Diabetes and Glucose Tolerance as Risk Factors for Cardiovascular Disease: The Framingham Study

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This report examines prospectively, in the Framingham cohort, the relation of diabetes and impaired glucose tolerance to each of the cardiovascular sequelae, taking into account age, sex, and associated cardiovascular risk factors. The incidence of cardiovascular disease, as well as the levels of cardiovascular risk factors, were found to be higher in diabetic than in nondiabetic men and women. The relative impact of diabetes on coronary heart disease, peripheral vascular disease, or stroke incidence was the same in men and women, but for cardiovascular mortality and cardiac failure the impact is greater for women. Present evidence suggests that alleviation of associated cardiovascular risk factors is the most promising course in reducing cardiovascular sequelae in diabetic patients. DIABETES CARE 2: 120–126, MARCH–APRIL 1979.

Despite the availability of effective hypoglycemic agents and more sensitive diagnostic methods allowing earlier treatment, physicians continue to encounter among their diabetic patients an excess incidence of coronary disease, strokes, renal failure, retinopathy, neuropathy, and cardiac failure.[1–5] There is a clear need to further explore the details of the relation of diabetes to cardiovascular disease.

The purpose of this report is to examine prospectively, in the Framingham cohort, the relation of diabetes and impaired glucose tolerance to each of the various cardiovascular sequelae, taking into account age, sex, and the associated cardiovascular risk factors. Twenty years of prospective data are available for this purpose. Also, the impact of the major risk factors on cardiovascular disease incidence will be examined comparing those with diabetes to those without diabetes.

Epidemiologic studies are hampered by vagaries of the definition of the diabetic state. Subjects at Framingham were considered to have "diabetes" when their casual blood sugar exceeded 150 mg/dl on at least two successive biennial examinations; when there was an abnormal glucose tolerance test (done by their own physician), or when they were receiving insulin or oral hypoglycemic agents.[6] Glucose "intolerance" was considered present when any of the foregoing, or a casual blood sugar exceeding 120 mg/dl, or glycosuria were present.[6] For purposes of analysis, participants were allowed to change their status with regard to glucose intolerance but not with regard to diabetes. That is, a person was classified as glucose intolerant at a particular exam only if he met the criteria at that exam. On the other hand, once a person was diagnosed as having diabetes, he was classified as having diabetes at the exam of diagnosis and at each successive exam.

PREVALENCE

The prevalence of diabetes increased with age in both sexes in the Framingham cohort. There was a higher prevalence in men in the younger age groups. This difference between the sexes decreased at older ages. The overall prevalence for men was 7.8% and for women 6.2% (Table 1).

Casual blood sugars also increased with age. In women, this was primarily a result of a progressive lengthening of the tail of the distribution. This suggests that their increasing prevalence of diabetes with age derives from persons who shift from the lower to the upper end of the distribution of blood sugar with progressing age. In men, the entire distribution seems to shift to higher levels in each progressive decade. This suggests a uniform deterioration of glucose tolerance with advancing age (Figure 1a and 1b).

TABLE 1
Prevalence of diabetes in specified age and sex groups

Age at exam (yr)	Prevalence in men (%)	Prevalence in women (%)
45–54	5.4	3.5
55–64	9.5	7.4
65–74	12.7	11.8
Total	7.8	6.2

Only persons free of CVD and RHD are included in the population. Prevalence is over the period of follow-up (see text).

RISK

For all age groups in both sexes the incidence of cardiovascular disease was higher among those with diabetes than among those without diabetes. Overall, the incidence of cardiovascular disease among diabetic men was roughly twice that among nondiabetic men. Among diabetic women the incidence of cardiovascular disease was almost three times that among nondiabetic women (Table 2).

AGE AND CARDIOVASCULAR RISK

The impact of diabetes on risk of cardiovascular disease appears to diminish with advancing age, particularly in women (Table 2). Although suggestive, this trend can not be demonstrated to be statistically significant. It suggests that late onset diabetes may have a different effect on the cardiovascular apparatus than early onset.

