Increased Vascular Disease Mortality Risk in Prediabetic Korean Adults Is Mainly Attributable to Ischemic Stroke

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Background and Purpose—Prediabetes is a known risk factor for vascular diseases; however, its differential contribution to mortality risk from various vascular disease subtypes is not known.

Methods—The subjects of the National Health Insurance Service in Korea (2002–2013) nationwide cohort were stratified into normal glucose tolerance (fasting glucose <100 mg/dL), impaired fasting glucose (IFG) stage 1 (100–109 mg/dL), IFG stage 2 (110–125 mg/dL), and diabetes mellitus groups based on the fasting glucose level. A Cox regression analysis with counting process formulation was used to assess the mortality risk for vascular disease and its subtypes—ischemic heart disease, ischemic stroke, and hemorrhagic stroke.

Results—When adjusted for age, sex, and body mass index, IFG stage 2, but not stage 1, was associated with significantly higher all-cause mortality (hazard ratio [HR], 1.26; 95% confidence interval [CI], 1.18–1.34) and vascular disease mortality (HR, 1.27; 95% CI, 1.08–1.49) compared with normal glucose tolerance. Among the vascular disease subtypes, mortality from ischemic stroke was significantly higher (HR, 1.60; 95% CI, 1.18–2.18) in subjects with IFG stage 2 but not from ischemic heart disease and hemorrhagic stroke. The ischemic stroke mortality associated with IFG stage 2 remained significantly high when adjusted other modifiable vascular disease risk factors (HR, 1.51; 95% CI: 1.10–2.09) and medical treatments (HR, 1.75; 95% CI, 1.19–2.57).

Conclusions—Higher IFG degree (fasting glucose, 110–125 mg/dL) was associated with increased all-cause and vascular disease mortality. The increased vascular disease mortality in IFG stage 2 was attributable to ischemic stroke, but not ischemic heart disease or hemorrhagic stroke in Korean adults. **(*Stroke*. 2017;48:840-845. DOI: 10.1161/STROKEAHA.116.015947.)**

Key Words: diabetes mellitus ■ glucose tolerance ■ stroke

Prediabetes, consisting of impaired fasting glucose (IFG) and impaired glucose tolerance, is defined as an intermediate hyperglycemic state that precedes overt diabetes mellitus (DM).[1,2] It is regarded as a metabolic condition closely associated with insulin resistance or metabolic syndrome, as well as a precursor stage of type 2 DM.[3] In addition, many previous studies have reported that prediabetes is a risk factor for the development of vascular diseases.[4–8]

Importantly, a few studies suggest that prediabetes contributes differently to each vascular disease subtype, including ischemic heart disease (IHD), ischemic stroke (IS), and hemorrhagic stroke (HS).[9–11] These suggest either heterogeneity of the prediabetic state or existence of different mechanisms through which dysglycemia leads to each vascular event. Furthermore, only a few studies have investigated the association between prediabetes and hard outcomes, the mortality risk associated with each vascular disease subtype.

Prediabetes is a highly flexible state that may progress to DM or regress to normal glucose tolerance (NGT), and most previous studies were limited in not considering this changeable nature of prediabetes. To date, only one study has shown that the high risk of vascular disease mortality is confined to the prediabetic subjects who progress to DM.[12] This dearth of relevant literature indicates the need for more sophisticated methodologies to understand the association between prediabetes and the risk of vascular disease events, or mortality.

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We, therefore, aimed to investigate the association between IFG and the all-cause and cause-specific mortality in a prospective manner, using a population-based large-scale cohort (2002–2013).

