM. However, high FPG was significantly associated with hypertension only in NFG/NGT (OR: 1.30; 95% CI, 1.18–1.44; *P*<0.001) and isolated IFG (OR: 1.23; 95% CI, 1.08–1.41; *P*=0.002) but not in isolated IGT, IFG plus IGT, and DM. High AUCglu was significantly associated with hypertension in NFG/NGT (OR: 1.40; 95% CI, 1.26–1.54; *P*<0.001), isolated IFG (OR: 1.15; 95% CI, 1.01–1.32; *P*=0.038), isolated IGT (OR: 1.21; 95% CI, 1.02–1.44; *P*=0.033), and IFG plus IGT (OR: 1.25; 95% CI, 1.08–1.45; *P*=0.004) but not in DM. High fasting IRI was significantly associated with hypertension in NFG/NGT, isolated IFG, isolated IGT, and DM but not in IFG plus IGT. Moreover, high AUCins was significantly associated with hypertension in NFG/NGT, isolated IFG, and IFG plus IGT but not in isolated IGT and DM. Similar results were obtained in the analysis for the category of SBP ≥140 mm Hg (Table 4).

The clinical characteristics of the NFG/NGT and DM groups after propensity matching are shown in Table 5. High FPG (OR: 1.35; 95% CI, 1.16–1.56; *P*<0.001) and AUCglu levels (OR: 1.51; 95% CI, 1.30–1.75; *P*<0.001) were significantly associated with hypertension in NFG/NGT but not in DM (Table 6). Similar results were confirmed in the analysis for the category of SBP ≥140 mm Hg (Table 7).

DISCUSSION

In this study, we investigated the interrelationships among the stages of impaired glucose metabolism, insulin resistance, plasma glucose level, serum IRI level, and the prevalence of hypertension in a large-scale Japanese population. First, our data provided strong evidence confirming that the prevalence of hypertension increased with progressing stages of impaired glucose metabolism in the order of isolated IFG or isolated IGT (these 2 were comparable), IFG and IGT, and DM, with the OR reaching ≈3 in DM. Second, HOMA-IR was associated with hypertension in NFG/NGT and all stages of impaired glucose metabolism, indicating that insulin resistance has a significant impact on BP throughout the stages of impaired glucose metabolism, including the stage before its onset. Third, the impact of plasma glucose and serum insulin levels on BP control may decline in the course of the developing stages.

Table 3. Univariate and Multivariate Logistic Regression Analyses for Hypertension in participants with different stages of impaired glucose metabolism

