Impaired Glucose Tolerance, Diabetes, and Cardiovascular Disease Risk Factor Profiles in the Elderly

The Honolulu Heart Program

BEATRIZ L. RODRIGUEZ, MD, PHD
JESS DAVID CURB, MD
CECIL M. BURCHFIEL, PHD
BOJI HUANG, MD, PHD
DAN S. SHARP, MD, PHD
GUIQING YE LU, MS
WILFRED FUJIMOTO, MD
KATSUHIKO YANO, MD

OBJECTIVE — The relationship between glucose tolerance status and other cardiovascular disease (CVD) risk factors was evaluated in a cohort of Japanese-American men (n = 3,741) ages 71–93 years who participated in the fourth examination of the Honolulu Heart Program in 1991–1993.

RESEARCH DESIGN AND METHODS — In this cross-sectional study, subjects were classified by reported diabetes and glucose tolerance status using questionnaires and the World Health Organization (WHO) criteria, respectively.

RESULTS — The prevalence of reported diabetes was 17%. Among the men who completed an oral glucose tolerance test and had no history of diabetes (n = 1,900), 23% were diagnosed as diabetic and 39% had impaired glucose tolerance (IGT) by WHO criteria. The CVD risk factor profiles of men with IGT and diabetes were significantly more adverse compared with men with normal glucose tolerance after adjustment for age. The rates of hypertension, mean levels of BMI, waist-to-hip ratio, triglycerides, and fasting insulin were higher in men with IGT and diabetes compared with normal subjects. Opposite trends were observed for HDL cholesterol. Two-hour insulin was significantly higher among men with IGT and previously undiagnosed diabetes. Men with known diabetes had a lower physical activity index and higher fibrinogen levels than normal subjects. No significant differences were observed for current smoking and alcohol intake. Differences in risk factor levels by glucose tolerance status remained after adjustment for age, physical activity, BMI, and waist-to-hip ratio.

CONCLUSIONS — These findings show that among elderly men of Japanese ancestry, impaired glucose tolerance and undiagnosed and known diabetes are highly prevalent, and these conditions are associated with adverse CVD factor profiles.

Previous research conducted in Hawaii suggests that Asians have rates of diabetes two to three times higher compared with whites (1). Previous reports also suggest that migrant Japanese men living in the U.S. have a higher prevalence of abnormal glucose tolerance compared with Japanese men living in Japan (2–4). In the Ni-Hon-San study carried out in 1965 in three populations of Japanese men residing in Hiroshima, Japan; Oahu, Hawaii; and the San Francisco Bay Area, California, 50 g of glucose were administered by mouth to nonfasting subjects, and serum glucose was measured at 1 h (5). Glucose levels were higher among the two migrant populations compared with the Japanese men in Japan. Moreover, although Japanese men aged 50–69 years living in Hawaii appeared to have higher glucose values compared with men living in California, it is not clear if this is because the oral glucose tolerance test (OGTT) was not administered to men with diabetes in California.

The Honolulu Heart Program is one of the original populations of the Ni-Hon-San Study. Previous reports from the Honolulu Heart Program have shown that impaired glucose tolerance (IGT) and diabetes are independent predictors of coronary heart disease (6,7). The fourth examination of the Honolulu Heart Program was conducted in 1991–1993, 26 years after the inception of the study, in a cohort of Japanese-American men who are now elderly. In the past, data on aspects of diabetes had been limited in this cohort. During the fourth examination conducted in 1991–1993, fasting glucose and insulin levels were measured in this population. In addition, a 2-h 75-g OGTT was also conducted. This has allowed us to use the World Health Organization (WHO) classification for diabetes and IGT (8) for the first time in this cohort. We have examined the cross-sectional relationships between glucose tolerance status and various cardiovascular disease (CVD) risk factors. The present analysis also includes a group of subjects with previously undiagnosed diabetes who were therefore unlikely to have modified their risk factor levels because of diagnosis.

From the Division of Clinical Epidemiology (B.L.R., J.D.C., B.H., G.Y.L., K.Y.), John A. Burns School of Medicine, The University of Hawaii at Manoa, Honolulu, Hawaii; The Honolulu Heart Program (C.M.B., D.S.S.), National Heart, Lung, and Blood Institute, National Institutes of Health, Honolulu, Hawaii; and the Department of Medicine (W.F.), University of Washington, Seattle, Washington.

Address correspondence and reprint requests to Beatriz L. Rodriguez, MD, PhD, Co-Principal Investigator, The Honolulu Heart Program, 347 North Kuakini St., Honolulu, HI 96817. E-mail: beatriz@hhs.cba.hawaii.edu.

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CVD, cardiovascular disease; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.