Methods

Study Population

The Korean National Health Insurance System (NHIS) cohort study (2002–2013) is a population-based longitudinal study consisting of nearly one million Koreans, a representative 2.2% sample of the national population data. The NHIS cohort was longitudinally constructed as an initial 2002 cohort of 1 025 340 Koreans, who were followed up to 2013. Briefly, the cohort data are composed of demographic information, medical and pharmacy records, biannual health examination data, and death records. The demographic information contains age, sex, socioeconomic status based on income, and residency. Annually, ≈10% to 15% of the cohort population received health examinations. The medical and pharmacy records contain individuals' disease codes, prescriptions, and medical histories. The date and cause of death recorded in the Korean National Statistical Office database were merged into this cohort. More detailed cohort information and data have been published previously.[13]

From the NHIS cohort, we selected study subjects (cases) aged >30 years who had received health examinations during 2002 to 2013 and classified them on the basis of their glucose tolerance state assessed through the fasting plasma glucose levels. In our cohort data, there were multiple records of fasting glucose levels and other covariates for each individual as they may have received a health screening several times during the study period (2002–2013). By rearranging the original cohort data using the counting process formulation, we could perform survival analysis using the time-dependent variables and reduce the possible loss of data. Moreover, we identified prediabetes and DM at the every moment when an event such as a death is occurred, depending on their fasting glucose levels, to minimize the confounding effects by changes in subjects' glucose tolerance states over time.

We excluded the subjects with cancer or vascular disease in 2002 to avoid a possible confounding effect on the mortality. The total number of participants was 499 239 and deaths were 16 482 during 2002 to 2013. Death records and the cause of death were identified until the last follow-up year, 2013.

This study was based on the data from the NHIS; therefore, informed consent was not obtained individually. The study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB number: ED14188).

Determinants of Glucose Tolerance State and Mortality

Individuals' glucose tolerance state was determined through fasting plasma glucose assessment during annual health examinations: NGT (fasting glucose <100 mg/dL), IFG stage 1 (100–109 mg/dL), IFG stage 2 (110–125 mg/dL), and DM (≥126 mg/dL). DM was also identified by disease codes for DM and prescribed glucose-lowering medications.

Causes of death were classified according to the Korean version of the *International Classification of Disease, Tenth Revision*: vascular disease (I00–I99), IHD (I20–I25), IS (I63–I66), and HS (I60–I62). The date and cause of deaths of each individuals were recorded in their medical records by physicians, and all of death records were included in the NHIS database.

Details for other variables were obtained from health examination data and medical records; body weight (kg), height (m), total cholesterol level (mg/dL), systolic and diastolic blood pressure (mm Hg) were measured after overnight fasting at regular medical checkup programs. Hypertension and dyslipidemia were identified by health examination data (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg for hypertension and total cholesterol ≥240 mg/dL for dyslipidemia) or disease codes or specific medications for those diseases.

Smoking status (current, former, or never), alcohol consumption (≥3 times/wk, ≤2 times/wk, or never), and physical activity (≥3 times/wk, ≤2 times/wk, or never) were obtained from questionnaires in the regular health examinations. The NHIS also provided individuals' socioeconomic status categorized into 20 groups based on income levels.

Statistical Analyses

Each subject had multiple time-dependent health-screening records as he/she received a health screening several times during the studying period of 2002 to 2013. There were lots of delayed entries of individuals who joined the cohort after the baseline. In accordance with the time-dependent nature of the health records and to include the delayed entries in the analysis, we used the counting process formulation for the Cox regression analysis.

The counting process formulation is a data-rearranging method based on the time interval of health screening such that the individuals' health records can be represented by multiple observations, each identifying the nonoverlapping time interval between consecutive health screenings; the values of covariates over that interval; and an indicator of whether death occurred during each interval. Once the data set has been reconstructed in this manner, the multiple observations from each individual become independent cases that then allow delayed entries to be included in the analysis. The time-dependent covariates are then treated as time-invariant covariates during each time interval. Moreover, the covariate values at the time of death are more likely to be missed than others, and the counting process formulation can reduce this loss of data, especially in the event time, by using the last observed covariate values as the values at the time of death.

