Title: Association between glucose tolerance and mortality among Japanese community-dwelling older adults aged over 75 years: 12-year observation of the Tosa Longitudinal Aging Study

Short running title: Seniors' glucose tolerance and mortality

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Abstract

Aim: Although the relationship between impaired glucose tolerance (IGT) and mortality has been investigated in diverse populations, few studies have focused on older populations. This study aimed to investigate the relationship between glucose tolerance and overall mortality among populations aged ≥75 years.

Methods: Data were obtained from the Tosa Longitudinal Aging Study, a community-based cohort survey conducted in Kochi, Japan. According to the results of a 75 g oral glucose tolerance test conducted in 2006, the participants were classified into four categories: normal glucose tolerance (NGT), impaired fasting glucose (IFG)/IGT, newly diagnosed diabetes mellitus (NDM), and known diabetes mellitus (KDM). The primary endpoint was overall mortality. Differences in overall mortality among the four categories were evaluated using the Cox proportional hazards model.

Results: During a median of 11.5 years of observation, 125 deaths of the 260 enrolled participants were recorded. The cumulative overall survival rate was 0.52, and the survival rates of NGT, IFG/IGT, NDM, and KDM were 0.48, 0.49, 0.49, and 0.25, respectively (log-rank test, $p = 0.139$). Adjusted hazard ratios (HRs) for mortality in IFG/IGT and NDM groups compared with the NGT group were 1.02 (95% confidence interval [CI], 0.66−1.58) and 1.11 (95% CI, 0.56−2.22), while mortality in the KDM group was significantly higher than that in the NGT group (HR, 2.43; 95% CI, 1.35−4.37).

Conclusion: Mortality did not differ significantly between the IFG/IGT, NDM, and NGT groups, but was higher in the KDM group than in the NGT group.

Keywords: diabetes mellitus, glucose intolerance, older adult, long-term mortality, community-based cohort

Introduction

It is known that the prevalence of diabetes is increase with age.[1] Diabetes is associated with a deterioration in physical and cognitive function,[2,3] and the treatment of diabetes in older adults is often difficult due to multiple morbidities, diversity of medical and social factors, and a higher incidence of treatment-related adverse events such as hypoglycemia.[4] The Global Burden of Disease Study 2019 found that the disease burden in disability adjusted life-years of diabetes ranked fifth in the ≥75-year age group,[5] confirming the high impact of the disease in older adults. The 75 g oral glucose tolerance test (OGTT) detects postprandial blood glucose elevation caused by impaired glucose tolerance (IGT) and is useful for detecting intermediate hyperglycemia and early diabetes.[6] Post-load intermediate hyperglycemia indicates IGT, and intermediate fasting hyperglycemia without post-load hyperglycemia indicates impaired fasting glucose (IFG). They are not only predictors of the future incidence of diabetes,[7] but also affect mortality.[8] Although previous population-based studies have shown that IGT and IFG are related to mortality among middle-aged individuals,[9–12] few studies have focused on older populations.[13–15] Studies have shown that IGT is related to mortality even among people aged ≥60 years; however,[14,15] to the best of our knowledge, no study has investigated it among the older population. Recently life expectancy has been extended, and it is conceivable that IGT may have an impact on prognosis even in the late

elderly. However, there have been no studies examining the long-term prognosis of IGT in subjects over 75 years of age.

We have been conducting the Tosa Longitudinal Aging Study (TLAS) since 2004. TLAS consisted of annual geriatric examination with the Comprehensive Geriatric Assessment (CGA) of older adults aged 75 years or older, annual health-related questionnaire surveys, and other intervention efforts. It aims to maintain and improve the health of the older residents by investigating a variety of health-related issues. This time, we focused on the issues associated with blood glucose levels. In 2006, we have performed an OGTT as part of the TLAS and it revealed the prevalence of IGT among community-dwelling older people in Japan[16]. By following these subjects for longer than 12 years, this study shows their long-term prognosis, whether the baseline glucose tolerance status is related to mortality among adults aged ≥75 years.