Variables	Univariate			Model 1			Model 2		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
NFG/NGT (n=7114)									
High HOMA-IR*	1.41	1.24–1.60	<0.001	1.49	1.31–1.70	<0.001	1.27	1.10–1.47	<0.001
Low Matsuda index*	1.54	1.35–1.75	<0.001	1.61	1.41–1.84	<0.001	1.43	1.24–1.64	<0.001
High FPG	1.41	1.28–1.56	<0.001	1.36	1.24–1.51	<0.001	1.30	1.18–1.44	<0.001
High AUCglu	1.56	1.42–1.72	<0.001	1.49	1.35–1.64	<0.001	1.40	1.26–1.54	<0.001
High fasting IRI*	1.37	1.20–1.56	<0.001	1.47	1.29–1.67	<0.001	1.25	1.09–1.44	0.002
High AUCins*	1.43	1.25–1.62	<0.001	1.43	1.25–1.63	<0.001	1.31	1.14–1.50	<0.001
Isolated IFG (n=3543)									
High HOMA-IR†	1.41	1.20–1.67	<0.001	1.53	1.29–1.81	<0.001	1.38	1.15–1.65	<0.001
Low Matsuda index†	1.35	1.15–1.59	<0.001	1.46	1.23–1.73	<0.001	1.31	1.09–1.57	0.003
High FPG	1.23	1.08–1.41	0.002	1.25	1.09–1.42	0.001	1.23	1.08–1.41	0.002
High AUCglu	1.21	1.06–1.38	0.004	1.20	1.06–1.38	0.006	1.15	1.01–1.32	0.038
High fasting IRI†	1.40	1.19–1.65	<0.001	1.52	1.28–1.80	<0.001	1.37	1.14–1.64	<0.001
High AUCins†	1.47	1.25–1.74	<0.001	1.48	1.25–1.75	<0.001	1.39	1.17–1.65	<0.001
Isolated IGT (n=2089)									
High HOMA-IR‡	1.52	1.22–1.89	<0.001	1.59	1.27–2.00	<0.001	1.37	1.07–1.77	0.013
Low Matsuda index‡	1.43	1.15–1.79	0.002	1.48	1.18–1.86	<0.001	1.26	0.98–1.62	0.067
High FPG	1.15	0.96–1.36	0.121	1.14	0.96–1.35	0.150	1.10	0.92–1.31	0.287
High AUCglu	1.23	1.04–1.46	0.017	1.23	1.03–1.46	0.020	1.21	1.02–1.44	0.033
High fasting IRI‡	1.47	1.18–1.83	<0.001	1.55	1.23–1.94	0.002	1.33	1.04–1.71	0.026
High AUCins‡	1.38	1.11–1.72	0.005	1.42	1.13–1.78	0.002	1.26	0.98–1.60	0.067
IFG plus IGT (n=2922)									
High HOMA-IR§	1.47	1.23–1.76	<0.001	1.61	1.34–1.94	<0.001	1.34	1.09–1.63	0.004
Low Matsuda index§	1.33	1.11–1.59	0.002	1.43	1.19–1.71	<0.001	1.18	0.97–1.43	0.100
High FPG	1.07	0.92–1.24	0.387	1.09	0.94–1.27	0.240	1.05	0.90–1.22	0.521
High AUCglu	1.24	1.07–1.43	0.005	1.26	1.09–1.46	0.002	1.25	1.08–1.45	0.004
High fasting IRI§	1.31	1.10–1.57	0.003	1.42	1.19–1.71	<0.001	1.15	0.94–1.41	0.162
High AUCins§	1.39	1.16–1.64	<0.001	1.48	1.23–1.77	<0.001	1.24	1.02–1.50	0.034
Diabetes mellitus (n=3498)									
High HOMA-IR‖	1.29	1.11–1.50	0.001	1.41	1.21–1.65	<0.001	1.25	1.06–1.48	0.008
Low Matsuda index‖	1.37	1.17–1.59	<0.001	1.44	1.24–1.68	<0.001	1.27	1.08–1.50	0.005
High FPG	0.93	0.81–1.07	0.34	1.00	0.86–1.15	0.955	0.98	0.85–1.14	0.811
High AUCglu	1.00	0.87–1.15	0.956	1.05	0.91–1.21	0.493	1.04	0.90–1.20	0.600
High fasting IRI‖	1.37	1.17–1.59	<0.001	1.47	1.26–1.72	<0.001	1.28	1.08–1.51	0.005
High AUCins‖	1.31	1.12–1.52	<0.001	1.32	1.13–1.54	<0.001	1.17	0.99–1.37	0.061

Low Matsuda index was defined as the lower half based on the median. High HOMA-IR was defined as the higher half based on the median in each category of impaired glucose metabolism. High FPG level, high AUCglu, high fasting IRI level, and high AUCins were defined as the higher half based on the median in each category of impaired glucose metabolism. Model 1 included age and sex. Model 2 included age, sex, body mass index, smoking, drinking, dyslipidemia, and cardiovascular disease. Hypertension was defined as taking antihypertensive medications and/or having systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. AUCglu indicates total area under the glucose curve; AUCins, total area under the insulin curve; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; NFG, normal fasting glucose; NGT, normal glucose tolerance; and OR, odds ratio.

