



Association between Serum Fructosamine and Mortality in Elderly Women

The Study of Osteoporotic Fractures

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Serum fructosamine levels can be used to estimate long-term serum glucose values and can be measured in frozen serum. The authors examined whether fructosamine levels were associated with mortality in a cohort of 9,704 white women (≥ 65 years of age) recruited from September 1986 to October 1988 at four clinical centers in the United States. A random sample of women who had died during a mean of 6 years of follow-up ($n = 55$) was compared with randomly selected controls ($n = 276$, 54 of whom had died). Fructosamine assays were performed blinded to vital status. Hazard ratios with 95% confidence intervals were adjusted for age, clinical center, smoking, hypertension, and serum albumin and cholesterol levels. Each standard deviation (46 μmol) increase in fructosamine level was associated with a 1.3-fold (95% confidence interval (CI) 1.0–1.6, $p = 0.04$) increased rate of all-cause mortality, including a 1.5-fold (95% CI 1.0–2.1, $p = 0.03$) increase in cardiovascular disease mortality. Elevated fructosamine levels ($>285 \mu\text{mol/liter}$) were associated with a 4.3-fold (95% CI 1.6–12, $p = 0.004$) increased rate of cardiovascular mortality; in women without a history of diabetes, the hazard ratio was 4.6 (95% CI 1.3–16, $p = 0.02$). Fructosamine level, or another indicator of glycemia, should be included when the risk of cardiovascular disease among older patients is evaluated. *Am J Epidemiol* 1999;149:471–5.

cardiovascular diseases; coronary disease; diabetes mellitus; fructosamine; mortality; risk factors

Fructosamine levels in serum indicate long-term serum glucose values by measuring the glycosylated protein concentration; thus, they can be used as a marker for either undiagnosed or poorly controlled diabetes mellitus (1–4). Fructosamine levels are measured by using a simple colorimetric assay in serum (1). They may be more reliable than the glycosylated hemoglobin level as an index of blood sugar control in diabetic patients, in part because fructosamine levels change within a few weeks in response to blood glucose levels (2). Fructosamine may be especially useful as an epidemiologic marker because it can be collected without a special dietary protocol, as would be necessary with fasting blood glucose or glucose tolerance tests. In addition,

fructosamine levels can be measured in banked frozen serum, whereas measurement of glycosylated hemoglobin levels requires anticoagulated blood.

Fructosamine levels are also influenced by nutritional status: as the serum protein level decreases, so does the measured fructosamine level. Indeed, a previous study in a population of nursing home residents found that lower fructosamine levels were associated with increased mortality (5).

We hypothesized that because of these countervailing effects, higher fructosamine levels would be associated with an increased risk of death from cardiovascular causes, whereas lower fructosamine levels might be associated with an increased risk of mortality from noncardiovascular causes, such as cancer. We tested these hypotheses in a case-cohort study that was nested within a larger prospective study. We used serum that had been obtained from participants during a baseline examination and compared fructosamine levels in subjects who died during follow-up with the levels in those who survived.

MATERIALS AND METHODS

Subjects

Ambulatory women aged 65 years or older who had not had bilateral hip replacements were recruited from

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Abbreviations: CI, confidence interval; HDL, high density lipoprotein; LDL, low density lipoprotein.

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September 1986 to October 1988 at four clinical centers: The Kaiser-Permanente Center for Health Research in Portland, Oregon; The University of Minnesota in Minneapolis, Minnesota; the University of Maryland in Baltimore, Maryland; and the University of Pittsburgh in Pittsburgh, Pennsylvania. Men and black women were excluded because of their relatively low incidence of osteoporotic fractures. Written informed consent was obtained from all participants after the appropriate institutional review boards had approved the study protocol.

Measurements

Participants completed a questionnaire that was reviewed by an interviewer during a 3-hour baseline examination. Unless otherwise noted, variables were dichotomized (yes/no). The questionnaire covered cigarette use (in pack-years), college education, current use of estrogen replacement therapy, and physician-diagnosed diabetes mellitus. During the baseline examination, we measured knee height (the distance from the floor to the knee), weight, and blood pressure; we also calculated a modified Quetelet index (6). Hypertension was defined as taking a diuretic medication or having a measured blood pressure of $>160/90$ mmHg.