Hence, in applying the counting process method, we identified prediabetes and diabeteDM at the moment when a death was occurred, depending on their fasting glucose levels in each observed date. We used the SAS program's PROC PHREG procedure for data analysis.[14]

Results

Table 1 displays the baseline characteristics of the 4 study groups (NGT, IFG stage 1, IFG stage 2, and DM) according to the glucose tolerance status during the entire study period (2002–2013). The total number of cohort participants was 499 239 (71 678 were the entries in the first year cohort [2002], 54 127 in 2003, 47 239 in 2004, 39 905 in 2005, 44 044 in 2006, 35 244 in 2007, 42 253 in 2008, 40 866 in 2009, 34 604 in 2010, 34 524 in 2011, 29 465 in 2012, and 25 290 in 2013). The prevalence of DM and IFG was 13.8% and 16.4%, respectively. Subjects' age, body mass index (BMI), and the presence of concomitant diseases such as hypertension and dyslipidemia exhibited an increasing trend from NGT to IFG to DM groups.

During the entire study period, a total of 16 482 deaths were recorded in the cohort. Among them, 14.6% (2418 deaths) were because of vascular diseases. Table 2 shows the adjusted hazard ratio (HR) of all-cause and vascular disease mortality in the IFG and DM groups, compared with the NGT group. In a minimally adjusted model (model A), IFG stage 2 and DM groups had significantly higher all-cause mortality (HR, 1.26; 95% confidence interval, 1.16–1.32 and HR, 1.53; 95% confidence interval, 1.48–1.58, respectively) and vascular disease mortality (HR, 1.27; 95% confidence interval, 1.08–1.49 and HR, 1.54; 95% confidence interval, 1.41–1.69, respectively). This trend was

Table 1. Characteristics of the 2002 to 2013 NHIS Cohort Participants According to Their Glucose Tolerance State

Characteristics	NGT	IFG Stage 1 (100–110 mg/dL of FPG)	IFG Stage 2 (110–125 mg/dL of FPG)	DM	*P* Value
Proportion, %	69.8	10.6	5.8	13.8	
Age, y	47.3±11.8	49.7±11.9	51.3±12.1	56.5±12.2	<0.0001
Male sex, %	51.8	60.7	64.9	59.7	<0.0001
BMI, kg/m^2	23.5±3.0	24.3±3.1	24.7±3.2	24.5±3.2	<0.0001
Smoking, %					<0.0001
Current	24.1	26.5	29.1	23.5	
Former	10.0	13.5	14.1	15.3	
Never	65.9	60.0	56.8	61.2	
Alcohol, %					<0.0001
Never	53.3	47.5	45.4	56.3	
<2 times/wk	36.7	37.6	36.4	29.2	
>3 times/wk	10.1	15.0	18.2	14.5	
Physical activity, %					<0.0001
Never	37.2	35.4	37.7	34.0	
<2 times/wk	26.8	26.9	26.2	23.0	
>3 times/wk	36.0	37.7	36.2	43.0	
Socioeconomic status, %					NS
Lower 30%	20.4	20.2	21.7	22.6	
Middle 40%	36.6	36.1	37.4	33.6	
Upper 30%	43.1	43.7	40.9	43.8	
Hypertension	13.9	20.3	25.0	45.3	<0.0001
Dyslipidemia	10.3	13.5	14.6	38.3	<0.0001
Fasting glucose, mmol/L	87.2±7.8	103.8±2.8	115.3±4.3	139.0±44.9	<0.0001
Systolic BP, mm Hg	121.3±15.1	125.3±15.3	128.0±15.9	127.6±16.0	<0.0001
Total cholesterol, mmol/L	194.3±35.4	201.7±36.8	204.7±38.6	196.9±40.3	<0.0001
Family history of DM, %	7.3	8.0	8.4	12.8	<0.0001

Data are presented as mean±SD or %. BMI indicates body mass index; BP, blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; IFG, impaired fasting glucose; NGT, normal glucose tolerance; NHIS, National Health Insurance System; and NS, nonsignificant.

maintained, although slightly attenuated, when adjusted for modifiable cardiovascular risk factors including hypertension and dyslipidemia (model B) or when adjusted not only for the risk factors included in model B but also medical treatments such as antihypertensive drugs, antithrombotics, and statins (model C). In contrast, the IFG stage 1 group did not show an increased mortality risk compared with the reference group.

