

Blood Glucose and Heart Failure in Nondiabetic Patients

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OBJECTIVE — Nondiabetic patients were studied to determine whether increasing blood glucose is associated with subsequent incidence of heart failure.

RESEARCH DESIGN AND METHODS — Baseline morning blood glucose determinations were evaluated with respect to subsequent heart failure using records from 20,810 nondiabetic patients. The onset of heart failure >1 year after initial glucose determinations was evaluated for patients who had 2–12 years of care. Patients were excluded if they had ever had the diagnosis of diabetes, had a diagnosis of heart failure <1 year after initial blood glucose determinations, had a blood glucose determination >125 mg/dl, or used corticosteroids, loop diuretics, insulin, or oral hypoglycemics.

RESULTS — Of the 20,810 patients studied, 916 patients developed heart failure over a total analysis time of 71,890 years at risk. Higher baseline morning glucose levels were associated with increased heart failure from 3.5% (glucose <90 mg/dl) to 3.8% (90–99 mg/dl) to 4.8% (100–109 mg/dl) to 6% (110–125 mg/dl) over a mean 4- to 5-year evaluation period. The incidence rate increased from 7.5 cases per 1,000 person-years (glucose <90 mg/dl) to 8.4 (90–99 mg/dl, NS) to 11.1 (100–109 mg/dl, $P < 0.001$) to 13.7 (110–125 mg/dl, $P < 0.0001$), an 83% increase in heart failure if baseline glucose was >109 mg/dl compared with <90 mg/dl. A Cox proportionate hazards model including age, sex, BMI, creatinine, hypertension, lipids, smoking, medications, and coronary disease showed a progressive increase in hazard ratio from 1.25 (glucose 90–99 mg/dl, $P < 0.05$) to 1.46 (100–109 mg/dl, $P < 0.001$) to 1.55 (110–125 mg/dl, $P < 0.001$) compared with glucose <90 mg/dl. Kaplan-Meier analysis showed increased glucose-associated risk with time.

CONCLUSIONS — Patients with higher baseline blood glucose levels in the absence of diabetes and after adjustment for covariants have a significantly increased risk of heart failure.

Diabetes Care 28:607–611, 2005

Although diabetes is associated with an increased incidence of heart failure (1,2), it is unclear whether increasing glucose in the absence of diabetes is a risk for heart failure. Subclinical states of increased blood glucose characterized as impaired glucose tolerance or impaired fasting glucose have been recognized to have pathologic consequences including macrovascular dis-

ease (3), increased mortality (4), and left ventricular hypertrophy (5). Because glucose intolerance may affect over 35 million adults in the U.S. (6) and the lifetime risk of heart failure may exceed 20% (7), associations between these common and potentially morbid conditions are of interest and clinical relevance.

Glucose intolerance and impaired fasting glucose are increasingly recog-

nized to not only be indications of risk for progression to diabetes, but also to have independent pathophysiologic significance that includes mortality (8), macrovascular complications including myocardial infarction or stroke (9,10), and cardiac effects including left ventricular hypertrophy (5) and concentric remodeling (11). Increased glucose may be relevant both with respect to independent glycemic effects and as a reflection of insulin resistance or hyperinsulinemia. Adverse effects may result from a diversity of mechanisms including increased reactive oxygen species, formation of advanced glycation products (12), changes in cardiac metabolism, and mitogenic effects of insulin (13). Although there is a basis to suggest that blood glucose may reflect a risk for heart failure even in the absence of diabetes, the association has not been extensively studied.

Heart failure is a common clinical problem with major morbidity and mortality. Although treatment has markedly improved, reversal of pathological changes and full restoration of function remains difficult. Consequently, identification of predisposing conditions and prevention of early cardiac injury would be very desirable. Because glucose intolerance is a common and potentially treatable condition, information concerning how increased glucose may contribute to other risk factors for heart failure is of particular clinical consequence.

The objective of the current study was to determine whether increased glucose in the absence of diabetes is a risk factor for heart failure. Because hyperglycemia is associated with processes that can contribute to heart failure (including coronary artery disease, hypertension, and obesity), the relevance of glucose was evaluated with multivariate regression models.

RESEARCH DESIGN AND METHODS

Subjects in this study received medical care from one or more of eight Veterans Affairs medical centers (Seattle, WA; Portland, OR; Boise, ID; Spokane, WA; Walla Walla, WA; Roseburg, OR; White City, OR; and Anchorage, AK).

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Received for publication 17 August 2004 and accepted in revised form 23 November 2004.