Methods

Data source

This study targeted 866 of 1016 residents of Tosa town who were aged ≥75 years at the registration period (population as of 2007); 150 residents who were hospitalized or lived in nursing homes were excluded. Data were obtained from the TLAS, a community-based cohort study on comprehensive geriatric function for older adults conducted annually in Tosa, a rural

town in Kochi Prefecture, Japan. The TLAS enrolled the entire community-dwelling older adult population recorded in the town registry office.

Postal questionnaire surveys for those aged ≥65 years and health check-ups, including a comprehensive geriatric assessment for those aged ≥75 years, are conducted annually. Residents who were hospitalized or lived in nursing homes were excluded. In 2006, in addition to the usual annual health checkup, a 75 g OGTT was conducted. OGTT was conducted among participants who did not receive diabetes medications. The present study used data from the TLAS questionnaire, health check-ups, and OGTT test as baseline data. Participants aged ≥75 years who underwent OGTT were included in the analysis. Participants who did not choose to undergo OGTT were excluded from the analysis; however, those who did not undergo OGTT because they were being treated with diabetes medication were included in the analysis.

All participants in the TLAS annual health check-ups were invited to a feedback session, including an educational session and individual counseling sessions by medical doctors. Additional community study sessions on diabetes were held, and contents of the study sessions were made available through newspapers and local magazines.

Glucose tolerance assessment

Participants underwent a 75 g OGTT in the fasting state. Fasting plasma glucose (FPG) and 2-h post-load glucose (2-h PG) levels were measured using the glucose oxidase method.

Glucose tolerance status was determined according to the 1999 World Health Organization (WHO) criteria.[17] Participants who had never been diagnosed or treated for diabetes, diabetes was classified based on FPG ≥126 mg/dl or 2-h PG ≥200 mg/dl; FPG <126 mg/dl and 2-h PG ≥140 mg/dl but <200 mg/dl were indicative of IGT; FPG of 110–125 mg/dl and 2-h PG <140 mg/dl were indicative of IFG; and FPG <110 mg/dl and 2-h PG <140 mg/dl were indicative of normal glucose tolerance (NGT). Participants were classified as having previously diagnosed diabetes (known diabetes mellitus, KDM) if they were being treated with an oral drug or insulin without undergoing a 75 g OGTT. Participants who reported a history of diabetes and were diagnosed with diabetes were also classified as KDM; otherwise, they were classified according to their 75 g OGTT. This classification was used to minimize misclassification due to participant misunderstandings. Among participants with a self-reported history of diabetes, some had near-normal blood glucose levels or "prediabetes," which is easily confused with diabetes and should be distinguished from known diabetes. Diabetes that had never been diagnosed was defined as newly diagnosed diabetes mellitus (NDM). Since only 3.5% (n = 9) of the participants were categorized as IFG, we combined the participants with IFG and IGT (IFG/IGT) into one group for the analysis.

Mortality

Participants were followed up for up to 12.8 years, starting from the date they underwent the OGTT in 2006 until April 1, 2019, i.e., the end of the follow-up period. Information on

mortality during the follow-up period was obtained from death certificates from 2006 to 2018 provided by the Ministry of Health, Labor, and Welfare. Deaths after 2019 were obtained from town registry.

Measurements and data collection

Data were collected from postal self-administered questionnaires on medical history, medications, smoking status, and activities of daily living (ADL). Smoking status was divided into two categories: current/former smoker or non-smoker. ADL was rated regarding independence on seven items: walking, ascending and descending stairs, feeding, dressing, toileting, bathing, and grooming. Each item of ADL was rated from 0 to 3; the total score ranged from 0 to 21, with lower scores indicating greater disability.[18] ADL score was assessed as a continuous value and dichotomized based on whether the score was 21 points (independent) or less (dependent). Body mass index (BMI) was calculated using height and weight measurements, and participants were divided into three groups based on score ranges of <20, 20–25, and ≥25. Blood pressure was measured twice in the sitting position using an automatic sphygmomanometer (HEM 757; Omron, Kyoto, Japan). Hypertension was defined as a systolic pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg or if the participant was taking antihypertensive medication. Participants underwent the Mini-Mental State Examination (MMSE) to assess cognitive function. MMSE scores ranged from 0 to 30, with higher scores indicating better cognitive performance.[19] MMSE score was assessed as a