*n=3878.
†n=2285.
‡n=1267.
§n=2021.
‖n=2927.

Several studies have reported a significant association between prediabetes and hypertension[21–23] and between DM and hypertension.[24,25] However, limited data have been available regarding the interrelationship between each prediabetes category and hypertension. In the present study, we divided the participants with

Table 4. Univariate and Multivariate Logistic Regression Analyses for SBP ≥140 mm Hg

Variables	Univariate			Model 1			Model 2		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
NFG/NGT (n=7114)									
High HOMA-IR*	1.45	1.26–1.66	<0.001	1.52	1.33–1.75	<0.001	1.40	1.20–1.63	0.001
Low Matsuda index*	1.49	1.30–1.70	<0.001	1.55	1.35–1.78	<0.001	1.42	1.22–1.65	<0.001
High FPG	1.41	1.27–1.56	<0.001	1.35	1.22–1.50	<0.001	1.29	1.16–1.44	<0.001
High AUCglu	1.57	1.41–1.74	<0.001	1.48	1.33–1.65	<0.001	1.37	1.23–1.52	<0.001
High fasting IRI*	1.42	1.24–1.62	<0.001	1.51	1.31–1.73	<0.001	1.40	1.20–1.63	<0.001
High AUCins*	1.37	1.20–1.57	<0.001	1.36	1.19–1.56	<0.001	1.27	1.10–1.47	0.001
Isolated IFG (n=3543)									
High HOMA-IR†	1.39	1.17–1.64	<0.001	1.49	1.26–1.76	<0.001	1.45	1.21–1.74	<0.001
Low Matsuda index†	1.36	1.15–1.61	<0.001	1.46	1.23–1.73	<0.001	1.38	1.15–1.66	<0.001
High FPG	1.20	1.05–1.37	0.009	1.20	1.05–1.38	0.007	1.18	1.02–1.35	0.023
High AUCglu	1.23	1.07–1.41	0.003	1.28	1.12–1.47	<0.001	1.24	1.08–1.43	0.003
High fasting IRI†	1.41	1.20–1.67	<0.001	1.52	1.28–1.80	<0.001	1.48	1.23–1.78	<0.001
High AUCins†	1.45	1.23–1.71	<0.001	1.46	1.23–1.72	<0.001	1.41	1.18–1.69	<0.001
Isolated IGT (n=2089)									
High HOMA-IR‡	1.38	1.10–1.72	0.005	1.42	1.14–1.79	0.002	1.32	1.02–1.70	0.037
Low Matsuda index‡	1.28	1.03–1.60	0.029	1.31	1.04–1.64	0.020	1.15	0.89–1.49	0.283
High FPG	1.21	1.02–1.44	0.032	1.20	1.01–1.44	0.039	1.21	1.00–1.45	0.044
High AUCglu	1.26	1.06–1.50	0.010	1.26	1.05–1.50	0.011	1.24	1.03–1.49	0.020
High fasting IRI‡	1.32	1.05–1.65	0.016	1.36	1.09–1.71	0.007	1.26	0.98–1.63	0.077
High AUCins‡	1.31	1.05–1.64	0.016	1.34	1.07–1.68	0.011	1.27	0.99–1.63	0.060
IFG plus IGT (n=2922)									
High HOMA-IR§	1.33	1.11–1.58	0.002	1.41	1.18–1.68	<0.001	1.26	1.03–1.53	0.023
Low Matsuda index§	1.20	1.01–1.43	0.043	1.25	1.05–1.50	0.012	1.11	0.92–1.35	0.276
High FPG	1.11	0.96–1.28	0.162	1.11	0.96–1.29	0.154	1.10	0.94–1.27	0.237
High AUCglu	1.18	1.02–1.36	0.026	1.18	1.02–1.37	0.028	1.18	1.01–1.37	0.032
High fasting IRI§	1.17	0.98–1.39	0.079	1.23	1.03–1.47	0.022	1.07	0.88–1.30	0.512
High AUCins§	1.24	1.04–1.48	0.015	1.29	1.08–1.54	0.005	1.17	0.97–1.40	0.093
Diabetes mellitus (n=3498)									
High HOMA-IR‖	1.35	1.17–1.57	<0.001	1.45	1.25–1.69	<0.001	1.37	1.16–1.62	<0.001
Low Matsuda index‖	1.41	1.22–1.64	<0.001	1.46	1.26–1.70	<0.001	1.33	1.13–1.57	<0.001
High FPG	1.04	0.91–1.19	0.606	1.09	0.95–1.25	0.226	1.08	0.93–1.24	0.303
High AUCglu	1.12	0.98–1.28	0.102	1.16	1.01–1.33	0.033	1.13	0.99–1.30	0.079
High fasting IRI‖	1.38	1.19–1.60	<0.001	1.46	1.26–1.70	<0.001	1.34	1.14–1.58	<0.001
High AUCins‖	1.22	1.06–1.42	0.007	1.23	1.06–1.48	0.005	1.12	0.95–1.31	0.176