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

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Table 1—Subgroup characteristics with respect to baseline glucose determinations

	<90 mg/dl	90–99 mg/dl	100–109 mg/dl	110–125 mg/dl
n	3,275	7,488	6,447	3,600
Years of care	4.7 ± 1.9	4.6 ± 2.0	4.5 ± 1.93	4.5 ± 1.94
Glucose (mg/dl)	84 ± 5.2	95 ± 2.8	104 ± 2.8	115 ± 4.5
Age (years)	57 ± 14	58 ± 13	59 ± 12	61 ± 12
BMI (kg/m ²)	28.1 ± 4.7	28.9 ± 4.8	29.7 ± 5.1	29.9 ± 5.2
Creatinine	1.0 ± 0.26	1.0 ± 0.26	1.0 ± 0.30	1.0 ± 0.30
Systolic blood pressure (mmHg)	134 ± 13	137 ± 13	138 ± 13	139 ± 13
Diastolic blood pressure (mmHg)	76 ± 8	77 ± 8	77 ± 8	77 ± 8
LDL (mg/dl)	128 ± 35	129 ± 35	128 ± 34	126 ± 34
HDL (mg/dl)	48 ± 15	47 ± 13	47 ± 13	46 ± 14
Triglycerides (mg/dl)	157 ± 91	168 ± 97	177 ± 99	187 ± 97
Coronary disease (%)	28	28	33	37
Smoker (%)	28	26	26	26
New heart failure diagnosis (%)*	3.5	3.7	4.8	6.0
Time to diagnosis (years)†	3.9 ± 1.8	3.4 ± 1.8	3.4 ± 1.7	3.4 ± 1.7

Data are means ± SD. Subgroups based on baseline morning glucose determinations had a similar period of follow-up care after initial laboratory studies. More patients in subgroups with higher glucose had a new diagnosis of heart failure during the period of care (glucose 100–109 or 110–125 compared with <90 mg/dl, $P < 0.05$). *Percentage of each group that had a new diagnosis of heart failure during their period of care; †time from first laboratory studies until the first diagnosis.

Data were extracted from the Veterans Affairs electronic medical record systems of each facility and aggregated into a Structured Query Language database without names, addresses, or other personal identifiers. The study was pursued as part of a larger project to develop automated methods for identification of associations between medication use, laboratory results, and medical outcomes. The project was reviewed and approved by the University of Washington Investigational Review Board.

Computer-based records that included laboratory testing were evaluated to identify nondiabetic subjects who had blood glucose determinations at least 1 year before the onset of heart failure and who had medical follow-up for at least 2 years. The record database included ICD-9 diagnostic information, medication use, laboratory data, and vital signs from 1994 through December 2003. Although over 200,000 unique records were available, many were not applicable to the study because they included <2 years of care, the patient had a diagnosis of diabetes, glucose determination was >126 mg/dl, or laboratory data had not been obtained. Records were excluded if there was any indication of possible diabetes including ICD-9 diagnosis of diabetes or a complication of diabetes (41,388 subjects), use of oral hypoglycemic agents (29,827 subjects), use of insulin (21,826 subjects), or blood glucose >126 mg/dl (7.0 mmol; 87,674 subjects). Because

glucocorticoids (oral or parenteral) can affect glucose determinations and use of loop diuretics can affect glucose as well as indicate patients being treated for heart failure, patients who used these medications before a diagnosis of heart failure were also excluded. Because heart failure may induce insulin resistance and contribute to increases in glucose, baseline glucose determinations were required at least 1 year before a first diagnosis of heart failure. With the objective of including predominantly fasting glucose determinations, only morning glucose determinations before 10:00 A.M. were included. After screening, 20,810 records were available for nondiabetic subjects with information concerning at least 2 years of care, ICD-9 diagnostic coding, and baseline information including age, sex, BMI, blood pressure, smoking status, glucose, creatinine, lipid determinations, and medications.

The onset of heart failure was identified from a new ICD-9 diagnosis (ICD-9 codes 402.11, 402.91, 428.1, 428.9, and 428.0) in the clinic or an initial admission for heart failure. Specificity of ICD-9–based heart failure diagnosis has been reported to approach 95%, although sensitivity may be in the range of 63% (14).

Statistical analysis

Subjects were compared between groups with baseline blood glucose <90, 90–99, 100–109, and 110–125 mg/dl, with respect to risk for subsequent heart failure

using Cox proportional hazards regression models and Kaplan-Meier survival analysis. Statistical significance was defined by a two-tailed P value <0.05. Data were aggregated using Microsoft SQL Server 2000 and analyzed using Stata SE version 8.0.