continuous value, and the participants were divided into three groups based on the score ranges of 0–23, 24–27, and 28–30.[20]

Blood chemical examinations included assessment of blood glucose, HbA1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), albumin, and creatinine levels. Low-density lipoprotein cholesterol (LDL) levels were estimated using the Friedewald formula. Dyslipidemia was defined as LDL ≥140 mg/dL, HDL ≤40 mg/dL, TG ≥150 mg/dL, and/or if the participant was taking cholesterol-lowering medication. The estimated glomerular filtration rate (eGFR) was calculated using the Isotope Dilution Mass Spectrometry-Modification of Diet in Renal Disease (IDMS-MDRD) formula.[21]

Statistical analysis

A one-way analysis of variance was used to examine the differences in normally distributed continuous variables among the categories of glucose tolerance. The Dunnett's test was used to compare the differences in each group with abnormal glucose tolerance in the NGT group (control). The chi-square test was used to examine the differences between the two categorical variables. The primary endpoint was overall mortality. The Kaplan–Meier method was used to assess cumulative survival in the four glucose tolerance groups, and the log-rank test was used to compare the differences between the groups. Cox proportional hazards models were used to assess overall mortality by glucose tolerance status. Age (a continuous variable) and sex were used as covariates in the basic model. In addition to age and sex, the following

covariates were analyzed in the multivariable adjusted model: BMI (categorical variable), albumin level (continuous variable), history of hypertension (dichotomized variable), history of dyslipidemia (dichotomized variable), and smoking status (dichotomized variable).

We used five multiple imputations to handle the uncertainty caused by missing values of potential confounders based on the assumption of missing at random. JMP pro ver.14.00 for Mac was used for statistical analyses. The multivariable adjustment model was performed with SPSS 28.0 for Mac.

Results

Study population

The study flow chart is shown in Figure 1. Of the 866 residents, 358 (41.3%) participated in health check-ups, among whom 241 underwent the OGTT. Nineteen participants who did not undergo OGTT due to undergoing diabetes treatment were also included in the analysis. The 98 participants without known diabetes who chose not to undergo OGTT were excluded from the analysis. Therefore, 260 participants with OGTT or known diabetes (30.0% of the target population) formed the final study population.

Baseline characteristics

Table 1 shows the baseline characteristics of the participants according to glucose tolerance status. The mean age of the enrolled 260 participants was 80.6 years (range, 75–96 years), and

38.8% were male. The participants were divided into four groups: NGT, n = 136 (52.3%); IFG/IGT, n = 72 (9 IFG and 63 IGT, 27.7%); NDM (n = 25, 9.6%); and KDM (n = 27, 10.4%). In the KDM group, 70.4% (n = 19) of the participants took diabetes medications. Compared with the NGT group, mean BMI, systolic blood pressure, TG, HDL cholesterol, and creatinine levels were significantly higher, and eGFR was significantly lower in the NDM and KDM groups. HbA1c levels were significantly higher in the NDM and KDM groups than in the NGT group, but not in the IFG/IGT group. Among the participants, 73.4% had an ADL score of 21. The mean ADL score and independence did not differ significantly between the four groups. Of the total participants, 52.7% had an MMSE score ≤27 points and 22.8% had an MMSE score ≤23 points. The mean MMSE scores in the NDM and KDM groups were significantly lower than in the NGT group. Among the 98 residents who chose not to undergo OGTT and were therefore excluded from the present analysis, the mean value of fasting glucose and prevalence of hypertension was higher, and the mean MMSE score was lower than that of the participants in this study.