CARDIOVASCULAR IMPACT IN THE SEXES

The relative impact of diabetes was substantially greater for women than for men. For each of the cardiovascular diseases morbidity and mortality was higher for diabetic women than nondiabetic men (Table 3). Among those with diabetes, the female advantage over men as regards cardiovascular mortality is lost. After adjustment for differences in other associated cardiovascular risk factors in the two sexes, the relative impact of diabetes on coronary heart disease, peripheral vascular disease, or stroke incidence was the same in men and women, but for cardiovascular mortality and cardiac failure the impact is still greater in women (Table 4). The reason for the greater susceptibility of women to these cardiovascular sequelae of diabetes is not clear.[7,8]

CARDIOVASCULAR RISK FACTORS IN DIABETES

Diabetic individuals, in general, have higher levels of cardiovascular risk factors than nondiabetic individuals.[3,9–16] Diabetic men in the Framingham cohort had higher blood pressures and were more obese. However, they smoked less and had lower serum total cholesterol.

Diabetic women in Framingham were more hypertensive and obese but, in addition, had higher serum total cholesterol values and smoked roughly the same as their non-

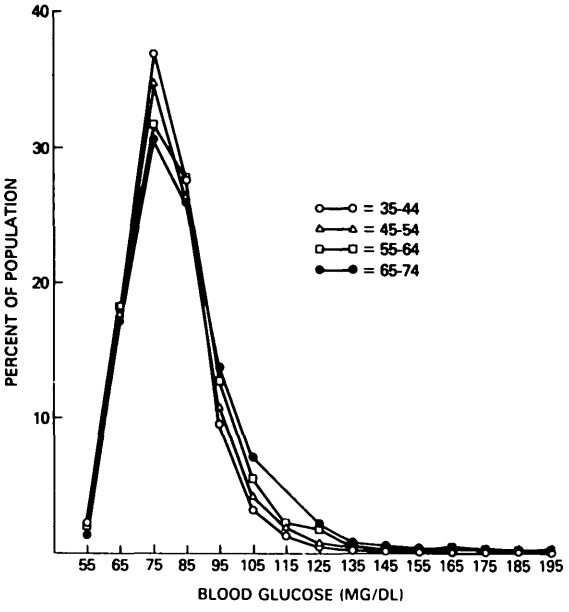

FIG. 1a. Distribution of blood glucose for women by age at examination —The Framingham Study examinations 1–9.

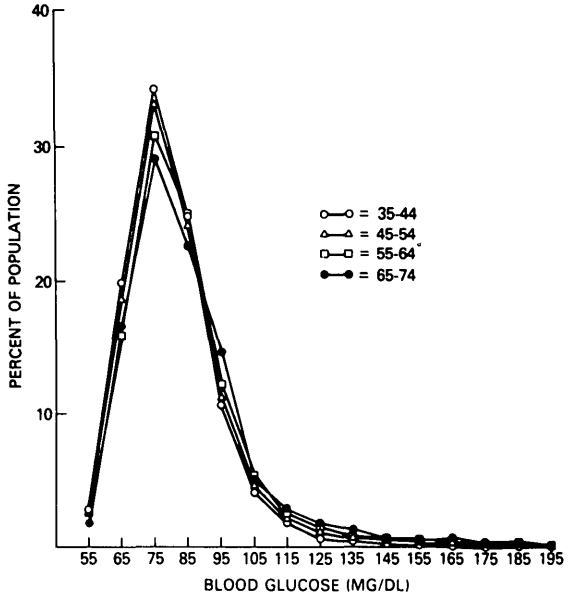

FIG. 1b. Distribution of blood glucose for men by age at examination —The Framingham Study examinations 1–9.

TABLE 2
Risk ratios for diabetes according to age (Framingham Study, 20-yr follow-up): average annual incidence of cardiovascular disease per 1000

Age (yr)	Men		Women	
	Diab/ nondiab	Risk ratio	Diab/ nondiab	Risk ratio
45–54	32/12	2.7	25/4	6.3
55–64	48/25	1.9	38/13	2.9
65–74	58/28	2.1	40/22	1.8
All ages (adjusted)	39/19	2.1	27/10	2.7

diabetic counterparts. High-density lipoprotein (HDL) cholesterol values were consistently lower in those with diabetes than in those without diabetes in both sexes (Table 5). Diabetic individuals of both sexes have a higher prevalence of ECG-LVH. Low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) values are both higher in diabetic than nondiabetic women. It is interesting to note that these lipoprotein elevations were present ten years before the onset of clinical evidence of diabetes.

The association of diabetes with a higher level of atherogenic traits suggests an explanation for the excess risk of cardiovascular sequelae in the diabetic population.