RESEARCH DESIGN AND METHODS

Study population

The Honolulu Heart Program began in 1965 following a cohort of 8,006 Japanese-American men living on Oahu, Ha-

Table 1—*Prevalence of glucose tolerance abnormalities among participants examined in the Honolulu Heart Program Fourth Examination*

	n	Overall	70–74 years old	75–79 years old	80–84 years old	85+ years old
Diabetes history or medications	3,741	17	17	19	17	12
Diabetes by WHO criteria (fasting glucose ≥140 or 2-h glucose ≥200)	1,900	23	21	22	25	27
IGT by WHO criteria (fasting glucose <140 and 2-h glucose ≥140 and <200)	1,900	39	40	38	38	37

Data are *n* or %. For diabetes history or medications, all individuals who participated in the fourth examination were included in these analyses (n = 3,741). For diabetes and IGT by WHO criteria, analyses were limited to subjects who had a complete OGTT and a negative medical history of diabetes (n = 1,900).

waii, who were born between 1900 and 1919. Details of the selection process and procedures of the baseline examination and subsequent follow-up for this cohort have been published previously (5,9–10). The fourth examination of the cohort was conducted during 1991–1993 when men were ages 71–93 years. A total of 3,741 men participated in the examination, representing 80% of the survivors of the cohort. Overall, 69% of the cohort men were examined at the clinic, 1% in nursing homes, and 10% at their homes. An additional 18% of the surviving men provided us with short telephone interviews. Data was gathered on 98% of the survivors of the cohort (n = 4,560).

Data collection

During the fourth examination, demographic information; anthropometric measurements; medical history; and fasting measures of glucose, insulin, total and HDL cholesterol, triglycerides, and fibrinogen were collected. A 2-h 75-g OGTT was also administered. Other measures included ankle-arm blood pressure, spirometry, and an assessment of health habits such as smoking, physical activity, and alcohol intake. Measures of cognitive function (CASI) were also conducted. All measures were obtained using standardized procedures.

OGTT

Subjects were on their usual diet during the days before the examination. After an overnight fast of at least 8 h, baseline blood samples were collected. Subjects then ingested a solution of glucose (75 g) in water over a few minutes, and a blood sample was drawn at 120 min for measurement of serum glucose (automated glucose oxidase method, University of Vermont) and insulin (radioimmunoassay developed in the Immunoassay Core Laboratory of Diabetes-Endocrinology Research Center, University of Washington [11,12]).

Subjects examined at home or in nursing home facilities did not receive the OGTT. Similarly, diabetic individuals receiving insulin (n = 94) did not have an OGTT. Other exclusion criteria for OGTT included gastrectomy, an active peptic ulcer within the last 3 months, stomach cancer, systolic blood pressure >200 mmHg, diastolic blood pressure >115 mmHg, refusal to perform the OGTT, or the participant fasting for <8 h. A total of 2,176 men completed the OGTT. Among those who had an OGTT, 13% had diabetes by history or medication use compared with 24% among those who did not complete the procedure. Because the diabetic status of the participants influenced whether subjects received the OGTT or not, analyses for the OGTT were limited to previously undiagnosed individuals.

Table 2—*Age-adjusted mean levels and percentages for selected CVD risk factors by glucose tolerance status in The Honolulu Heart Program*

	Normal	IGT	Unknown diabetes	Known diabetes
n	738	734	428	652
Hypertension ≥140/90 or medications (%)	68	77*	80*	77*
BMI (kg/m^2)	23.3	23.9*	24.1*	23.8*
Waist-to-hip ratio	0.94	0.94*	0.95*	0.95*
Triglycerides (mg/dl)	130	151*	163*	159*
HDL (mg/dl)	53	51*	49*	48*
Fasting insulin (μU/ml)	12	14	16	29*
2-h insulin (μU/ml)	89	140*	140*	94
Fasting glucose (mg/dl)	101	105*	120*	146*
2-h glucose (mg/dl)	112	167*	254*	285*
Physical activity index	32	31	31	30*
Fibrinogen (mg/dl)	300	303	310*	316*
Cholesterol (mg/dl)	191	193	193	187*
Current smoking (cigarettes/day)	12	16	12	16
Current drinking (oz/month)	20	22	25	19

Data are % or means. For percentages and 2-h insulin, analyses were limited to 2,552 subjects who had a medical history of diabetes (n = 652) or a complete OGTT (n = 1,900). Current smoking, n = 249; current drinking, n = 1,185; 2-h insulin, n = 2,160; and glucose, n = 2,176. *P < 0.05, normal group as reference.