RESULTS— Subject groups were defined by baseline glucose determinations, with comparisons between subjects with baseline glucose <90, 90–99, 100–109, and 110–125 mg/dl. As shown in Table 1, characteristics of the groups were similar, although the higher glucose groups had slightly greater age, BMI, and blood pressure. Over the average 4- to 5-year period of care after an initial glucose determination, higher glucose was associated with more new diagnoses of heart failure (Table 1). The incidence rate of heart failure (Fig. 1) progressively increased from 7.5 cases per 1,000 person-years (baseline glucose <90 mg/dl) to 8.42 cases per 1,000 person-years (glucose 90–99 mg/dl, NS) to 11.1 cases per 1,000 person-years (glucose 100–109 mg/dl, $P < 0.001$) to 13.7 cases per 1,000 person-years (glucose 110–125 mg/dl, $P < 0.0001$). Thus, over the period of study, patients without diabetes but with a baseline glucose of 110–126 mg/dl had an 83% increase in heart failure compared with patients who had baseline glucose <90 mg/dl (Fig. 1, $P < 0.0001$).

Multivariate regression analysis was performed to evaluate the risk of in-

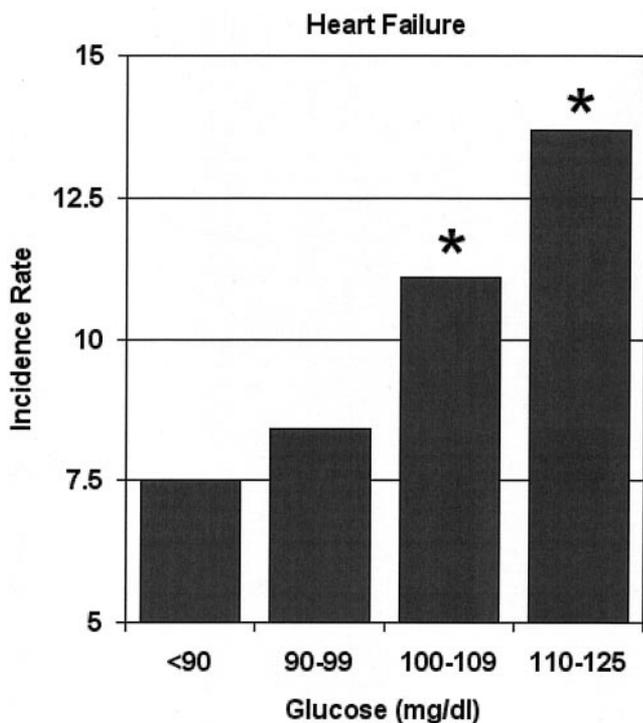


Figure 1—Incidence (cases per 1,000 person-years) of heart failure was significantly increased for patients with higher glucose levels of 100–109 mg/dl ($n = 6,447$, $P < 0.001$) or 110–125 mg/dl ($n = 3,600$, $P < 0.0001$) compared with those who had a baseline glucose level <90 mg/dl ($n = 3,275$). The subset with baseline glucose levels of 90–99 mg/dl had an incidence rate that was not significantly increased ($n = 7,488$, $P > 0.05$).

increased glucose in the context of additional factors that may be associated with heart failure. A Cox proportionate hazards regression model was constructed with inclusion of age, sex, BMI, creatinine, blood pressure, hypertension, coronary disease, smoking, LDL, HDL, triglycerides, and use of medications including thiazide diuretics, hydroxymethylglutaryl-CoA reductase inhibitors (statins), ACE inhibitor, angiotensin receptor blockers, and β -adrenoceptor antagonists. Cox regression (including 20,810 records comprising 71,890 years at risk and 926 instances of new heart failure diagnosis) demonstrated a glucose-associated increased hazard ratio for heart failure from 1.25 (glucose 90–99 mg/dl [95% CI 1.0–1.55], $P = 0.046$) to 1.46 (glucose 100–109 mg/dl [95% CI 1.17–1.81], $P = 0.001$) to 1.55 (glucose 110–125 mg/dl [95% CI 1.23–1.96], $P < 0.001$) compared with glucose <90 mg/dl as shown in Fig. 2. Components initially studied in the regression model that did not show significance, including creatinine, LDL, HDL, sex, and statin use. Age (hazard ratio 1.04, $P < 0.01$), BMI

(hazard ratio 1.036, $P < 0.01$), smoking (hazard ratio 3.73, $P < 0.01$), coronary artery disease (hazard ratio 1.56, $P < 0.01$), hypertension (hazard ratio 1.35, $P < 0.01$), use of ACE inhibitors (hazard ratio 3.08, $P < 0.01$), angiotensin receptor blockers (hazard ratio 1.52, $P < 0.01$), and hydrochlorothiazide (hazard ratio 4.01, $P < 0.01$) were associated with increased risk for heart failure. Use of β -blockers was associated with reduced risk of heart failure (hazard ratio 0.78, $P < 0.01$). Although medication use was identified retrospectively and any relationships to heart failure are complex, because increased glucose in the range of 90–126 mg/dl remained a significant hazard with or without inclusion of medications or other components of the model, it appeared that increased glucose was an independent risk for heart failure.