The same analyses were conducted for each vascular disease subtype (Table 3). Among the total vascular disease deaths, IHD was the most frequent cause of death (34.5%), followed by IS (23.9%) and HS (22.4%). The independence between mortality from vascular disease subtypes and fasting glucose levels was rejected with *P* value of 0.001, showing that mortality from IS was positively related to IFG stage 2, and mortality from HS was negatively related to DM. Subjects with DM had a significantly higher mortality risk because of all vascular disease subtypes. On the contrary, in all adjustment models, IFG stage 2 subjects exhibited an increased IS mortality, but not IHD or HS mortality. In particular, the subjects with IFG stage 2 had even higher IS mortality risk than those with DM in a full adjustment model including medical treatments (HR, 1.75 versus 1.41 in model C). Similar to the results of analysis for vascular disease mortality, the IFG stage 1 group did not demonstrate a different mortality risk associated with any of the vascular disease subtypes compared with the NGT group.

We further investigated whether specific subgroups in the IFG stage 2 group had a higher all-cause or vascular disease mortality risk than others. All subgroups had significantly risky effects on all-cause and vascular disease mortality except for dyslipidemia on vascular disease mortality. HRs were calculated by summing the main effects of each specific subgroup and IFG stage 2 and their interaction effect, although only 2 interaction effects between alcohol and IFG stage 2 and between BMI and IFG stage 2 on all-cause mortality were significant (Tables I and II in the online-only Data Supplement).

Table 2. Risk (Hazard Ratio) of All-Cause and Vascular Disease Mortality in Patients With Impaired Fasting Glucose and DM

	NGT	IFG Stage 1 (100–110 mg/dL of FPG)	IFG Stage 2 (110–125 mg/dL of FPG)	DM
All-cause mortality (n=16 482)				
No. of deaths	6485	1689	1206	7102
Model A	1.00	1.01 (0.95–1.06)	1.26 (1.18–1.34)	1.53 (1.48–1.58)
Model B	1.00	1.03 (0.97–1.09)	1.24 (1.16–1.32)	1.55 (1.49–1.61)
Model C	1.00	1.03 (0.96–1.11)	1.26 (1.16–1.37)	1.47 (1.40–1.54)
Vascular disease mortality (n=2418)				
No. of deaths	923	229	182	1084
Model A	1.00	0.94 (0.81–1.09)	1.27 (1.08–1.49)	1.54 (1.41–1.69)
Model B	1.00	0.93 (0.80–1.08)	1.16 (0.98–1.38)	1.54 (1.41–1.70)
Model C	1.00	0.97 (0.81–1.17)	1.22 (0.99–1.51)	1.41 (1.25–1.59)

Model A: adjusted for age, sex, and BMI; Model B: adjusted for age, sex, BMI, alcohol, smoking, physical activity, SES, systolic BP, and total cholesterol; Model C: adjusted for age, sex, BMI, alcohol, smoking, physical activity, SES, antihypertensive drugs, antithrombotics, and statins. BMI indicates body mass index; BP, blood pressure; DM, diabetes mellitus; IFG, impaired fasting glucose; NGT, normal glucose tolerance; and SES, socioeconomic status.

Discussion

Our results indicate that prediabetes is capable of differentially contributing to the mortality from each vascular disease subtypes in the general population; compared with NGT, a higher degree of IFG (stage 2, 110–125 mg/dL of fasting plasma glucose) was associated with a significantly higher mortality risk from IS but not from IHD or HS. Given that the IFG stage 2 was also associated with a higher vascular disease mortality, our results further suggest that this increased vascular disease mortality was mainly attributable to the increased IS mortality. In contrast, a lower degree of IFG (stage 1, 100–109 mg/dL of fasting plasma glucose) did not increase mortality because of vascular disease or any of its subtypes.