Low Matsuda index was defined as the lower half based on the median. High HOMA-IR was defined as the higher half based on the median in each category of impaired glucose metabolism. High FPG level, high AUCglu, high-fasting IRI level, and high AUCins were defined as the higher half based on the median in each category of impaired glucose metabolism. Model 1 included age and sex. Model 2 included age, sex, body mass index, smoking, drinking, and presence of antihypertensive medication, dyslipidemia, and cardiovascular disease. AUCglu indicates total area under the glucose curve; AUCins, total area under the insulin curve; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRI, immunoreactive insulin; NFG, normal fasting glucose; NGT, normal glucose tolerance; and OR, odds ratio.

*n=3878.
†n=2285.
‡n=1267.
§n=2021.
‖n=2927.

prediabetes into 3 groups (ie, isolated IFG, isolated IGT, and IFG plus IGT) based on 75-g OGTT results. The proportion of participants with hypertension similarly increased in isolated IFG and isolated IGT compared with NFG/NGT, and a further increased rate of hypertension was observed in IFG plus IGT. These findings suggest that the impact of IFG on BP may be similar to that of IGT and that IFG and IGT may have additive effects on BP.

Table 5. Balancing of Sample Size and Characteristics After Propensity Matching

Variables	NFG/ NGT	Diabetes Mellitus	*P* Value
n	3124	3124	
Age, y, mean±SD	65.4±8.3	65.3±8.5	0.423
Female, n (%)	1467 (47)	1498 (48)	0.432
BMI, kg/m^2, mean±SD	23.8±2.9	23.8±3.0	0.840
Smoker, n (%)			0.983
Never	1927 (62)	1933 (62)	
Current	700 (22)	699 (22)	
Former	497 (16)	497 (16)	
Habitual drinker, n (%)	736 (24)	707 (23)	0.384
Dyslipidemia, n (%)	434 (14)	421 (14)	0.632
History of CVD, n (%)	387 (12)	375 (12)	0.643
Participants between January 1982 and March 2003			
n	2330	2330	
Age, y, mean±SD	64.3±8.8	64.2±8.9	0.476
Female, n (%)	1172 (50)	1156 (50)	0.639
BMI, kg/m^2, mean±SD	23.4±2.8	23.4±2.8	0.820
Smoker, n (%)			
Never smoker	1515 (65)	1500 (64)	0.835
Current	562 (24)	565 (24)	
Former	253 (11)	265 (11)	
Habitual drinker, n (%)	496 (21)	500 (21)	0.886
Dyslipidemia, n (%)	254 (11)	244 (10)	0.635
History of CVD, n (%)	263 (11)	242 (11)	0.322

Differences between the 2 groups were compared using the Wilcoxon rank sum or χ^2 test. BMI indicates body mass index; CVD, cardiovascular disease; NFG, normal fasting glucose; and NGT, normal glucose tolerance.

