Impaired fasting glucose concentrations in nondiabetic patients with ischemic heart disease: A marker for a worse prognosis

Enrique Z. Fisman, MD,[a] Michael Motro, MD,[a] Alexander Tenenbaum, MD, PhD,[a] Valentina Boyko, MS,[b] Lori Mandelzweig, MPH,[b] and Solomon Behar, MD[b] ***Tel-Hashomer, Israel***

Background The issue of whether glucose concentrations below the diabetic threshold may be predictive of increased cardiovascular risk has not yet been fully elucidated. The current study evaluates the prognosis of nondiabetic patients with ischemic heart disease (IHD) and impaired fasting glucose (IFG) over a 7.7-year follow-up period.

Methods A total of 11,853 patients with documented coronary artery disease aged between 45 and 74 years were examined. Patients were divided into 3 groups on the basis of their fasting blood glucose levels at screening: nondiabetic individuals, patients with IFG, and undiagnosed diabetic patients. Patients who were on any type of pharmacologic antidiabetic treatment were excluded from the study. Mortality rates were assessed separately for each group.

Results The population comprised 9773 nondiabetic patients (82.4%, glucose up to 109 mg/dL), 1258 patients with IFG levels (10.6%, glucose 110-125 mg/dL), and 822 diabetic subjects (7%, glucose ≥126 mg/dL). Patients were followed up from 6.2 to 9.0 years (mean follow-up period 7.7 ± 1.5 years). Crude mortality was lower in the nondiabetic subjects than in the 2 other groups. All-cause mortality in the nondiabetic group was 14.3% compared to 20.1% in patients with IFG and 24.3% in the undiagnosed ($P < .001$). Multivariate adjustment showed the lowest mortality in nondiabetic subjects, who exhibited a survival rate of 0.86 at the end of the follow-up, wherease the lowest survival–0.75–was seen among undiagnosed diabetic patients ($P = .0001$). An intermediate value of 0.78 was documented for patients with IFG ($P < .01$). After multivariate analysis, with nondiabetic patients as the reference group, IFG was identified as a consistent predictor of increased all-cause and IHD mortality with hazard ratios of 1.39 (95% confidence interval 1.21-1.59) and 1.29 (95% confidence interval 1.01-1.64), respectively.

Conclusions The main finding of this study is the substantially increased mortality rate among nondiabetic coronary patients with IFG, who had fasting glucose levels markedly lower than hitherto acknowledged as defining overt diabetes. (Am Heart J 2001;141:485-90.)

Glucose concentrations that are higher than the diabetes threshold constitute a well-established risk factor for heart disease. However, whether values below this threshold may be predictive of increased cardiovascular risk has not yet been fully elucidated and the issue is controversial. Although both early[1] and recent[2] observations did not find a consistent association between asymptomatic fasting hyperglycemia and coronary disease, other studies have argued that glucose levels in nondiabetic patients were directly related to cardiovascular risk.[3,4]

The current American Diabetes Association (ADA) criteria for defining diabetes from fasting blood glucose levels of ≥126 mg/dL (7 mmol/L) were based on the fact that both the incidence and prevalence of microvascular disease—such as retinopathy and nephropathy—that represent a specific complication of diabetes, increased at this concentration.[5] These criteria replaced the previous World Health Organization (WHO) ones, which required fasting glucose levels of ≥140 mg/dL (7.7 mmol/L) for the diagnosis of diabetes[6] and were provisionally agreed to by a WHO consultation.[7] In addition, in an attempt to simplify the diagnosis of diabetes, the need for an oral glucose tolerance test in routine practice was removed from the ADA recommendations. Levels of 110 to 125 mg/dL were designated impaired fasting glucose (IFG), a new category that partially overlaps positive tolerance tests.[5]

This new ADA category for diabetes is not based on

From the [a]Cardiac Rehabilitation Institute and the [b]Bezafibrate Infarction Prevention Study Coordinating Center, Neufeld Cardiac Research Institute, Chaim Sheba Medical Center, Tel-Hashomer, affiliated with the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
Submitted June 5, 2000; accepted November 29, 2000.
Reprint requests: Enrique Z. Fisman, MD, Cardiac Rehabilitation Institute, Chaim Sheba Medical Center, 52621 Tel-Hashomer, Israel.
E-mail: zfisman@post.tau.ac.il

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the prevalence of macrovascular complications such as ischemic heart disease, and the long-term prognostic significance of IFG in coronary patients is unclear. The current study evaluates the prognosis of nondiabetic subjects with known ischemic heart disease (IHD) and IFG over a 7.7-year follow-up period.