The prevalence of prediabetes is increasing worldwide, with the current prevalence estimated at >30% in various regions and ethnic groups.[3] Likewise, in Korea, an alarming increase in prediabetes prevalence has been reported, from 21.5% in 2006 to 25.0% in 2013.[15] A growing body of epidemiological evidence has demonstrated that prediabetes or dysglycemia

Table 3. Risk (Hazard Ratio) of Mortality From Each Vascular Disease Subtypes in Patients With Impaired Fasting Glucose and DM

	NGT	IFG Stage 1 (100–110 mg/dL of FPG)	IFG Stage 2 (110–125 mg/dL of FPG)	DM
IHD mortality (n=834)				
No. of deaths	293	84	53	404
Model A	1.00	1.06 (0.83–1.35)	1.14 (0.85–1.52)	1.76 (1.51–2.06)
Model B	1.00	1.10 (0.85–1.41)	1.06 (0.77–1.45)	1.82 (1.55–2.14)
Model C	1.00	1.09 (0.80–1.50)	0.99 (0.66–1.48)	1.74 (1.42–2.13)
Ischemic stroke mortality (n=577)				
No. of deaths	199	45	53	280
Model A	1.00	0.84 (0.61–1.17)	1.60 (1.18–2.18)	1.77 (1.47–2.13)
Model B	1.00	0.78 (0.55–1.11)	1.51 (1.10–2.09)	1.82 (1.50–2.21)
Model C	1.00	0.66 (0.42–1.06)	1.75 (1.19–2.57)	1.41 (1.09–1.82)
Hemorrhagic stroke mortality (n=541)				
No. of deaths	238	53	39	211
Model A	1.00	0.90 (0.66–1.23)	1.10 (0.77–1.58)	1.36 (1.11–1.66)
Model B	1.00	0.85 (0.63–1.16)	1.00 (0.70–1.44)	1.31 (1.08–1.60)
Model C	1.00	0.98 (0.67–1.41)	1.09 (0.69–1.72)	1.23 (0.95–1.59)

Model A: adjusted for age, sex, and BMI; Model B: adjusted for age, sex, BMI, alcohol, smoking, physical activity, SES, systolic BP, and total cholesterol; Model C: adjusted for age, sex, BMI, alcohol, smoking, physical activity, SES, antihypertensive drugs, antithrombotics, and statins. BMI indicates body mass index; BP, blood pressure; DM, diabetes mellitus; IFG, impaired fasting glucose; IHD, ischemic heart disease; NGT, normal glucose tolerance; and SES, socioeconomic status.

below the diabetic range is associated with increased vascular disease incidence and mortality.[6,7,16–18] However, some level of uncertainty exists, mainly in defining the fasting glucose cutoff value that is associated with an increased vascular disease risk and the type of vascular disease that demonstrates higher risk in the prediabetics. Although the newer IFG criteria (fasting glucose 100–125 mg/dL) defined by the American Diabetes Association in 2003 was based on the risk of developing DM in the future,[2] most large-scale studies, including the DECODE (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe); Hoorn; and the Framingham heart study, generally indicated that the cutoff fasting glucose value associated with increased cardiovascular risk is 110 mg/dL (the 1997 American Diabetes Association criteria for IFG).[7,12,18] The results of our study are concordant with these findings.

Furthermore, given that vascular disease reflects pathophysiologically and clinically heterogeneous vascular events, conflicting results have been reported for the association between prediabetes and the risk of various vascular disease subtypes. For instance, the Asia Pacific Cohort study reported that fasting plasma glucose in the prediabetic range was an important risk determinant of both IHD and stroke.[5] Similarly, the Korean Heart study observed that a higher degree of IFG was associated with an increased risk of incident IHD and IS but not HS.[9] In contrast, the Funagata study and the KNHS study (Korean National Health Insurance System) demonstrated that prediabetes increased the risk of incident IS, but not IHD and HS.[10,11] The differences in the results of these studies could be explained by the differences in the study population, the study population size, and the study duration; however, these results strongly indicated different underlying mechanisms through which glucose dysregulation contributed to IHD, IS, and HS. Moreover, because few studies have addressed the prediabetes–vascular disease subtype association in terms of the related mortality, our findings may provide a new insight into their relationship. We demonstrated that prediabetes was strongly associated with IS mortality, even after adjusting for known cardiovascular risk factors but not with IHD or HS mortality. Interestingly, our finding is in concurrence with the results of the large-scale Korean cohort study—the KNHS study, which reported that prediabetes increased the incidence of IS alone and not the other vascular disease subtypes. The researchers explained that dysglycemia may have a more direct negative impact on IS as it comprises both micro- and macrovascular atherosclerotic lesions, which is different from the predominately macrovascular lesions of IHD.[11,19]