Blood was collected between 9 a.m. and 2 p.m., after a woman had been seated for 10 minutes. Women had been instructed to eat a nonfat breakfast to prevent lipemia. Serum was stored for approximately 1 week at -20°C and then shipped on dry ice for subsequent storage at -190°C .

All assays were performed blinded to vital status. We measured fructosamine levels by using a standard colorimetric assay based on the ability of ketoamines to reduce nitroblue tetrazolium to formazan (Endocrine Sciences, Calabasas Hills, California); the upper limit of normal was $285\ \mu\text{mol/liter}$. Serum total cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride levels were measured by using an automated chemistry analyzer; low density lipoprotein (LDL) cholesterol levels were estimated. Albumin was measured by using serum protein electrophoresis.

Follow-up

Each participant or her designated proxy returned a postcard to the clinical center every 4 months. This procedure was supplemented by telephone calls to those whose postcards were late and by an annual questionnaire. We reviewed the death certificates and hospital discharge summaries of those women who died. A blinded investigator at the coordinating center classified the causes of death by using *International*

Classification of Diseases, Ninth Revision, Clinical Modification codes as follows: cardiovascular disease, codes 394–440; coronary heart disease, codes 410–414; stroke, codes 431–438; and cancer, codes 140–239. Using a case-cohort design, we randomly selected cases ($n = 55$) from the 1,125 women who died during the first 6 years of follow-up. Controls ($n = 276$) were selected randomly from the entire cohort; 54 died during follow-up, for a total of 109 deaths.

Analysis

Baseline attributes of the women who died and of those who lived were compared by using t tests or chi-square tests, as appropriate. We used a modification of the proportional hazards (Cox) model that accounts for a case-cohort sampling design (7) to adjust for potential confounders, such as age, clinical center, history of hypertension, pack-years of smoking, serum albumin, and HDL and LDL cholesterol levels. Mortality hazard ratios with 95 percent confidence intervals are reported here. We used models with quadratic terms and divided women into quintiles of fructosamine, LDL cholesterol, and HDL cholesterol levels to look for J- and U-shaped associations. Statistical significance was set at $p < 0.05$.

RESULTS

Of the 109 deaths, 41 were due to cardiovascular disease, including 14 from coronary heart disease and 13 from stroke. Cancer caused 44 of the remaining deaths. As expected, the women who died were older, more likely to be hypertensive, and had a greater smoking history than those who lived (table 1).

The distribution of fructosamine levels was approximately normal, with evidence of a secondary peak (figure 1). Fructosamine levels (mean (standard deviation)) were substantially higher in those women with a history of diabetes (336 (86) $\mu\text{mol/liter}$) than in those without such a history (251 (30) $\mu\text{mol/liter}$). Of the 299 women without a history of diabetes, 19 (6 percent) had fructosamine levels of more than $285\ \mu\text{mol/liter}$, the upper limit of normal in the laboratory.

Higher fructosamine levels were associated with increased mortality, in particular from cardiovascular diseases: each standard deviation increase in fructosamine was associated with about a 50 percent increase in cardiovascular mortality (table 2). This association was found in all women and when the analysis was restricted to women without a history of diabetes. Indeed, because the standard deviation of fructosamine was lower and the hazard ratio was slightly higher when women with diabetes were excluded, the association between fructosamine and

TABLE 1. Characteristics of women aged ≥ 65 years recruited in 1986–1988 to determine an association between fructosamine levels and mortality, the Study of Osteoporotic Fractures, United States