Both IFG and IGT are manifestations of insulin resistance, but the main organ of insulin resistance differs between the 2 prediabetes categories. IFG is characterized by severe hepatic insulin resistance with slight insulin resistance in the skeletal muscle, whereas IGT is characterized by severe insulin resistance in the skeletal muscle with modest hepatic insulin resistance.[13,14] HOMA-IR, estimated using the homeostasis model assessment, represents hepatic insulin resistance,[15,16] whereas the Matsuda index reflects insulin resistance in the whole body, including the skeletal muscle.[17] In this study, we confirmed higher HOMA-IR in isolated IFG compared with isolated IGT, whereas a lower Matsuda index in isolated IGT was compared with isolated IFG. The difference in the main site of insulin resistance between IFG and IGT did not apparently make a difference in the extent of contribution to hypertension; however, these impairments had additive effects on BP in IFG plus IGT.

Insulin resistance causes an increase in both plasma glucose and serum insulin levels.[9] Hyperglycemia causes hyperosmolarity, leading to fluid shift from the intracellular compartment to the extracellular compartment, which results in plasma volume expansion.[10] Hyperinsulinemia causes an increase of sodium reabsorption from renal tubules, renin secretion, and sympathetic nervous activity.[11] Thus, elevated circulating levels of both glucose and insulin themselves could be a direct mediator of BP elevation in insulin resistance. In the present study, an interesting observation is that elevated circulating levels of glucose and insulin, both in fasting and post–glucose-loaded state, were statistically associated with hypertension only in the early stages (NFG/NGT and isolated IFG). In the more advanced stages (eg, isolated IGT, IFG plus IGT, and DM), the association of hyperglycemia with hypertension gradually diminished with the progression of impaired glucose metabolism. The impact of hyperinsulinemia on hypertension seemed to decline in the advanced stages. This observation may support the speculation that increases in the levels of circulating glucose and/or insulin may play more prominent roles in the initiation of hypertension in the early stages of altered glucose metabolism than in the later stages. However, it is still unclear why the statistical associations between glucose/insulin and hypertension were gradually lost with progression of impaired glucose metabolism. The chronic elevation of plasma glucose and insulin levels could promote atherosclerosis and could cause resultant vascular resistance through numerous pathways, including the formation of advanced glycation end products, increases in vascular oxidative stress and inflammation,[12,26] a reduction of nitric oxide production, and an increase in VCAM1 (vascular cell adhesion molecule 1) level.[27,28] Therefore, a possible explanation is that in the advanced stage of impaired glucose metabolism, vascular resistance may be a main contributor to BP elevation, likely resulting in a diminished impact of plasma glucose and serum insulin levels on BP.[29]

Study Limitations

This study has several limitations. First, because of a cross-sectional study design, a causal relationship between impaired glucose metabolism and hypertension cannot be inferred. Second, in this study, NFG/NGT results revealed participants who had suspicious impaired glucose metabolism at the time of their general health examinations. This selection bias may limit the generalizability of our findings. Third, hypertension was defined as taking antihypertensive medications and/or having SBP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg based on a 1-time BP measurement, although the current clinical guidelines recommend the mean value of 2 measurements on at least 2 different occasions.[18] Fourth, the prevalence of obesity and pathophysiology in DM showed ethnic

Table 6. Univariate and Multivariate Logistic Regression Analyses for Hypertension in the Propensity Score–Matched Groups