Kaplan-Meier survival analysis showed that patients with higher baseline glucose had a progressive increase in incidence of heart failure that may approach 14% after 8 years (Fig. 3).

CONCLUSIONS— The results of this study demonstrate that increasing glucose in the absence of diabetes is asso-

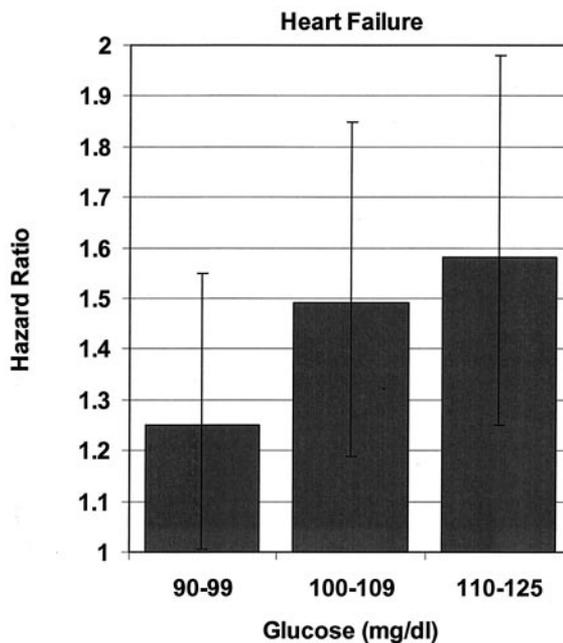


Figure 2—Cox proportionate hazards regression analysis with adjustment for age, sex, BMI, creatinine, blood pressure, diagnoses of hypertension and coronary artery disease, smoking, LDL, HDL, triglycerides, and use of thiazide diuretic, hydroxymethylglutaryl-CoA reductase inhibitor, ACE inhibitor, angiotensin receptor, or β -blockers ($n = 20,810$, 92,700 years at risk, 926 heart failure cases, $P < 0.0001$). Data represent hazard ratios compared with the subset with baseline glucose levels <90 mg/dl with 95% CI.

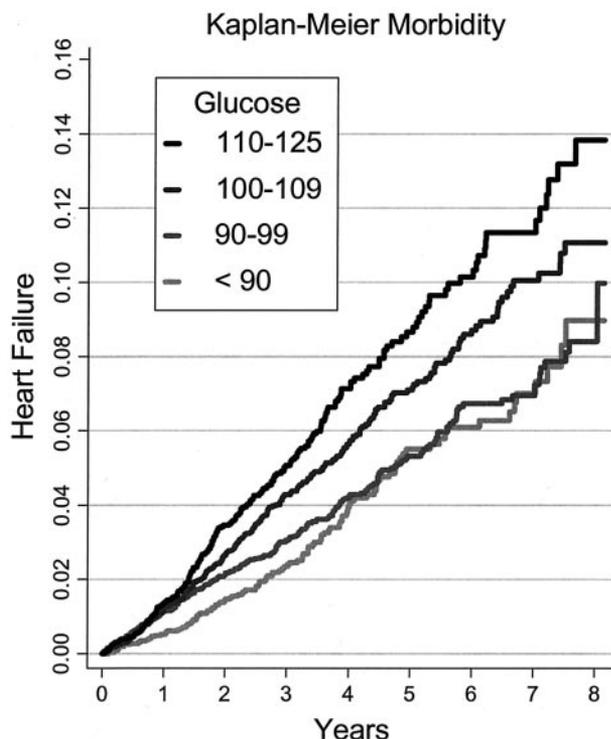


Figure 3—Kaplan-Meier survival analysis of patients with a baseline glucose level <90, 90–99, 100–109, or 110–125 mg/dl as shown.

ciated with greater incidence of heart failure independent of other recognized risk factors including age, weight, renal failure, hypertension, and coronary artery disease. Because glucose intolerance is an increasingly common problem (15), the association with risk for heart failure is of potentially major clinical consequence. The association of glucose intolerance with heart failure may be consistent with previously recognized adverse effects including macrovascular disease, increased mortality, and left ventricular hypertrophy (8). Both the relative increase in risk for heart failure (83% greater if glucose >109 mg/dl) and the progressive increase in incidence that appeared to approach 14% after 8–9 years suggest that increases in glucose warrant consideration with respect to risk for heart failure.