Characteristic	Random sample of the cohort (n = 276)		Those who survived during follow-up* (n = 222)		Those who died during follow-up† (n = 109)		p value‡
	Mean (SD)§	%	Mean (SD)	%	Mean (SD)	%	
Age (years)	72.3 (5.5)		71.5 (5.1)		75.0 (6.1)		<0.0001
History of diabetes		9		8		13	0.17
Hypertension		40		36		50	0.01
College education		14		15		11	0.35
Current cigarette smoking		10		10		11	0.77
Lifetime smoking (pack-years)	11 (19)		10 (17)		15 (22)		0.02
Current estrogen therapy		13		13		8	0.23
Weight (kg)	66.7 (12.9)		67.4 (12.8)		65.0 (13.9)		0.12
Modified Quetelet index (kg/m ²)	25.4 (4.7)		25.6 (4.7)		24.6 (5.0)		0.09
Serum cholesterol (mg/dl)	242 (42)		240 (41)		244 (50)		0.46
LDL§ cholesterol (mg/dl)	157 (39)		155 (39)		160 (39)		0.30
HDL§ cholesterol (mg/dl)	53 (16)		53 (16)		50 (15)		0.11
Creatine clearance (ml/min)	63 (18)		65 (18)		57 (21)		0.0004
Albumin (g/dl)	3.7 (0.4)		3.7 (0.4)		3.6 (0.3)		0.20
Fructosamine ($\mu\text{mol/liter}$)	257 (39)		254 (37)		271 (59)		0.001
Fructosamine $>285 \mu\text{mol/liter}$		11		9		19	0.005
Fructosamine $>285 \mu\text{mol/liter}$ or history of diabetes		14		12		23	0.009

* Mean, 6 years.

† Includes 55 women who died and were selected as cases and 54 women from the random sample who died during follow-up.

‡ Comparing those who died with those who survived.

§ HDL, high density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

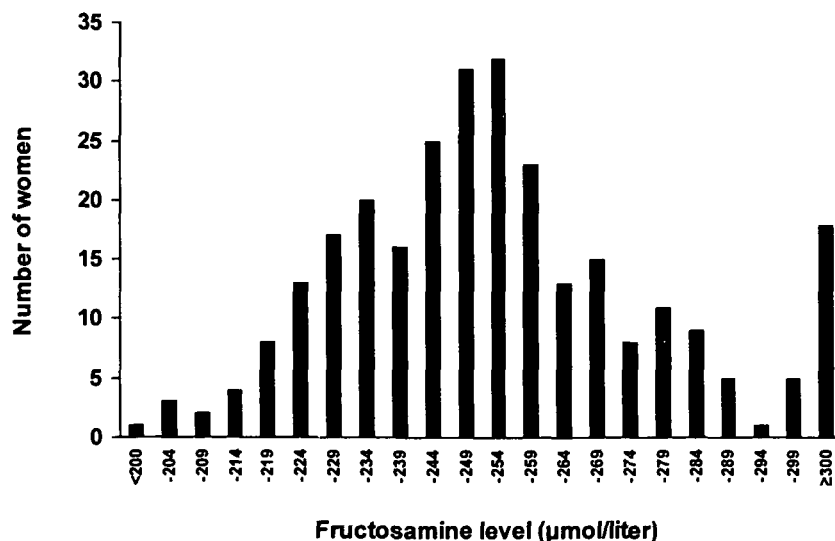


FIGURE 1. Distribution of fructosamine levels, measured in serum obtained during a 1986–1988 baseline examination, in 276 women randomly selected from a cohort of 9,704 women aged 65 years or older participating in the Study of Osteoporotic Fractures. From left to right, each solid bar represents a range of fructosamine levels—<200, 200–204, 205–209, etc.

cardiovascular mortality may be slightly stronger in the group without known diabetes. The observed hazard ratio of 1.7 per 30 $\mu\text{mol/liter}$ for women without diabetes corresponds to a hazard ratio of almost 2.3 per 46 $\mu\text{mol/liter}$.