Variables	Univariate			Model 1			Model 2		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
NFG/NGT (n=3124)									
High HOMA-IR*	1.51	1.28–1.77	<0.001	1.58	1.33–1.87	<0.001	1.30	1.08–1.55	0.005
Low Matsuda index*	1.69	1.43–1.99	<0.001	1.76	1.49–2.08	<0.001	1.50	1.25–1.80	<0.001
High FPG	1.46	1.26–1.68	<0.001	1.41	1.22–1.63	<0.001	1.35	1.16–1.56	<0.001
High AUCglu	1.66	1.44–1.92	<0.001	1.61	1.39–1.86	<0.001	1.51	1.30–1.75	<0.001
High fasting IRI*	1.45	1.23–1.71	<0.001	1.52	1.29–1.80	<0.001	1.25	1.04–1.49	0.018
High AUCins*	1.52	1.29–1.79	<0.001	1.52	1.28–1.79	<0.001	1.35	1.14–1.61	<0.001
Diabetes mellitus (n=3124)									
High HOMA-IR*	1.25	1.05–1.48	0.009	1.38	1.16–1.64	<0.001	1.25	1.04–1.50	0.018
Low Matsuda index*	1.36	1.15–1.61	<0.001	1.42	1.20–1.68	<0.001	1.28	1.07–1.54	0.008
High FPG	0.97	0.84–1.12	0.682	1.04	0.90–1.20	0.621	1.02	0.88–1.19	0.799
High AUCglu	1.03	0.89–1.19	0.705	1.08	0.93–1.25	0.311	1.07	0.92–1.24	0.402
High fasting IRI*	1.33	1.13–1.58	<0.001	1.45	1.22–1.73	<0.001	1.31	1.09–1.57	0.041
High AUCins*	1.32	1.12–1.56	0.001	1.33	1.12–1.58	<0.001	1.20	1.00–1.43	0.046

Low Matsuda index was defined as the lower half based on the median. High HOMA-IR was defined as the higher half based on the median in each category of impaired glucose metabolism. High FPG level, high AUCglu, high fasting IRI level, and high AUCins were defined as the higher half based on the median in each category of impaired glucose metabolism. Model 1 included age and sex. Model 2 included age, sex, body mass index, smoking, drinking, and presence of dyslipidemia and cardiovascular disease. AUCglu indicates total area under the glucose curve; AUCins, total area under the insulin curve; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IRI, immunoreactive insulin; NFG, normal fasting glucose; and NGT, normal glucose tolerance.

*n=2330.

differences among the white, black, and Asian populations. In the study conducted in Japan, most participants were nonobese. This may limit the application of our findings to other ethnicities. Fifth, we did not have data on the duration between the onset and diagnosis of DM. Duration of DM may affect the association

Table 7. Univariate and Multivariate Logistic Regression Analyses for SBP ≥140 mm Hg in the Propensity Score–Matched Groups

Variables	Univariate			Model 1			Model 2		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
NFG/NGT (n=3124)									
High HOMA-IR*	1.63	1.37–1.94	<0.001	1.70	1.43–2.03	<0.001	1.58	1.30–1.92	<0.001
Low Matsuda index*	1.70	1.43–2.02	<0.001	1.76	1.48–2.10	<0.001	1.58	1.30–1.92	<0.001
High FPG	1.39	1.20–1.62	<0.001	1.35	1.16–1.57	<0.001	1.30	1.11–1.52	0.001
High AUCglu	1.63	1.40–1.90	<0.001	1.58	1.35–1.84	<0.001	1.45	1.24–1.70	<0.001
High fasting IRI*	1.54	1.30–1.84	<0.001	1.61	1.35–1.92	<0.001	1.47	1.21–1.79	<0.001
High AUCins*	1.39	1.17–1.65	<0.001	1.38	1.16–1.64	<0.001	1.22	1.01–1.47	0.035
Diabetes mellitus (n=3124)									
High HOMA-IR*	1.30	1.11–1.53	0.002	1.41	1.19–1.67	<0.001	1.33	1.11–1.59	0.002
Low Matsuda index*	1.42	1.21–1.67	<0.001	1.47	1.25–1.74	<0.001	1.35	1.12–1.61	0.001
High FPG	1.08	0.94–1.24	0.298	1.14	0.99–1.31	0.078	1.12	0.96–1.30	0.145
High AUCglu	1.12	0.97–1.29	0.108	1.17	1.01–1.34	0.034	1.13	0.98–1.31	0.095
High fasting IRI*	1.38	1.17–1.62	<0.001	1.48	1.25–1.76	<0.001	1.39	1.16–1.67	<0.001
High AUCins*	1.25	1.06–1.47	0.008	1.26	1.07–1.48	0.006	1.13	0.95–1.35	0.158