Overall mortality

Of the enrolled participants, 239 (91.9%) could be followed up until April 1, 2019 (end of the follow-up period) or until their death, with a median observation period of 11.5 years. The association between glucose tolerance status and overall mortality is shown in Table 2. During the observational period, 125 deaths occurred, yielding a cumulative overall survival

rate of 0.52. Survival rates in the NGT, IFG/IGT, NDM, and KDM groups were 0.48, 0.49, 0.49, and 0.25, respectively. The Kaplan–Meier curve for unadjusted cumulative survival is shown in Figure 2. There were no significant differences between the glucose tolerance status groups (log-rank test, p = 0.139). Adjusted hazard ratios (HRs) for the IFG/IGT group compared with the NGT group were 0.95 (95% confidence interval [CI], 0.62–1.44) in the age- and sex-adjusted model and 1.02 (95% CI, 0.66–1.58) in the multivariable adjusted model. The mortality rate was significantly higher in the KDM group than in the NGT group (age- and sex-adjusted model: HR, 1.87; 95% CI, 1.05–3.14; multivariable adjusted model: HR, 2.43; 95% CI, 1.35–4.37). No significant differences were found between the NDM and NGT groups (age- and sex-adjusted model: HR, 0.89; 95% CI, 0.44–1.63; multivariable adjusted model: HR, 1.11; 95% CI, 0.56–2.22).

Discussion

In this 12-year follow-up study of overall mortality among community-dwelling older adults aged ≥75 years, only the KDM group showed a worse prognosis than the NGT group by multivariate analysis. The mean MMSE scores in the NDM and KDM groups were significantly lower than in the NGT group.

IGT/IFG could not predict mortality in adults aged ≥75 years. Mild hyperglycemia is common in older adults,[22] and 27% of the participants in this study showed IFG or IGT. A

previous meta-analysis[8] estimated the relative risk of IGT to NGT for all-cause mortality to be 1.32 (95% CI, 1.23–1.40). The meta-analysis included 11 studies of subjects aged 25-93 years; nine studies included subjects whose average age was in the 50-60s, while two studies included subjects whose average age was over 70 years. Although most previous studies have targeted middle-aged populations, there have been three cohort studies on mortality related to IGT among people aged ≥60 years. Of these studies, one reported no statistical differences due to the short observation period,[13] and the other two reported that the mortality rate in the IGT group was higher than that in the NGT group.[14,15] These three previous studies included a younger population than in our study. The impact of IGT on mortality risk has been reported to decrease with advancing age in some cohort studies[12,15]; therefore, in this study, we evaluated the impact of IGT among older populations. In 2006, when this study was started, the average life expectancy of Japanese was 79.0 years for males and 85.8 years for females, and the life expectancy at 80 years was 6.09 years for males and 8.13 years for females[23]. The average age of our participants and our cohort mortality rate were higher than those reported in previous studies. In our population, other factors may have a greater impact on mortality than IGT.

KDM had a worse prognosis than NGT, even in the older adult population, as expected and consistent with previous studies.[9–13] An earlier age of onset of diabetes and longer duration of the disease have also been reported to have a greater impact on mortality.[24] Our

results indicated that diabetes remains a prognostic factor in the population. Due to the small number of cases, the risk of NDM is difficult to interpret.

The mean MMSE scores in the NDM and KDM groups were significantly lower than in the NGT group. Cognitive impairment is a risk factor for hypoglycemia in patients with diabetes treated with glucose-lowering agents.[25] Diabetes and hypoglycemia are factors that impair ADL.[26] The MMSE and ADL scores would act as intermediate variables in the causal diagram between glucose tolerance and mortality. Because older diabetes patients with physical and cognitive decline have a poor prognosis.[27] In our study, ADL scores did not differ significantly between the four groups. Since our study invited people who could walk to the health checkup site, people with poor ADL might be less likely to be included in our study.