Methods

Subjects

The initial population consisted of 12,402 patients. Of these, 549 were excluded from analysis because of missing data. Thus the final study sample comprised 11,853 patients aged 45 to 74 years with a previous myocardial infarction (0.5 to 5 years before commencement of follow-up) or documented coronary disease (within 2 years preceding the examination), screened for participation but not included in the Bezafibrate Infarction Prevention (BIP) study.[8]

The design, major features, and ethical guidelines of the BIP study have been previously reported.[8] In brief, between February 1, 1990, and October 30, 1992, all eligible patients underwent a complete medical examination and biochemical blood tests; historic medical data, as well as data on drug therapy, were recorded. The major exclusion criteria for the BIP study were permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant diseases, estrogen replacement therapy, and insulin-dependent diabetes mellitus.

The patients included in the current analysis were divided into 3 groups on the basis of their fasting blood glucose concentrations at screening: (1) nondiabetic patients (glucose up to 109 mg/dL), (2) patients with IFG (glucose 110-125 mg/dL) and (3) undiagnosed diabetic patients (glucose ≥126 mg/dL). Subjects who were on any type of pharmacologic antidiabetic treatment were excluded from this analysis.

Laboratory methods

Cooled blood samples, collected in the 18 participating centers by standard equipment and procedures, were transferred to the study's central laboratory; all analyses were performed on a Boehringer Hitachi 704 random access analyzer as detailed in a previous report.[9]

Determination of additional variables and definitions

Data on medical history, clinical findings, and drug intake were recorded by the interviewing physician. The diagnosis of IHD was made in patients with either documented myocardial infarction or in whom there was also a positive exercise test, evidence of myocardial ischemia revealed by radionuclear studies, or angiographic evidence of at least 60% stenosis of one major coronary artery.[8]

Patients without a previous history of type 2 diabetes who were hyperglycemic (fasting blood glucose concentration of ≥126 mg/dL) were defined as undiagnosed diabetics, and individuals with fasting concentrations of 110 to 125 mg/dL were considered as patients with IFG. This allocation is in keeping with the criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus of the ADA.[5] Hypertension in undiagnosed diabetic patients was defined according to the criteria of the Working Group on Hypertension in Diabetes.[10]

Mortality data were obtained by matching the patients' identification numbers with their life status in the Population Registry. Each matched record was checked for correct identification. Death certificates and diagnosis on hospital discharge were coded according to the system described in the International Classification of Diseases, Ninth Revision (ICD-9), in which ischemic heart disease is denoted by codes 410 to 414.[11]

Statistical analysis

To evaluate the prognosis of nondiabetic subjects with known coronary artery disease and IFG over the 7.7-year follow-up period, data were analyzed with SAS software (SAS Institute, Cary, NC).[12] Continuous variables were reported as mean values ± SD. Significance was determined with the chi-square test for categorical variables and analysis of variance for continuous variables. Age-adjusted mortality rates per 1000 person years were computed with a special SAS macro.[13] Actuarial survival curves by treatment groups were produced with use of the LIFETEST procedure.[14] The log-rank test was used for comparing the curves. Multivariate analysis of mortality was performed with the stepwise Cox proportional hazard model (PHREG procedure) to account for differing lengths of follow-up and correlation with covariates. Adjustment was made for age, sex, total cholesterol, triglycerides, previous myocardial infarction, functional class, hypertension, peripheral vascular disease, anginal syndrome, chronic obstructive pulmonary disease, smoking status, and body mass index. Hazard ratio and 95% confidence limits were calculated. The significance levels for entering and removing an explanatory variable were set at .15 and .10, respectively.

Results

Baseline data

The nondiabetic population consisted of 9773 individuals (82.4% of the total population), 1258 patients (10.6%) had IFG levels, and 822 were diabetic (7%).

The main clinical characteristics and laboratory values of all patients are presented in Table I. The majority of the patients in all groups were men and had sustained a myocardial infarction in the past. The prevalence of peripheral vascular disease was low in all groups but relatively higher in undiagnosed diabetic patients. No differences among groups were documented with respect to chronic lung disease and past or current smoking.

Total cholesterol was higher in the undiagnosed diabetics, but no differences were documented for low-density lipoprotein cholesterol. High-density lipoprotein was higher in nondiabetic patients. Triglycerides were significantly higher in the undiagnosed diabetic individuals.

Mortality data

Patients were followed up from 6.2 to 9.0 years (mean follow-up period 7.7 ± 1.5 years). During this

Table I. Baseline characteristics of the study populations

	Nondiabetics (n = 9773)	IFG (n = 1258)	Undiagnosed diabetics (n = 822)	*P* value
Age (y)	59.6 ± 7.2	60.3 ± 6.6	60.2 ± 6.8	NS
Weight (kg)	74.7 ± 11.3	77.3 ± 11.8	78.2 ± 12.4	<.001
Body mass index (kg/m^2)	26.4 ± 3.4	27.3 ± 3.5	27.7 ± 3.7	<.001
Men	7990 (82)	1050 (84)	700 (85)	NS
Myocardial infarction	6993 (72)	909 (72)	587 (72)	NS
Peripheral vascular disease	303 (3)	35 (3)	41 (5)	.02
NYHA class ≥2	2455 (26)	370 (30)	239 (30)	<.001
Hypertension	2945 (30)	431 (34)	299 (36)	<.001
Chronic lung disease	287 (3)	27 (2)	28 (3.5)	NS
Current smokers	1139 (12)	152 (12)	109 (13)	NS
Past smokers	5191 (53)	695 (55)	459 (56)	NS
Glucose (mg/dL)	93 ± 9	117 ± 5	160 ± 43	<.001
Total cholesterol (mg/dL)	224 ± 39	226 ± 41	227 ± 40	.005
HDL cholesterol (mg/dL)	38.3 ± 10.2	36.7 ± 9.6	36.2 ± 9.6	.01
LDL cholesterol (mg/dL)	155.9 ± 33.9	156.6 ± 34.8	153.9 ± 34.4	NS
Triglycerides (mg/dL)	146.5 ± 77	168.3 ± 100	189.9 ± 114	<.001

Values in parentheses indicate percentage. *NS,* Not significant; *NYHA,* New York Heart Association; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein.

Table II. Crude mortality during an average 7.7-year follow-up period among the study patients

Mortality types	Nondiabetics (n = 9773)	IFG (n = 1258)	Undiagnosed diabetics (n = 822)	*P* value
All-cause	1398 (14.3)	253 (20.1)	200 (24.3)	<.001
IHD	469 (4.8)	79 (6.3)	76 (9.2)	<.001
Others	627 (6.4)	116 (9.2)	84 (10.2)	<.001
Unknown	302 (3.1)	58 (4.6)	40 (4.9)	<.001

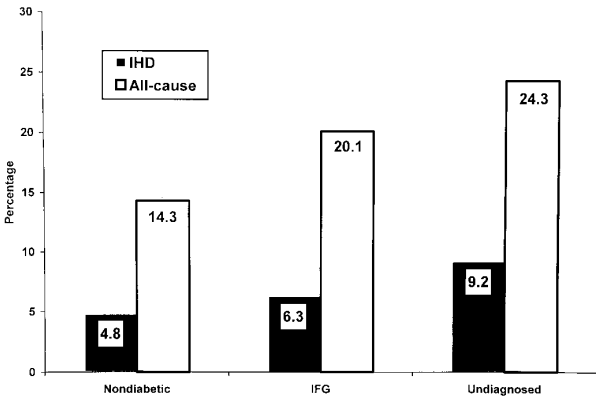
Values in parentheses indicate percentage.

period, crude all-cause and IHD mortality were lower in nondiabetic subjects than in the 2 other groups (Table II). All-cause and IHD mortality were 14.3% and 4.8% in nondiabetic patients, 20.1% and 6.3% in IFG, and 24.3% and 9.2% in undiagnosed subjects, respectively ($P <$ .001, Figure 1).

Actuarial survival curves for all-cause mortality for the three study groups are presented in Figure 2. Multivariate adjustment showed the lowest mortality in nondiabetic subjects, who exhibited a survival rate of 0.86 at the end of the follow-up, whereas the lower survival—0.75—was seen in undiagnosed diabetics ($P = .0001$). An intermediate value of 0.78 was documented for patients with IFG ($P < .01$).

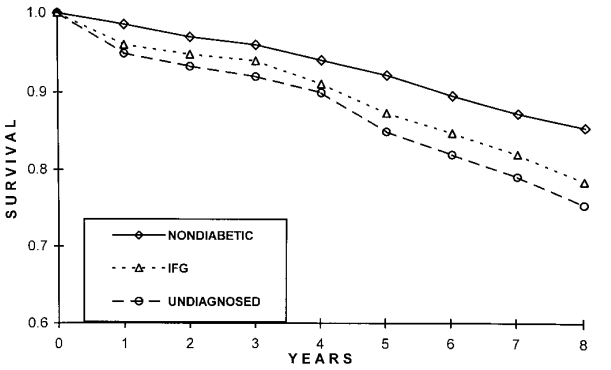
A multivariate analysis was performed, adjusting for age, sex, total cholesterol, triglycerides, previous myocardial infarction, cerebrovascular accident, functional class, peripheral vascular disease, anginal syndrome, chronic obstructive pulmonary disease, smoking status, and body mass index (Table III). After adjustment for these variables, with nondiabetic

Figure 1



Crude all-cause and IHD mortality in nondiabetic subjects, patients with IFG, and undiagnosed diabetic patients. Mortality in the undiagnosed group was significantly higher than in the nondiabetic group; intermediate values were seen in IFG ($P <$ .001).

Figure 2



Multivariate adjusted survival curves for all-cause mortality in nondiabetic subjects, patients with IFG, and undiagnosed diabetic patients. Note that at the end of the follow-up patients with IFG had a significantly higher mortality than nondiabetic individuals did ($P < .01$).

Table III. Hazard ratios for all-cause and IHD mortality in the hyperglycemic groups during an average 7.7-year follow-up period

Mortality types	IFG (n = 1258)	Undiagnosed diabetics (n = 822)
All-cause	1.39 (1.21-1.59)	1.62 (1.39-1.90)
IHD	1.29 (1.01-1.64)	1.79 (1.39-2.31)

Nondiabetic patients represent the reference group. Values in parentheses indicate 95% confidence interval.

patients as the reference group, IFG was identified as an independent predictor of increased all-cause and IHD mortality with hazard ratios of 1.39 (95% confidence interval 1.21-1.59) and 1.29 (95% confidence interval 1.01-1.64), respectively.

Discussion

The recent redefinition of diabetes[5] was not based on either the risk for cardiovascular disease or for all-cause mortality. Therefore there is no a priori reason for the diabetes glucose thresholds to be relevant to the risk for these outcomes, and there is no reason that the glucose-cardiovascular relationship should not extend below the diabetes thresholds.[15] The prognostic significance of IFG on macrovascular complications is still unclear.

The rate of cardiovascular disease has decreased in the general population, but it has remained stable or even increased in diabetics. Coronary patients with undiagnosed diabetes present a significantly increased long-term mortality.[16] Subjects with diabetes have increased morbidity and early mortality related to cardiovascular and microvascular complications.[17] The current report deals with long-term survival in a cohort of nondiabetic coronary patients with IFG. The main observation derived from the results of this study is the substantially increased mortality rate among these individuals.

Survival

It is well established that all major cardiovascular risk factors—hypertension, smoking, hyperlipidemia—act as independent contributors to heart disease in both diabetic and nondiabetic patients. Several additional factors simultaneously affect the development of coronary disease and diabetes, such as insulin resistance, coagulation abnormalities, obesity, physical inactivity, heredity, sex, and advancing age. These predisposing conditions constitute the metabolic syndrome and exacerbate the major risk factors.[18] The role of hyperglycemia in this context was recently highlighted. Although there is no evidence that mild hyperglycemia per se promotes atherogenesis or plaque rupture, a 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study determined that a high blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic subjects.[19] Most studies have provided support for a strong association between hyperglycemia and cardiovascular mortality.[5-7,20-24] Previous findings of our laboratory showed that, after adjustment for all other risk factors, both men and women with asymptomatic hyperglycemia had the same elevated mortality rate as those with confirmed diabetes.[25] In the current study coronary patients with IFG were characterized by a worse outcome, with a greater hazard ratio for both all-cause and IHD mortality.

Some early prospective studies of hyperglycemia and coronary disease showed no association between them, and other studies showed a positive association that was not persistent after adjustment for covariates.[26] On the contrary, later studies[19,27] are in keeping with our findings. The main cause of the discrepancies is that current diagnostic criteria were not in use when the early studies were conducted.[28] Thus, regardless of the underlying mechanisms that could explain the findings of this report, our results are in accordance with growing epidemiologic evidence that the risk for cardiovascular events does extend below the diabetic microvascular threshold.[29,30]

Study limitations

This was a prospective observational study where data were collected for different purposes, and we were aware of certain limitations. First, the majority of patients were men, so the degree to which the conclu-

sions apply to women is unclear. An earlier report from the same register showed a relative risk of death of 1.6 for all hyperglycemic patients, which rose to 2.4 when women were analyzed separately.[25] However, this finding probably does not affect the results because in the current study sex distribution was similar in all groups. Second, coding errors of ICD-9 are conceivable. Third, only a single glucose determination was performed at entry and no information was available regarding duration of hyperglycemia. In this context, it should be noted that some population studies indicate that cardiovascular mortality may not be dependent on duration of hyperglycemia because it is equally prevalent in both established and newly diagnosed diabetes.[31,32] Thus, despite these limitations, the results of our study may contribute to characterize the epidemiology of individuals with impaired levels of fasting glucose among a population with clinically established coronary disease.

Clinical implications

A body of evidence is accumulating that suggests that all levels of dysglycemia, even those below current WHO and ADA diagnostic levels, are associated with increased cardiovascular risk.[3,30,33-37] These levels may be as low as 5.5 mmol/L (100 mg/dL).[15]

Our study is in keeping with this concept. The principal finding of the current report is the substantially increased mortality rate among nondiabetic coronary patients with IFG, who had fasting glucose levels markedly lower than hitherto acknowledged as defining overt diabetes. Thus the current study indicates that this new ADA category is a marker for worse prognosis in nondiabetic coronary patients, further supporting the hypothesis that there is a close—albeit not necessarily linear—relationship between glucose and cardiovascular disease that begins at normal levels and rises into the diabetic range. Problem-oriented prospective clinical trials are necessary to determine whether modification of dysglycemia translates into improved clinical outcomes or whether elevated glucose levels are simply markers of an underlying metabolic syndrome.

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Appendix

Bezafibrate Infarction Prevention (BIP) Study Group

Participating Centers and Committee Membership
Scientific Committee:

Jacob Agmon, MD, Solomon Behar, MD, Avraham Shotan, MD, Uri Goldbourt, PhD, Eran Graff, PhD, Eliezer Kaplinsky, MD, Yehezkiel Kishon, MD, Henrietta Reicher-Reiss, MD, Joshua Waysbort, MD, and Daniel Brunner, MD.

Participating Centers, Responsible Investigators and Physicians:

Assaf Harofe Hospital, Zrifin: Zwi Schlesinger, MD, and Aharon Friedenson, MD; Barzilai Medical Center, Ashkelon: Leonardo Reisin, MD, and Jamal Jafari, MD; Beilinson Medical Center, Petach Tikva: Samuel Sclarovsky, MD, Yaakov Friedman, MD, and Bruno Ostfeld, MD; Bnei-Zion Hospital, Haifa: Edward Abinader, MD, and Shmuel Rochfleish, MD; Carmel Hospital, Haifa: Abraham Palant, MD, and Hanan Schneider, MD; Central Haemek Hospital, Afula: Tiberio Rosenfeld, MD, and Suleiman Khalid, MD; Edith Wolfson Medical Center, Holon: Yehezekiel Kishon, MD, Rene Rotzak, MD, and Anatoly Davidov, MD; Hasharon Hospital, Petach Tikva: Izhar Zahavi, MD, Janash Vitrai, MD, and Dror Diker, MD; Hillel-Yaffe Hospital, Hadera: Benyamin Pelled MD, Joseph Pardu, MD, and Jacob Galamidi, MD; Ichilov Hospital, Sourasky Medical Center, Tel-Aviv: Shlomo Laniado, MD, Libi Sherf, MD, Shimon Braun, MD, and Yemima Eschar MD; Kaplan Hospital, Rehovot: Avraham Caspi, MD, Alexander Arditi, MD, Shulamit Botwin, MD, Lydia Arkavi, MD, and Moshe Ziv, MD; Meir Hospital, Sapir Medical Center, Kfar-Saba: Daniel David, MD, Daniel Weisenberg, MD, Mira Kohanovski, MD; Naharia Hospital, Naharia: Nathan Rougin, MD, and Alicia Glusman-Vazan, MD; Rambam Medical Center, Haifa: Walter Markiewitz, MD, and Diav Motlak, MD; Rivka Ziv Hospital, Tzfat: Alon Marmour, MD, Michael Flich, MD, and Rachel Solomon, MD; Shaare Zedek Medical Center, Jerusalem: Dan Tzivoni, MD, and Jonathan Balkin, MD; Sheba Medical Center, Tel Hashomer: Babeth Rabinowitz, MD, Eddy Barasch, MD, and Zohar Brill, MD; Soroka Medical Center, Be'er Sheba: Alexander Battler, MD, Noa Liel, MD, and Bronislav Tsatskis, MD.

Review and Advisory Board:

Gerd Assmann, MD, Peter Bauer, PhD, Shlomo Eisenberg, MD (deceased), Lewis H. Kuller, MD, Baruch Modan, MD (chairman), and James Schoenberger, MD.

Principal Investigators:

Daniel Brunner, MD, Jacob Agmon, MD, and Elieser Kaplinsky, MD.

Steering Committee:

Members of the Scientific Committee and Directors of Participating Centers.

Scientific Committee:

Jacob Agmon, MD, Israel Bar Yehuda, Solomon Behar, MD, Daniel Brunner, MD (chairman), Avraham Caspi, MD, Uri Goldbourt, PhD, Eran Graff, PhD, Elieser Kaplinsky, MD, Yehezekiel Kishon, MD, P. Dieter Lang, MD, Henrietta Reicher-Reiss, MD, Avraham Shotan, MD, Joachim Vollmar, MSc, and Joshua Waysbort, MD.

Coordinating Center:

Jacob Agmon, MD, Yisrael Bar-Yehuda, Solomon Behar, MD, (medical director), Daniel Brunner, MD, Uri Goldbourt, PhD, Elieser Kaplinsky, MD, Henrietta Reicher-Reiss, MD, and Avraham Shotan, MD.

Central Laboratory:

Daniel Brunner, MD, Eran Graff, PhD (director), Sara Schwartz, MSc, Joshua Waysbort, MD, Shoshana Schwartz, BSc, Tova Haimi, BSc, Rachel Lingel, Frima Nir, and Ruth Sticlaru.

Critical Events and End Point Committee:

Chaim Almog, MD, Alexander Battler, MD, and Monty Zion, MD.

Stroke Monitoring:

David Tanne, MD.

Safety Evaluation:

Siegfrid Heimstra, MD, and Eugene Heyman, PhD.

Epidemiology, Statistics, Computing, and Scientific Programming:

Michal Benderly, MSc, Miriam Cohen, Mark Goldberg BA, Uri Goldbourt, PhD, and Lori Mandelzweig, MPH.