Low Matsuda index was defined as the lower half based on the median. High HOMA-IR was defined as the higher half based on the median in each category of impaired glucose metabolism. High FPG level, high AUCglu, high fasting IRI level, and high AUCins were defined as the higher half based on the median in each category of impaired glucose metabolism. Model 1 included age and sex. Model 2 included age, sex, body mass index, smoking, drinking, and presence of antihypertensive medication, dyslipidemia, and cardiovascular disease. AUCglu indicates total area under the glucose curve; AUCins, total area under the insulin curve; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; IRI, immunoreactive insulin; NFG, normal fasting glucose; NGT, normal glucose tolerance; OR, odds ratio; and SBP, systolic blood pressure.

*N=2330.

between hyperglycemia/hyperinsulinemia and hypertension because of its association with vascular damage.[30] However, our study population comprised only participants with newly diagnosed impaired glucose metabolism using a 75-g OGTT performed during a general health checkup. The participants had no history of DM treatment. Therefore, we believe that the impact of DM duration is minimal in this study. Finally, we did not assess possible confounding factors such as the renin–angiotensin system and chronic inflammation, which contribute to both BP elevation and impaired glucose metabolism.

Perspectives

We demonstrated a distinct correlation between the stages of impaired glucose metabolism, including prediabetes in 2 different forms and DM, and the prevalence of hypertension in a large population. Furthermore, our statistical analysis revealed that hyperglycemia and hyperinsulinemia were significant contributors to the presence of hypertension only in the early stages of impaired glucose metabolism (NFG/NGT and isolated IFG). This observation supports the speculation that hyperglycemia or hyperinsulinemia may be an important factor that initiates hypertension in an early stage of insulin resistance. A recent study has shown that participants with both prediabetes and hypertension had around a 2-fold risk of CVD but that prediabetes without hypertension did not confer an increased risk of CVD.[31] These findings suggest that coexistence of hypertension is a critical determinant of the prognosis in patients with impaired glucose metabolism. In the context of the previous notions that early treatment of DM had been advantageous to reduce cardiovascular events (legacy effect), studies investigating the effect of early intervention of impaired glucose metabolism on BP may be important. Our present observations may provide a basis for such studies.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S4

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Supplemental Material

Definition of dyslipidemia in this study

Of the 19,248 participants, 18,921 had data on fasting serum total cholesterol, HDL cholesterol, triglyceride, and calculated LDL cholesterol levels. When dyslipidemia was defined as taking anti-hyperlipidemic medications and/or having an LDL-cholesterol level of ≥140 mg/dL and/or HDL cholesterol level of <40 mg/dL and/or triglyceride level of ≥150 mg/dL, 11,695 participants (61.8%) had dyslipidemia. The results of univariate logistic regression analysis for hypertension are as follows:

Table S1. Univariate logistic regression analysis for hypertension (n = 18921).

Variables	N	OR	95% CI	P
Anti-hyperlipidemic medications	19248	0.92	(0.84–0.99)	0.033
Anti-hyperlipidemic medications and/or LDL-cholesterol ≥140 mg/dL, HDL cholesterol <40 mg/dL, and/or triglyceride ≥150 mg/dL	18921	0.97	(0.91–1.03)	0.363

On the bases of these analyses, we selected the definition “taking antihyperlipidemic medications” as dyslipidemia in this study.