Our study had several limitations. First, the number of participants corresponded to 30.0% of the original target TLAS population. Since OGTT was optional, 27.3% of participants without a history of diabetes chose not to undergo OGTT, and the baseline characteristics of the participants excluded from this study without OGTT showed higher fasting glucose and lower mean MMSE scores than the participants included in this study. In addition, the TLAS includes feedback and educational sessions. Therefore, participants in this study might have a better health status and health awareness than the entire population, which may limit the generalizability of our study. If the less healthy residents were also included, the overall

mortality rate would increase. However, considering the length of time to takes for IGT to affect mortality, it is assumed that the difference between NGT and IGT groups will not be greater, and the mortality of diabetic groups may increase due to the inclusion of poorly controlled, complicated diabetic patients are included.

Second, due to the small number of cases, we were unable to make a significant interpretation of NDM and could not analyze IGT and IFG separately. Future studies with larger populations are needed.

Conclusion

This study analyzed 12-year mortality using OGTT in community-dwelling older adults aged ≥75 years. Higher mortality was found among those with long-standing diabetes, but no significant differences were detected between those with IFG/IGT and NGT. This finding could provide a basis for reassessing the clinical importance of IGT and appropriate care in future older adult populations.

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Declarations

Ethics approval and consent to participate

The study protocol was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee (C-1292), and all procedures conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Restrictions apply to the availability of data generated or analyzed in this study to preserve confidentiality. The corresponding author will request details of the restrictions and conditions under which access to some data may be provided.

Competing interests

The authors declare that they have no competing interests.

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Figure 1. Study flow diagram.