The observation that increased glucose indicates risk for heart failure is of potential clinical importance regardless of whether glucose is an independent risk or a covariant with other recognized heart failure risk factors including age, obesity, and coronary disease. Because our current data indicate that the association is significant even after adjustment for relevant covariants, glucose appears to be an independent risk factor for heart failure

with potential relevance to heart failure prevention and treatment. Although the relationship of hyperglycemia to heart failure is complicated by the converse observation that heart failure can also induce insulin resistance and diabetes (16), in the current study baseline glucose levels were determined at least 1 year before a diagnosis of heart failure and increases in glucose appeared to be the initial event. Furthermore, increased baseline glucose was associated with a progressive increase in incidence of heart failure over the subsequent years. These data suggest that the processes associated with increased blood glucose, including insulin resistance and hyperinsulinemia, may potentially contribute to the pathogenesis of heart failure.

Past studies and theoretical mechanisms are consistent with the proposition that increasing glucose has a continuous association with risk for heart failure, even at concentrations below the cutoffs for a diagnosis of diabetes. Increases in fasting glucose have been associated with risk for heart failure in diabetes (17). Adverse consequences from increased glucose are not limited to the range defined for diabetes, because glucose intolerance has been associated with risk for macrovascular disease and mortality (4,10,18).

Specifically with respect to cardiac disease, glucose intolerance and insulin resistance have been associated with left ventricular hypertrophy (5) and diastolic dysfunction (19). A diversity of potential mechanisms of adverse consequences with glucose intolerance have been reported, including direct effects of hyperglycemia, consequences from hyperinsulinemia, or associated metabolic changes such as increased free fatty acids. Hyperglycemia may induce nonenzymatic protein glycosylation, protein kinase C activation, oxidative stress, and increased tumor necrosis factor- α (20) with consequences that may include myocyte apoptosis and fibrosis. High free fatty acid levels have cardiotoxic effects including disruption of plasma membrane integrity, elevation of intracellular calcium, and increased sympathetic activity (2). Hyperinsulinemia has been associated with collagen deposition and myocardial fibrosis (21). Although poor glycemic control has been associated with an increased risk of heart failure (22), the lower threshold for adverse glucose effects has not been clearly established. To the extent that hyperinsulinemia precedes recognized hyperglycemia, it is plausible that the disease process starts with very modest changes in blood glucose.

The observation that increased glucose in the absence of diabetes is associated with risk for heart failure may have ramifications with respect to therapeutic intervention. However, although insulin infusion may improve exercise function in heart failure (23) and some animal data suggest that good glycemic control can improve cardiac function (24), there is little clinical evidence that improved glycemic control can improve cardiac function and prevent heart failure. Unfortunately, clinical evaluation is difficult. Because both hyperglycemia and hyperinsulinemia may have adverse cardiac effects, patients with insulin resistance and treatments that cause hyperinsulinemia may be distinct subsets with respect to outcome. Multiple comorbidities associated with glucose intolerance and diabetes (including coronary disease, hypertension, and renal failure) contribute in the pathogenesis of heart failure and complicate interventions to evaluate efficacy from improved glycemic control. Finally, because our current data suggest that even modest degrees of hyperglycemia and associated insulin resistance may

have pathological significance, a relatively stringent degree of glycemic control may be required if the threshold for adverse cardiac consequences is a relatively low glucose level. Nevertheless, the magnitude of the problem of glucose intolerance provides marked incentive for further investigation to determine whether lifestyle changes or therapeutic interventions that improve glycemic control may reduce the risk of heart failure.

In summary, an association of increasing glucose with subsequent risk for heart failure has been demonstrated with a population of predominantly male, nondiabetic veterans. The relationship appeared to be relatively continuous without a clear lower threshold. These results suggest that glucose intolerance is an additional indication for careful clinical evaluation with respect to risks for subsequent heart failure. Prospective studies will be required to determine whether intervention to improve glycemic control can provide value with respect to prevention of heart failure.

Acknowledgments—This work was supported by grants from the American Heart Association and the MSTI/MSMRI Research Institute and was performed using facilities of the Department of Veterans Affairs.

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