The association between fructosamine and cardiovascular mortality was confined largely to women with elevated fructosamine levels ($>285 \mu\text{mol/liter}$). These women had a 4.3-fold (95 percent confidence interval (CI) 1.6–12, $p = 0.004$) higher rate of cardiovascular

TABLE 2. Multivariable hazard ratios for the association between fructosamine levels and mortality, by cause of death,* among women aged ≥ 65 years recruited in 1986–1988, the Study of Osteoporotic Fractures, United States

Cause of death	Hazard ratio (per SD†)	95% confidence interval	p value
<i>All women‡</i>			
All causes	1.3	1.0–1.6	0.04
Cardiovascular disease	1.5	1.0–2.1	0.03
Coronary heart disease	1.6	0.9–2.6	0.11
Stroke	1.7	1.0–2.9	0.04
Noncardiovascular causes	1.1	0.9–1.5	0.42
Cancer	1.2	0.9–1.6	0.34
<i>Women with known diabetes excluded§</i>			
All causes	1.3	0.9–1.7	0.13
Cardiovascular disease	1.7	1.1–2.6	0.01
Coronary heart disease	2.4	1.4–4.1	0.002
Stroke	1.3	0.7–2.7	0.41
Noncardiovascular causes	1.0	0.7–1.4	0.93
Cancer	1.1	0.7–1.6	0.78

* Analyses were adjusted for age, clinical center, pack-years of smoking, and serum albumin; analyses of cardiovascular disease mortality were also adjusted for hypertension and for high density lipoprotein and low density lipoprotein cholesterol levels.

† SD, standard deviation.

‡ SD for fructosamine, 46 $\mu\text{mol/liter}$.

§ SD for fructosamine, 30 $\mu\text{mol/liter}$.

mortality than those with levels of ≤ 285 $\mu\text{mol/liter}$ (table 3). When this analysis was restricted to women without a history of diabetes, the hazard ratio was similar (4.6, 95 percent CI 1.3–16, $p = 0.02$). Women with either an elevated fructosamine level (>285 $\mu\text{mol/liter}$) or a history of diabetes had a 3.6-fold (95 percent CI 1.4–9.3, $p = 0.009$) higher rate of cardiovascular mortality.

We also found a significant association between serum LDL cholesterol levels and cardiovascular mortality among all women and when those with a history of diabetes were excluded (table 3). This association was also found for mortality due to coronary heart disease; among all women, the adjusted hazard ratio was 2.5 per standard deviation (95 percent CI 1.5–4.4, $p = 0.001$).

Among those women without a history of diabetes, fructosamine levels were not associated with mortality due to noncardiovascular diseases (hazard ratio = 1.0 per standard deviation, 95 percent CI 0.7–1.4, $p = 0.93$) or cancer (hazard ratio = 1.1 per standard deviation, 95 percent CI 0.7–1.6, $p = 0.78$). We found no evidence of J- or U-shaped associations between fructosamine, LDL cholesterol, or HDL cholesterol levels and total, cardiovascular, or noncardiovascular mortality.

There was a strong and consistent inverse association between serum albumin levels and cardiovascular mortality (table 3). However, among women without a history of diabetes, we found no evidence that serum

TABLE 3. Multivariable models* of cardiovascular mortality among women aged ≥ 65 years recruited in 1986–1988 to determine an association between fructosamine levels and mortality, the Study of Osteoporotic Fractures, United States

Variable	Hazard ratio	95% confidence interval	p value
<i>All women</i>			
Fructosamine (per SD,† 46 $\mu\text{mol/liter}$)	1.5	1.0–2.1	0.03
Albumin (per SD, 0.4 g/dl)	0.6	0.4–0.8	0.002
LDL† cholesterol (per SD, 39 mg/dl)	1.6	1.1–2.3	0.02
Age (per 5 years)	1.8	1.3–2.5	0.0006
Fructosamine >285 $\mu\text{mol/liter}$	4.3	1.6–12	0.004
Albumin (per SD, 0.4 g/dl)	0.6	0.5–0.9	0.004
LDL cholesterol (per SD, 39 mg/dl)	1.5	1.0–2.2	0.04
Age (per 5 years)	1.8	1.3–2.5	0.0006
<i>Women with known diabetes excluded</i>			
Fructosamine (per SD, 30 $\mu\text{mol/liter}$)	1.7	1.1–2.6	0.01
Albumin (per SD, 0.4 g/dl)	0.6	0.4–0.9	0.004
LDL cholesterol (per SD, 37 mg/dl)	1.8	1.3–2.6	0.0007
HDL cholesterol (per SD, 15 mg/dl decline)	1.5	1.0–2.3	0.06
Age (per 5 years)	1.8	1.2–2.5	0.002
Fructosamine >285 $\mu\text{mol/liter}$	4.6	1.3–16	0.02
Albumin (per SD, 0.4 g/dl)	0.7	0.5–1.0	0.06
LDL cholesterol (per SD, 37 mg/dl)	1.7	1.3–2.6	0.0004
HDL cholesterol (per SD, 15 mg/dl decline)	1.4	1.0–2.0	0.07
Age (per 5 years)	1.9	1.4–2.7	0.0001

* Analyses were adjusted for clinical center, hypertension, and pack-years of smoking; models for all women were also adjusted for high density lipoprotein (HDL) cholesterol levels.

† LDL, low density lipoprotein; SD, standard deviation.

albumin levels were associated with mortality due to noncardiovascular causes (hazard ratio = 1.0 per standard deviation, 95 percent CI 0.8–1.3, $p = 0.93$) or cancer (hazard ratio = 1.2, 95 percent CI 0.9–1.5, $p = 0.33$). Results were similar for all women.

DISCUSSION

Our results confirm that undiagnosed diabetes is common in the elderly (8). We found that 6 percent of elderly women without a history of diabetes had fructosamine levels of more than 285 $\mu\text{mol/liter}$, the upper limit of normal in the laboratory. Elevated fructosamine levels were associated with a substantial increase in cardiovascular mortality, regardless of whether a woman knew whether she had diabetes. These findings complement the extensive literature showing that diagnosed diabetes is a risk factor for cardiovascular disease and that other measures of glucose control, such as hyperglycemia or glycosylated hemoglobin levels, correlate with the risk of cardiovascular disease among patients with known diabetes (9–15).

Lower levels of fructosamine were not associated with increased noncardiovascular mortality. One small prior study in a nursing home population found that fructosamine was inversely associated with mortality, suggesting that fructosamine may serve as a marker for ill health and malnutrition (5). We recently found, for example, that women with very low fructosamine levels have an increased risk of hip fracture (16). Serum albumin levels, a more traditional measure of protein malnutrition, were not associated with the risk of noncardiovascular mortality, even though we measured them directly by using serum protein electrophoresis. Lower serum albumin levels were associated with an increased risk of cardiovascular mortality, as two other studies (17, 18) found.

Whether or not serum lipid levels are a risk factor for cardiovascular disease in elderly women has been controversial (19–21). We found that serum LDL and probably HDL cholesterol levels were associated with cardiovascular mortality, in particular that due to coronary heart disease, in this study of women aged 65 years or older.

Our study has several important limitations. We enrolled ambulatory elderly white women. We did not measure fasting or random blood glucose levels in the cohort. Information on nonfatal disease outcomes other than fractures was not obtained, and a relatively small number of deaths were included in our analyses. Serum samples had been stored for several years before the assays were performed, and we cannot verify the long-term stability of fructosamine levels—a bell-shaped distribution with a secondary peak above the upper limit of normal of 285 $\mu\text{mol/liter}$ in the laboratory—and the observation that the levels were substantially higher among those patients with self-reported diabetes both suggest that the assay was valid. Finally, although cause of death was assigned blinded to a knowledge of fructosamine levels, it is difficult to determine a single cause of death in elderly women.

If the reasonable assumption is made that many, if not all, of the women with elevated fructosamine levels in our sample had diabetes, these results emphasize the importance of diabetes as a cardiovascular risk factor in older women (10, 22, 23). Fructosamine level, or some other marker of diabetes status, should be included when evaluating a woman's risk of cardiovascular disease.

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