Prevalence of diabetes and IGT

The prevalence of known diabetes was based on the question "has a doctor told you that you have diabetes or high blood sugar?" or the reported use of insulin or pills for diabetes. Prevalence estimates of undiagnosed diabetes and IGT are based on the WHO classification; that is, a fasting glucose ≥140 mg/dl or a 2-h glucose ≥200 mg/dl is diagnostic of diabetes, and a fasting glucose of 140–199 mg/dl indicates IGT (8).

RESULTS

The prevalence of reported diabetes among all participants of the fourth examination was 17%. A telephone interview conducted with nearly all surviving cohort members who were not examined (nonrespondents) provided identical results. Similarly, the rates of diabetes and mean 1-h 50-g postload glucose values were nearly identical at baseline (in 1965) for the men who participated in the fourth examination and the survivors who were invited but did not participate in the examination (8 vs. 9% and 161 vs. 159 mg/dl, respectively). This suggests that our sample of men was not biased.

Results of the OGTT in an analysis that included only men without history of diabetes (n = 1,900) identified a large number of previously undiagnosed diabetic patients and subjects with IGT by WHO criteria (Table 1). Among these men, 23% had undiagnosed diabetes and 39% had IGT. If these rates are extrapolated to the overall study population (as opposed to only men without history of diabetes), the prevalence rates would be 19% for undiagnosed diabetes and 32% for IGT. Thus, we estimate that ~68% of the overall population of Japanese-American men 71–93 years old living in Hawaii have glucose tolerance abnormalities.

The CVD risk factor profiles of men with IGT and diabetes were significantly more adverse compared with men with normal glucose tolerance after adjustment for age (Table 2). Hypertension prevalence and mean levels of BMI, waist-to-hip ratio, triglycerides, and fasting and 2-h glucose levels were higher in subjects with IGT and diabetes compared with normal subjects. Fasting insulin was higher among known diabetic subjects than among normal subjects. Opposite trends were observed for HDL cholesterol. Two-hour insulin was significantly higher among men with IGT and previously undiagnosed diabetes. Although men with known diabetes had 2-h insulin levels similar to levels observed among normal subjects, they had higher plasma glucose levels. Thus, the 2-h insulin levels are low with respect to concurrent glucose levels in known diabetic subjects. Men with known diabetes also had a lower physical activity index and higher fibrinogen levels. No significant differences were observed for current smoking and alcohol intake. After adjustment for age, physical activity, BMI, and waist-to-hip ratio, subjects with abnormal glucose tolerance still had a more adverse risk factor profile compared with subjects with normal glucose tolerance status (data not shown).

Among the diabetic subjects who reported taking medications for diabetes and who completed the OGTT, 59% had fasting values >140 mg/dl and 95% had 2-h glucose values >200 mg/dl.

CONCLUSIONS— Diabetes and IGT are highly prevalent among men of Japanese ancestry living in Hawaii. This study also showed that a large proportion of the subjects had undiagnosed diabetes based on the WHO criteria. Fujimoto et al. (13) conducted a study among Japanese-American men living in Seattle and found that the estimated prevalence of diabetes was 20% (including previously diagnosed and undiagnosed), and an additional 36% of the men had IGT. Because the Japanese-American men participating in the Seattle study were younger than the Honolulu Heart Program population (average age 61 vs. 78 years old), the difference in the prevalence rates observed may be explained by age differences.

The present study demonstrates that men with abnormal glucose tolerance have a more adverse CVD risk factor profile compared with men with normal glucose tolerance status after adjustment for age, as well as after adjustment for age, physical activity, BMI, and waist-to-hip ratio. Japanese-American men in Hawaii are a relatively lean population compared with other ethnic groups in the U.S. Based on 2-h insulin levels, men with IGT and unknown diabetes had higher insulin levels compared with normal subjects, reflecting a compensatory mechanism that occurs early in the course of the disease. The elevated immunoreactive insulin levels observed in subjects with diabetes are due to not only true insulin but also to proinsulin and its split products. Men with previously diagnosed diabetes may have had a more advanced islet β-cell lesion, as evidenced by their relatively low 2-h insulin levels despite elevated concurrent glucose levels.

Previous research (14–19) has shown that subjects with abnormal glucose tolerance also have more adverse CVD risk factor profiles compared with men with normal glucose tolerance. Our results of elderly men of Japanese ancestry are consistent with these observations. Previous reports from the Honolulu Heart Program (7,20) and other studies (21–24) suggest that men with diabetes and asymptomatic hyperglycemia are at increased risk of having coronary heart disease and stroke. The Honolulu Heart Program is the largest minority population-based study of the elderly with a focus on diabetes and CVD. No other study conducted in the U.S. has as many subjects age 85 years and older. The findings of this investigation show that among elderly men of Japanese ancestry, IGT and undiagnosed and known diabetes are highly prevalent, and these conditions are associated with an adverse CVD risk factor profile.

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