In addition, we presented the results of the multivariate logistic regression analysis for hypertension using the definition “Anti-hyperlipidemic medications and/or an LDL-cholesterol level of ≥140 mg/dL, HDL cholesterol level of <40 mg/dL, and/or triglyceride level of ≥150 mg/dL as follows:

Table S2. Univariate and multivariate logistic regression analysis for hypertension (n = 18921)

	OR	95% CI	P
NFG/NGT	1		
Isolated IFG	1.62	(1.49–1.76)	<.001
Isolated IGT	1.62	(1.46–1.79)	<.001
IFG plus IGT	2.09	(1.90–2.29)	<.001
Diabetes	2.69	(2.46–2.94)	<.001
The model included age, sex, body mass index, smoking, drinking, and dyslipidemia, and cardiovascular disease.			

No significant differences in results were observed in a comparison between the two definitions of dyslipidemia.

Table S3. Serum immunoreactive insulin (IRI) concentrations, total areas under the insulin curves, and insulin resistance indices

determined using chemiluminescent enzyme immunoassays between April 2003 and December 2017.

N	3236	1258	822	901	571	P
Serum IRI, μU/mL						
0 min	5.1 ± 2.9	6.6 ± 3.7[*†]	6.0 ± 4.0[*]	7.3 ± 4.1[*†‡]	8.1 ± 5.8[*†‡]	<.001
30 min	45.1 ± 32.8	45.6 ± 34.6	43.7 ± 35.1	39.3 ± 27.3	31.9 ± 26.6	<.001
60 min	53.1 ± 41.7	64.9 ± 47.7	55.2 ± 44.8	57.7 ± 37.8	50.8 ± 39.1	<.001
120 min	35.1 ± 26.5	41.4 ± 30.9	65.9 ± 53.4	66.1 ± 43.6	71.4 ± 62.4	<.001
AUCins, μU/mL·h	81.2 ± 51.6	93.9 ± 56.5[*]	97.7 ± 71.6[*]	97.8 ± 56.5[*]	91.8 ± 69.8[‡§]	<.001
HOMA-IR	1.16 ± 0.69	1.71 ± 0.98[*†]	1.40 ± 0.95[*]	1.93 ± 1.10[*†‡]	2.39 ± 1.87[*†‡§]	<.001
Matsuda index	10.8 ± 6.96	7.78 ± 4.84[*†]	5.90 ± 3.52[*]	4.64 ± 2.60[*†‡]	4.07 ± 3.15[*†‡§]	<.001

P values were calculated using Kruskal–Wallis test. The Steel–Dwass post hoc test was used for multiple comparison testing.
[*]P < 0.001 vs. NFG/NGT, [†]P < 0.001 vs. iIGT, [‡]P < 0.001 vs. iIFG, [§]P < 0.001 vs. IFG plus IGT.

Table S4. Univariate and multivariate logistic regression analyses of hypertension in participants who underwent blood pressure assessments using a mercury sphygmomanometer between January 1982 and December 2012 (n = 18333).

Variables	Univariate			Model 1			Model 2		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
NFG/NGT	1			1			1		
Isolated IFG	1.73	(1.59–1.88)	<.001	1.71	(1.57–1.86)	<.001	1.59	(1.46–1.73)	<.001
Isolated IGT	1.79	(1.62–1.98)	<.001	1.71	(1.55–1.90)	<.001	1.59	(1.44–1.77)	<.001
IFG plus IGT	2.45	(2.24–2.68)	<.001	2.42	(2.21–2.65)	<.001	2.09	(1.91–2.30)	<.001
Diabetes	3.02	(2.77–3.29)	<.001	3.12	(2.86–3.40)	<.0001	2.62	(2.39–2.86)	<.001

Model 1 included age and sex. Model 2 included age, sex, body mass index smoking, drinking, and the presence of dyslipidemia, and cardiovascular disease. Hypertension was defined as taking anti-hypertensive medications and/or having systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg.