The Association Between Glucose Abnormalities and Heart Failure in the Population-Based Reykjavík Study

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OBJECTIVE — Diabetes is an independent risk factor for heart failure, whereas the relation between heart failure and abnormal glucose regulation (AGR) needs further evaluation. We studied this combination in the Reykjavík Study.

RESEARCH DESIGN AND METHODS — The Reykjavík Study, a population-based cohort study during 1967–1997, recruited 19,381 participants aged 33–84 years who were followed until 2002. Oral glucose tolerance tests and chest X-rays were obtained from all participants. Cases were defined in accordance with World Health Organization criteria for type 2 diabetes or AGR (impaired glucose tolerance or impaired fasting glucose) and European Society of Cardiology guidelines for heart failure.

RESULTS — The overall prevalence of type 2 diabetes and heart failure was 0.5% in men and 0.4% in women, while AGR and heart failure were found in 0.7% of men and 0.6% of women. Among participants with normal glucose regulation, heart failure was diagnosed in 3.2% compared with 6.0 and 11.8% among those with AGR and type 2 diabetes, respectively. The prevalence of type 2 diabetes in the age-group 45–65 years increased in both sexes during the period (*P* for trend = 0.007). The odds ratio was 2.8 (95% CI 2.2–3.6) for the association between type 2 diabetes and heart failure and 1.7 (1.4–2.1) between AGR and heart failure.

CONCLUSIONS — There is a strong association between any form of glucometabolic perturbation and heart failure. Future studies in this field should focus on all types of glucose abnormalities rather than previously diagnosed diabetes only.

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Type 2 diabetes, a disease of increasing prevalence, is a risk factor for heart failure (1,2). Poor glucometabolic control, as reflected by a high HbA_{1c}, increases the risk of developing heart failure (3). Diabetic patients are more prone to develop heart failure during an ischemic event, despite comparable size of myocardial injury, and their prognosis is more unfavorable than that in nondiabetic patients (4).

The prevalence of heart failure combined with diabetes was 10 and 15%, respectively, among elderly Italians. Moreover, a higher proportion of patients with than without heart failure developed diabetes over time (5). Although there are reports on the relationship of either diabetes or impaired glucose tolerance and heart failure (6,7), the association of the total spectrum of glucose abnormalities and heart failure, as well as the prevalence and risk factors for heart failure, has, to our knowledge, not been studied in a large epidemiological study.

The Reykjavík Study is a population-based study that included glucose tolerance tests for almost every participant. The present study reports on the prevalence of glucose abnormalities and heart failure and their combination in this population.

RESEARCH DESIGN AND METHODS

— All inhabitants in the Reykjavík metropolitan area at 1 December 1966 and born 1907–1935 were invited to participate in the study, as previously reported (8). Those who participated (n = 19,381) were divided into groups according to date and year of birth. They were subsequently attending the study at six time intervals (between 1967 and 1997). Patients aged 50–65 years were represented at all occasions, which allowed for a comparison of prevalence over time. The case subjects in this study were participants with a diagnosis of type 2 diabetes, abnormal glucose regulation (AGR), and/or heart failure at their first visit to the Reykjavík Study, and the prevalence groups were composed as such. The remaining participants served as control subjects, and data from their first visit were used for comparative analysis. Follow-up was until 2002. Attendance rate varied between 65 and 77%, declining somewhat over time. Altogether, 9,323 men and 10,058 women attended at least one visit.

Before the first visit, the participants answered a standardized questionnaire regarding a number of health-related factors (8,9). A medical examination was performed that included height, weight, BMI (kg/m^2), blood pressure, electrocardiogram (ECG), and a chest X-ray (cardiomegaly defined as heart size >550

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Abbreviations: AGR, abnormal glucose regulation; ECG, electrocardiogram; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Prevalence of type 2 diabetes, abnormal glucose regulation, and heart failure in the Reykjavík Study*

Age-groups (years) by sex	Total study population	Normal glucose regulation		Abnormal glucose regulation		Diabetes	
		Total	With heart failure	Total	With heart failure	Total	With heart failure
Male							
30–39	540	509 (94.3)	7 (1.3)	25 (4.6)	0 (0)	5 (0.9)	0 (0)
40–49	2,863	2,574 (89.9)	51 (2.0)	214 (7.5)	4 (1.9)	72 (2.5)	9 (12.5)
50–59	4,110	3,482 (84.7)	139 (4.0)	450 (11.0)	30 (6.7)	171 (4.2)	20 (11.7)
60–60	1,226	962 (78.5)	60 (6.2)	183 (14.9)	16 (8.7)	77 (6.3)	7 (9.1)
≥70	584	401 (68.7)	24 (6.0)	112 (19.2)	14 (12.5)	70 (12.0)	11 (15.7)
All	9,323	7,928 (85.0)	281 (3.5)	984 (10.6)	64 (6.5)	395 (4.2)	47 (11.9)
Female							
30–39	593	562 (94.8)	6 (1.1)	27 (4.6)	0 (0)	2 (0.3)	0 (0)
40–49	2,671	2,443 (91.5)	39 (1.6)	189 (7.1)	1 (0.1)	34 (1.3)	2 (5.9)
50–59	4,441	3,878 (87.3)	109 (2.8)	448 (10.1)	27 (6.0)	110 (2.5)	12 (10.9)
60–69	1,530	1,230 (80.4)	59 (4.8)	205 (13.4)	13 (6.3)	91 (6.0)	5 (5.5)
≥70	823	609 (74.0)	35 (5.7)	124 (15.1)	14 (11.3)	88 (10.7)	19 (21.6)
All	10,058	8,722 (86.7)	248 (2.8)	993 (9.9)	55 (5.5)	325 (3.2)	38 (11.7)

Data are *n* (%).

ml/m^2 for men and >500 ml/m^2 for women) (10). Each participant underwent an oral glucose tolerance test (OGTT; 50 g glucose in 250 ml water) at each visit until 1990. Blood glucose (in milligrams per deciliter) was determined before (fasting) and 1.5 h after the glucose load, first by means of a chemical method and then changing to a hexokinase enzymatic method. Following a protocol amendment in 1990, the investigation of the glucometabolic state was based on fasting serum glucose (11). Participants gave their informed consent, and the National Bioethics Committee approved the study, as did the Data Protection Authority.

Definitions of heart failure and glucose status

Heart failure was defined according to the European Society of Cardiology guidelines as the combination of at least two symptoms (dyspnea, tiredness, or ankle edema) and one objective evidence of cardiac engagement, as disclosed by the ECG (Q-wave myocardial infarction according to MONICA [Monitoring Cardiovascular Disease] criteria [9], left bundle branch block, or left ventricular hypertrophy) or the chest X-ray (pulmonary congestion, cardiomegaly, or left ventricular enlargement).

Glucometabolic abnormalities were categorized as type 2 diabetes (fasting serum glucose ≥7.0 mmol/l [≥126 mg/dl] or OGTT serum glucose ≥11.1 mmol/l [≥200 mg/dl]) or AGR (newly diagnosed impaired glucose tolerance or impaired fasting glucose; fasting serum glucose 6.1–6.9 mmol/l [110–126 mg/dl] or OGTT serum glucose 7.8–11.0 mmol/l [140–200 mg/dl]). These conditions were defined according to information from the questionnaire or as newly diagnosed type 2 diabetes or AGR based on OGTT or, from 1990, fasting serum glucose.

For risk description, participants were divided into four groups: group 1, participants with glucometabolic abnormalities and heart failure; group 2, participants with glucometabolic abnormalities only; group 3, participants with heart failure only; and group 4, participants free of glucometabolic abnormalities and heart failure.

Statistical analysis

Prevalence was defined as the number of participants with type 2 diabetes or AGR or heart failure at their first study visit divided by the total number of participants in the Reykjavík Study. Prevalence was stratified by age and sex. Time trends for prevalence of the cases and reference groups are presented in 10-year strata from the time of diagnosis. The effect of risk factors for the association of glucose status and heart failure were estimated using linear and logistic regression with age adjustment. The Mantel-Haenszel method and logistic regression with age adjustment was used to estimate odds ratios (ORs). Significance levels are given as absolute *P* values if not <0.001.

RESULTS — The overall prevalence of type 2 diabetes was 3.7% (n = 720) and heart failure 3.8% (n = 733) in the total population of 19,381 participants (Table 1). The prevalence of heart failure increased significantly with the presence of AGR ($P < 0.0001$) and type 2 diabetes ($P < 0.0001$) (Fig. 1). The prevalence of AGR, type 2 diabetes, and heart failure increased by age. Considering the age-group 50–65 years only, the prevalence of AGR remained stable during the study period ($P = 0.23$), whereas the prevalence of type 2 diabetes ($P = 0.007$) increased in the participants aged 50–65 years for both sexes. The prevalence of heart failure remained stable for men (from 5.4 to 4.8%, $P = 0.19$) but decreased among women (from 4.9 to 3.3%, P for trend = 0.004) at the end of the study period.

The age-adjusted strength of the association (OR) of heart failure and type 2 diabetes was 2.7 (95% CI 1.9–3.8) for men and 2.8 (1.9–4.1) for women, while the strength of the age-adjusted association between AGR and heart failure was 1.6 (1.2–2.1) among men and 1.7 (1.2–2.4) among women. The median age of men and women was 53 years. The period-adjusted ORs were 4.8 (2.5–9.0) for men aged <53 years and 2.5 (1.7–3.7) for men aged ≥53 years. This difference did not reach statistical significance (P = 0.08). The corresponding numbers for women were 3.1 (1.0–8.7) for those <53 years and 3.4 (2.3–5.1) for those ≥53 years ($P = 0.86$).

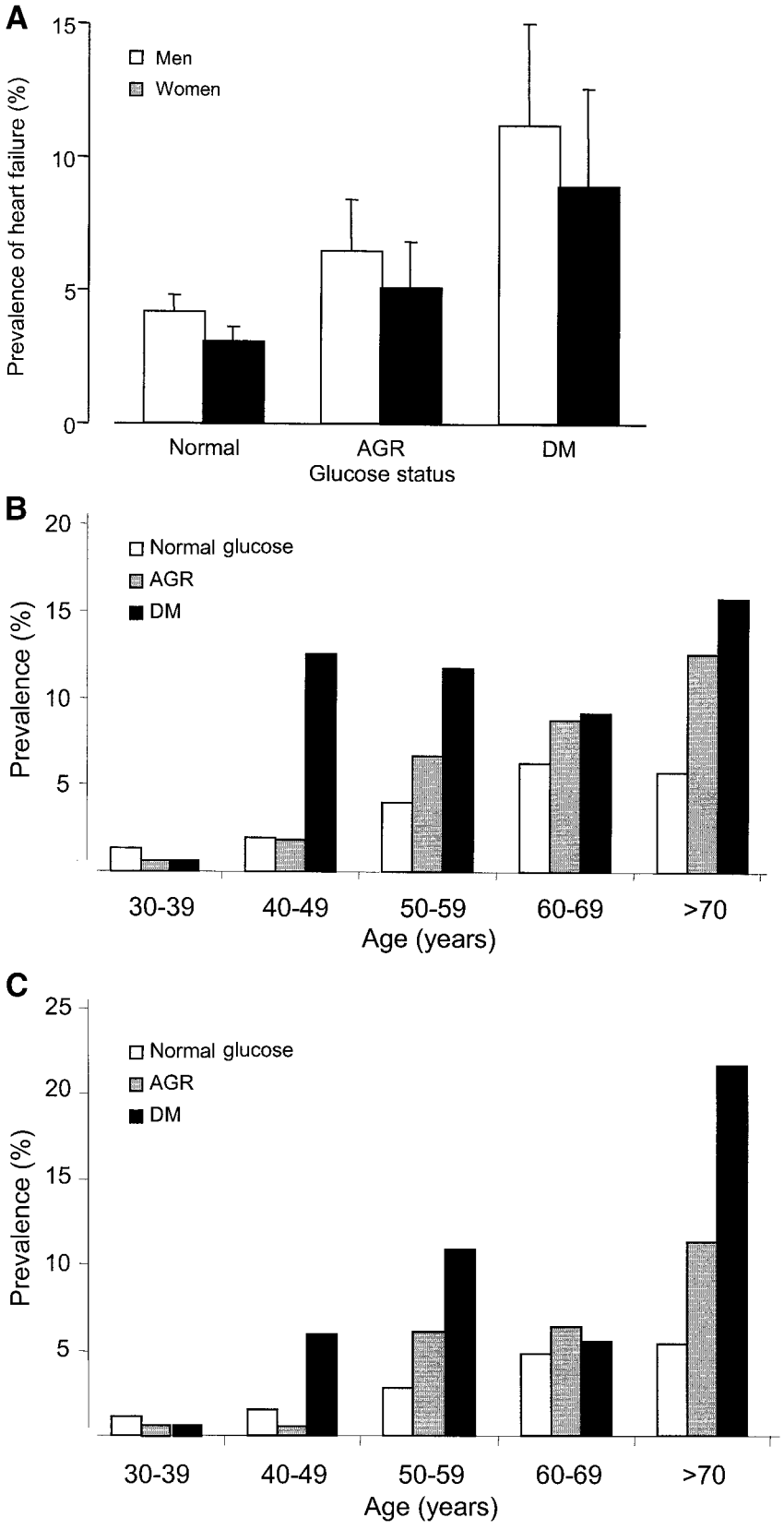

Figure 1—A: *Age-adjusted prevalence of heart failure according to glucose regulation in male (□) and female (■) participants in the Reykjavík Study.* B: *Prevalence of heart failure by age and glucose abnormalities in men.* C: *Prevalence of heart failure by age and glucose abnormalities in women.*

Age, weight, BMI, heart rate, and systolic and diastolic blood pressure were highest ($P < 0.001$) in participants having both glucose abnormalities and heart failure, declined in those with either glucose abnormality or heart failure, and lowest in the reference group. Current smoking was most prevalent in groups 3 and 4 ($P < 0.03$) and previous smoking in groups 1 and 2 ($P < 0.0001$). A family history of diabetes was most common among participants with type 2 diabetes ($P < 0.0001$). Cholesterol levels did not differ significantly among the four groups with or without glucose abnormalities. Triglycerides were highest in group 1 ($P < 0.0001$) and free fatty acids in AGR group 1 ($P < 0.0001$). Sedimentation rate and uric acid were highest in group 1 and gradually decreased to the lowest level in group 4 ($P < 0.0001$).

ECG abnormalities, besides those included in the heart failure definition, were most common in group 1 and declined to the lowest level in group 4 ($P < 0.0001$). Treatment with diuretic agents and/or digitalis, as well as with a nonsteroidal anti-inflammatory drug, was most frequent in the heart failure group ($P < 0.0001$).

CONCLUSIONS — The prevalence of glucose abnormalities and heart failure increased with age. Heart failure was found in 11.8% of participants with type 2 diabetes and 6.0% with AGR but only in 3.2% of control subjects. Age, weight, BMI, heart rate, triglycerides, and systolic and diastolic blood pressure were significant concomitant coronary risk factors in participants with type 2 diabetes and heart failure, either combined or as separate diseases. The strength of the association between heart failure and type 2 diabetes was 2.7 (95% CI: 1.9–3.8) for men and 2.8 (1.9–4.1) for women and somewhat lower between AGR and heart failure (1.6 [1.2–2.1] for men and 1.7 [1.2–2.4] for women).

The diagnostic criteria for heart failure vary due to acknowledged difficulties in defining this condition epidemiologically. The diagnosis is based on a combination of symptoms and signs of cardiac disease (12). The protocol for the Reykjavík Study did not include a heart failure algorithm, and echocardiography was not routinely used at the time the study was initiated. The combination of reported tiredness and breathlessness and the out-

come of ECG or chest X-ray provided an opportunity to diagnose heart failure in concordance with the present guidelines issued by the European Society of Cardiology (12). There is still a risk for false-positive and -negative diagnosis. However, in the Framingham Study, signs of cardiac dysfunction, such as heart enlargement on chest X-ray and left ventricular hypertrophy on ECG, were highly predictive for deteriorating cardiac function (13). Moreover, only 8–15% of asymptomatic people with hypertension, diabetes, coronary artery disease, or previous myocardial infarction had systolic dysfunction when screened with echocardiography (14).

During the time of this study, the definition of glucometabolic state was changed from the use of OGTT to the use of fasting glucose only. As demonstrated by the GAMI (Glucose Abnormalities in Patients with Myocardial Infarction) and DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) studies (15,16), the use of fasting blood glucose alone will not disclose people with impaired glucose tolerance and will miss some cases of diabetes. Thus, if anything, the present study underestimates the true prevalence of these conditions and their relations to heart failure. Another factor of potential impact on glucose categorization is that this study used 50 g glucose rather than the currently used 75 g glucose for OGTTs. This is, however, compensated by blood samples taken 1.5 rather than 2 h after glucose ingestion as currently practiced. Thus, the potential underestimation should be, at least to some extent, corrected for by the timing of the glucose determinations.