Another possible explanation is the ethnic difference. The Asian population is more vulnerable to intracerebral vascular events than other populations; in a global comparative risk assessment study, hyperglycemia-related stroke burden was significantly higher in Asians, especially those from the East Asian region, than in the Western population.[20] Moreover, the number of IS deaths is higher in the East Asians than in the number of IHD deaths, as has been shown in several Asian studies, including this study. Notably, the increased susceptibility to IS rather than IHD among people with prediabetes has mostly been reported in studies conducted on Asian study cohorts.[10,11,21]

We further noted that the subjects with prediabetes in our study cohort possessed a relatively lean phenotype compared with those in the Western population. Most studies in the Western countries have shown that the BMI of prediabetic subjects was usually in the 25 to 30 kg/m^2 range[4,7,16,22]; however, the mean BMI of the IFG stage 2 group in our study cohort was only 24.2 kg/m^2. Because prediabetes is a group of highly heterogeneous phenotypes and metabolic states, their cardiovascular risks are expected to vary depending on each individuals' own risk factors. The findings of The Global Burden of Metabolic Risk Factors for Chronic Disease Collaboration study provided important suggestions to interpret our results. The study reported that obesity contributes differently to the risk of stroke and coronary heart disease; the effect of increasing BMI on the risk of vascular diseases was more pronounced on coronary heart disease than stroke, and conversely, the influence of metabolic mediators besides obesity was stronger on stroke than on coronary heart disease.[23] Accordingly, the increased susceptibility to stroke rather than IHD that we observed may partly be explained by the lean and metabolically unhealthy phenotype of the Asian prediabetics.

As stated before, prediabetes is a flexible metabolic state. Large-scale observation studies have reported that ≈25% of the subjects with prediabetes regressed to NGT, whereas another 25% progressed to overt DM over a 3- to 5-year follow-up period.[24,25] Consequently, most previous studies were fundamentally biased in not adjusting for the changing glucose tolerance state of the participants over time. In this context, the increased vascular disease risk observed only in the subjects who progressed to overt DM in the Hoorn study is suggestive. We eliminated this bias in our study by using the counting process analyses, which allowed the determination of glucose tolerance state as cases each year, which could then reflect regression to NGT and progression to overt DM. In fact, using a traditional Cox regression analysis to examine our data, we did not find an increased all-cause or cause-specific mortality risk in the IFG stage 2 group (data not shown).

This study still has several limitations. Because of the lack of relevant data, we could not use postprandial glucose or glycohemoglobin levels for analysis, even though they reportedly associate more significantly with increased vascular disease risk. Thus, our results may not be generalizable to all subjects with prediabetes, including isolated impaired glucose tolerance cases. Next, there exists a population bias in our study as we only used data from people who voluntarily participated in the health checkup programs and were thus probably more concerned about their health than those who did not participate in the checkups. Finally, we focused on mortality of each vascular diseases, not the incidence of them. So, the results of this study should be interpreted as the risk of fatal vascular events in subjects with prediabetes, rather than development of all types of vascular events.

Summary

To summarize, we observed that subjects with prediabetes, especially those with a higher fasting plasma glucose (110–125 mg/dL), had a significantly higher risk of ischemic stroke mortality. Therefore, an evaluation of the stroke-associated modifiable risks and formulation of stroke prevention

strategies should be undertaken. Further investigations are needed to evaluate the different mechanisms underlying the development of IHD and stroke and to design beneficial strategies to decrease each vascular disease risks.

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Disclosures

None.

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