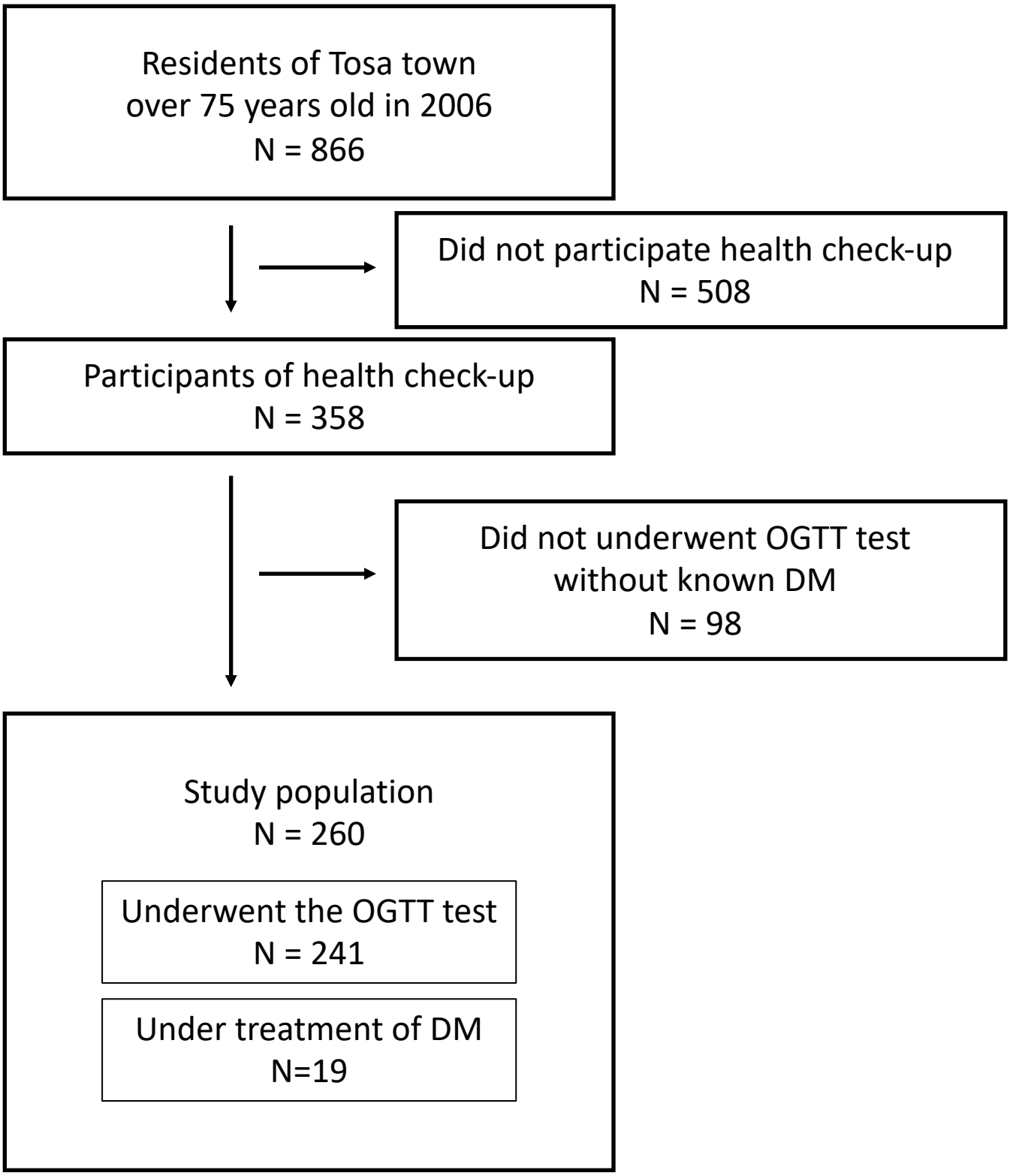
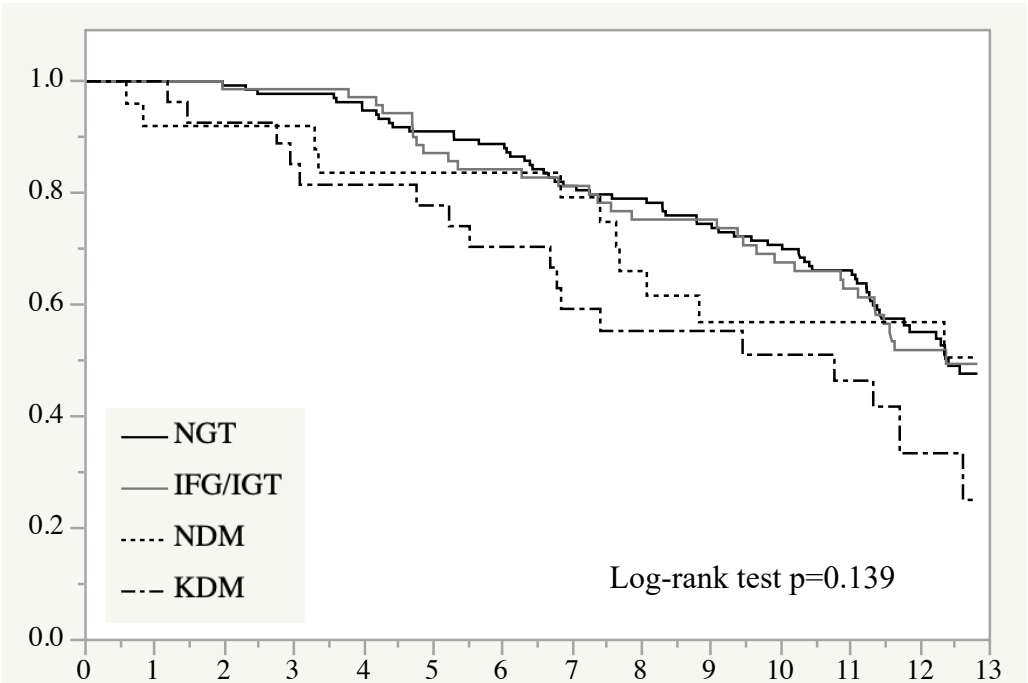


Figure 2. Survival curves for study subjects according to glucose tolerance groups.