A unique strength of this study is the oral glucose tolerance testing, which offers an opportunity not only to study participants with established type 2 diabetes but also to identify people with newly detected type 2 diabetes or AGR. Moreover, the large population-based study population made it possible to adjust for several risk factors and for ischemic heart disease.

The prevalence of heart failure was 3–4% in participants with normal glucose metabolism, 6% in those with AGR, and 12% in those with type 2 diabetes. The prevalence of heart failure is similar to that in the Rotterdam Study (6). Amato et al. (5) studied an elderly Italian population and reported a higher prevalence of heart failure (9.5%), of whom 29.6% had diabetes. An explanation is the higher age (74.2 years) in their population. The prevalence of heart failure combined with type 2 diabetes increased gradually from zero in men and women <40 years of age to 14.3 and 22.7%, respectively, in those >70 years of age. Similar observations were made in the Framingham Study (17,18). The proportion of AGR in this study seems to be higher than overt type 2 diabetes in patients with heart failure. This novel finding underlines that the risk with hyperglycemia does not begin at levels used as a cutoff for type 2 diabetes. It supports the suggestion that glucometabolic abnormalities confer risk on a continuous scale for heart failure (19,20).

Hypertension, coronary artery disease, and impaired glucose tolerance are important risk factors for heart failure (13). Reports from the Medicare study showed that hypertension was more common in diabetic patients with heart failure than in the U.S. census population (21). Similar results were found in the present study, where raised blood pressure was significantly higher in participants with disturbed glucose regulation and, in particular, among those with both glucose abnormalities and heart failure. This is in accordance with previous reports from the Reykjavík Study underlining the strong relation between increased levels of blood glucose and hypertension (22). The importance of this association is further supported by Iribarren et al. (3), who showed an increase of HbA_{1c} by 1% to be related to increased risk for heart failure by 8%.

One may assume that metabolic factors related to the glucometabolic abnormalities negatively influence myocardial function or that there are common denominators for the development of disturbed glucose regulation and myocardial dysfunction. Type 2 diabetes and related conditions are characterized by increased insulin resistance and/or decreased insulin production. This restricts myocardial energy production via glucose oxidation. In contrast, β-oxidation of free fatty acids is enhanced. Myocardial cells are supplied with free fatty acids either from endogenous cardiac triglyceride stores or exogenous sources in the blood (23). This is a likely explanation for the increased levels of triglycerides and free fatty acids observed in participants with AGR. Interestingly these levels were high not only in participants with diabetes but also in those with AGR. The levels were lower in participants without both glucose abnormalities and heart failure and in those with heart failure only. Free fatty acid oxidation is more energy consuming than glucose oxidation and diminishes aerobic glycolysis, shifting myocardial metabolism in an anaerobic direction. It has been proposed that repeated intracellular accumulation of free fatty acids and its metabolites may cause myocardial dysfunction (23).

Another finding in the Reykjavík Study may lead to an alternate explanation of the link between glucometabolic pertubations and myocardial dysfunction. Participants with glucose abnormalities and/or heart failure had increased levels of sedimentation rate, indicating enhanced inflammatory activity. Young et al. (24) proposed that metabolic conditions play a significant role in cardiac adaptation and remodelling. This leads to an increase of myosin heavy chain β, altered troponin T molecules, diminished storage of creatinine phosphatases, and decreased sarcoplasmatic ATP-ase activity, which may result in myocyte hypertrophy associated with impaired contractile function and less effective energy supply (24,25). Hyperglycemia-induced activation of protein kinase C may alter the function of endothelial nitric oxide synthase into superoxide generator, thus producing free radicals, which are potent stimulators of programmed cell death, which is substantially enhanced in diabetic hearts (25). The activation may also act on pancreatic β-cells, thereby further compromising their function, adding to glucometabolic disturbance, and strengthening the relation between myocardial dysfunction and glucometabolic perturbations.

The prevalence of glucose abnormalities and heart failure increases with age. The prevalence of heart failure is doubled in participants with AGR and again doubled in type 2 diabetes. The association of glucose abnormalities and heart failure is strong. Glucose abnormalities other than type 2 diabetes are related to the occurrence of heart failure. It may be argued that such patients should be detected and intensively treated with glucose-lowering drugs, with the hope of improving their risk profile.

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