Number at risk

NGT	136	136	134	132	128	122	119	109	106	100	94	86	47
IFG/IGT	72	72	71	70	69	62	58	55	51	50	45	41	23
NDM	25	24	24	23	21	20	20	19	16	12	12	12	10
KDM	27	27	26	24	23	22	20	17	15	14	12	11	5

NGT, normal glucose tolerance; IFG/IGT, impaired fasting glucose and impaired glucose tolerance; NDM, newly diagnosed diabetes mellitus; KDM, known diabetes mellitus.

Tables

Table 1. Baseline characteristics of the glucose tolerance category groups.

	NGT		IFG/IGT		NDM		KDM		P-value
N	136	(52.3%)	72	(27.7%)	25	(9.6%)	27	(10.4%)	
Age, y	80.2	(0.34)	80.8	(0.56)	81.3	(0.80)	81.0	(0.98)	0.541
Male	51	(37.5%)	29	(40.3%)	12	(48.0%)	9	(33.3%)	0.707
Fasting plasma glucose level, mg/dl	96.0	(0.56)	103.1	(1.13)**	111.8	(3.37)**	140.6	(7.09)**	<.001
2-hour postload glucose level, mg/dl	106.8	(1.89)	155.9	(3.10)**	227.8	(8.82)**	242.9	(15.4)**	<.001
Hemoglobin A1c (%)	5.7	(0.03)	5.7	(0.04)	6.1	(0.10)**	6.8	(0.14)**	<.001
<5.5	32	(23.5%)	11	(15.3%)	1	(4.0%)	0	(0%)	<.001
5.5-5.9	83	(61.0%)	38	(52.8%)	10	(40.0%)	2	(7.4%)	
6.0-6.4	18	(13.2%)	18	(25.0%)	8	(32.0%)	3	(11.1%)	
6.5-7.0	0	(0%)	2	(2.8%)	4	(16.0%)	9	(33.3%)	
7.0-7.4	0	(0%)	0	(0%)	1	(4.0%)	3	(11.1%)	
≥7.5	0	(0%)	0	(0%)	1	(4.0%)	3	(11.1%)	
Missing	3	(2.2%)	3	(4.2%)	0	(0%)	7	(25.9%)	
Body mass index, kg/m^2	22.8	(0.25)	22.9	(0.37)	23.8	(0.51)	24.5	(0.70)*	0.023
<20	23	(16.9%)	10	(13.9%)	1	(4.0%)	2	(7.4%)	0.223
20-24	85	(62.5%)	43	(59.7%)	14	(56.0%)	16	(59.3%)	
≥25	28	(20.6%)	19	(26.4%)	10	(40.0%)	9	(33.3%)	
Hypertension†	61	(44.9)	44	(61.1%)	14	(56.0%)	17	(63.0%)	0.085
Systolic blood pressure, mmHg	128.8	(1.75)	132.8	(1.96)	139.6	(4.25)*	139.5	(3.82)*	0.009
Diastolic blood pressure, mmHg	70.5	(0.87)	72.1	(1.17)	74.2	(2.14)	71.6	(1.73)	0.335
Antihypertensive medication use	38	(27.9%)	32	(44.4%)	9	(36.0%)	10	(37.0%)	0.121
Dyslipidemia‡	61	(44.9%)	34	(47.2%)	14	(56.0%)	16	(59.3%)	0.463
Total cholesterol, mg/dL	196.4	(2.89)	190.4	(4.24)	180.8	(5.58)	187.3	(5.51)	0.124
HDL cholesterol, mg/dL	55.8	(1.16)	53.9	(1.77)	48.5	(2.59)*	49.9	(2.59)	0.038
Triglycerides, mg/dL	93.5	(3.29)	101.1	(5.20)	131.7	(10.8)**	121.8	(11.5)**	<.001
Lipid-lowering medication use	14	(10.3%)	11	(15.3%)	4	(16.0%)	12	(44.4%)	0.013
Albumin, mg/dL	4.3	(0.02)	4.34	(0.03)	4.4	(0.06)	4.4	(0.05)	0.332
Creatinine, mg/dl	0.80	(0.02)	0.87	(0.03)	0.94	(0.05)*	0.90	(0.05)	0.013
eGFR, mL/min/1.73m^2	61.9	(1.17)	57.5	(1.61)	54.0	(2.73)*	54.5	(2.62)*	0.004
Smoking									
Current/Former	65	(47.8%)	36	(50.0%)	16	(64.0%)	19	(70.4%)	0.410
Never	40	(29.4%)	18	(25.0%)	5	(20.0%)	6	(22.2%)	

Missing	31	(22.8%)	18	(25.0%)	4	(16.0%)	2	(7.4%)	
Basic Activities of Daily Living (0-21)	20.3	(0.18)	20.4	(0.24)	19.3	(0.41)	19.9	(0.38)	0.088
21 (independent)	85	(62.5%)	49	(68.1%)	13	(52.0%)	19	(70.4%)	0.452
< 21 (dependent)	28	(20.6%)	16	(22.2%)	9	(36.0%)	7	(25.9%)	
Missing	23	(16.9%)	7	(9.7%)	3	(12.0%)	1	(3.7%)	
Mini-Mental Sate Examination (0-30)	26.4	(0.39)	25.8	(0.39)	23.8	(1.10)*	24.4	(0.72)*	0.012
28-30	59	(43.0%)	25	(34.7%)	7	(28.0%)	4	(14.8%)	0.018
24-27	39	(29.0%)	26	(36.1%)	7	(28.0%)	12	(44.4%)	
0-23	20	(15.0%)	15	(20.8%)	9	(36.0%)	9	(33.3%)	
Missing	18	(13.0%)	6	(8.3%)	2	(8.0%)	2	(7.4%)	

Data are n (%) or mean (standard error)

* $P < 0.05$ compared to NGT, ** $P < 0.01$ compared to NGT.

†Hypertension defined as blood pressure $\geq$ 140/90 mm Hg and/or use of antihypertensive medication. ‡ Dyslipidemia defined as LDL $\geq$ 140 mg/dL and/or HDL $\leq$ 40 mg/dL and/or TG $\geq$ 150 mg/dL, and/or taking cholesterol-lowering medication.

NGT, normal glucose tolerance; IFG/IGT, impaired fasting glucose and impaired glucose tolerance; NDM, newly diagnosed diabetes mellitus; KDM, known diabetes mellitus; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.

Table 2. Number of deaths, cumulative survival rate and adjusted hazard ratios for mortality by glucose tolerance category and other variables

				Mortality Risk					
	Number of deaths		Cumulative survival rate	Age and sex adjusted			Multivariable adjusted†		
	n	(%)		Hazard Ratio	(95% confidence Interval)	P-value	Hazard Ratio	(95% confidence Interval)	P-value
NGT	64	(47.1%)	0.48	1.0			1.0		
IFG/IGT	33	(45.8%)	0.49	0.95	(0.62 - 1.44)	0.828	1.02	(0.66-1.58)	0.929
NDM	11	(44.0%)	0.49	0.89	(0.44 - 1.63)	0.728	1.11	(0.56-2.22)	0.765
KDM	17	(63.0%)	0.25	1.87	(1.05 - 3.14)*	0.034	2.43	(1.35-4.37)**	0.003

* $P < 0.05$, ** $P < 0.01$.

†Adjusted for age, sex, body mass index, albumin, history of hypertension, history of dyslipidemia, and smoking status.

NGT, normal glucose tolerance; IFG/IGT, impaired fasting glucose and impaired glucose tolerance; NDM, newly diagnosed diabetes mellitus; KDM, known diabetes mellitus.