NET AND JOINT EFFECT

Although the higher level of risk factors in the diabetic group might suggest it, the excess risk of cardiovascular sequelae in diabetes in general, and for diabetic women in particular (compared with men), is not entirely a function of a higher level of cardiovascular risk factors.

Multivariate analysis carried out to determine the impact of diabetes on cardiovascular disease, taking other risk factors into account,[6,17] indicates that the impact of diabetes

TABLE 3
Average annual age adjusted incidence/1000 of specified cardiovascular events, according to sex and diabetic status (Framingham cohort; men and women ages 45–74 yr)

	Men		Women	
	Diabetic	Non-diabetic	Diabetic	Non-diabetic
Cardiovascular disease	39.1	19.1	27.2	10.2
Cardiovascular disease death	17.4	8.5	17.0	3.6
Congestive heart failure	7.6	3.5	11.4	2.2
Intermittent claudication	12.6	3.3	8.4	1.3
Atherothrombotic brain infarction	4.7	1.9	6.2	1.7
Coronary heart disease	24.8	14.9	17.8	6.9

can not be entirely attributed to the associated risk factors (Table 4). Although the risk of cardiovascular sequelae can not be accounted for solely by the associated risk factors, the impact of diabetes varies over a wide range depending on their level (Figure 2). Diabetic individuals with optimal levels of other risk factors appear to have no excess risk as compared to the average risk. This may explain why diabetic persons have fewer cardiovascular sequelae in some less affluent societies.[18–21]

High-risk diabetic individuals, in great jeopardy of cardiovascular sequelae, can be identified for prophylaxis from their cardiovascular risk profile (Figure 2). This provides a more logical basis for determining the urgency for corrective measures and the nature of the disease.

As judged by the size of the coefficients for the regression of cardiovascular incidence on the various risk factors (suitably standardized to place them on equal footing as regards units of measurement) diabetes is less important than some other risk factors. For men, it has the smallest impact of the major risk factors (Table 6). For women, the impact exceeds that of cigarettes (Table 7).

TABLE 4
Relative risks of cardiovascular (CV) events for diabetes vs. nondiabetes (Framingham Study; men and women ages 45–74 yr)

Relative risks	Factor of increased risk											
	Any CV disease		Mortality from CV dis.		Cardiac failure		Brain infarct		Coronary disease		Intermittent claudication	
	M	F	M	F	M	F	M	F	M	F	M	F
Unadjusted	2.5	3.7	2.6	7.2	2.8	7.7	3.3	5.6	1.9	3.6	4.7	8.9
Age adjusted	2.2	2.8	2.1	4.9	2.2	5.4	2.7	3.8	1.7	2.7	4.0	6.4
Risk factor adjusted*	2.1	2.0	1.7	3.3	1.8	3.8	2.2	2.2	1.7	2.1	4.2	5.0

Adjusted relative risk is calculated as exp, (B), where B is the estimated logistic coefficient of diabetes in a logistic function containing the additional factors listed.

* Adjusted for age, systolic BP, cigarettes/day, CHOL, ECG-LVH.

IMPACT ON VARIOUS CARDIOVASCULAR SEQUELAE

Clinical studies have long emphasized the complication of occlusive peripheral arterial disease. Prospective population studies in Framingham and elsewhere have confirmed this impression, showing that the impact of diabetes is greater for occlusive peripheral arterial disease (Table 4). The reason for this is obscure considering that the arterial lesions produced in the head, heart, and limbs of the diabetic individual are very similar.

The relative impact of diabetes is least for coronary heart disease, but coronary heart disease is nevertheless the most common sequela of diabetes, much as it is in the nondiabetic population (Tables 3 and 7).

There is also a surprisingly strong relationship to the development of cardiac failure. And for women, the impact on stroke incidence is noteworthy (Tables 3 and 4). Cardiac failure is a noteworthy sequela of diabetes, particularly in women (Table 4). It cannot be attributed to interim overt coronary heart disease nor can it be attributed to a higher level of atherogenic traits.[5] It seems to occur in marked excess particularly in insulin-treated diabetes.[5]

IMPACT OF RISK FACTORS IN DIABETES

Since the impact of diabetes on the incidence of cardiovascular disease can not be attributed entirely to a higher level of cardiovascular risk factors, it is possible that such precursors of cardiovascular disease have a greater effect in those with diabetes than in nondiabetic individuals. However, it would appear that the impact of diabetes on the cardiovascular system does not derive from an altered ability to contend with known risk factors.

Judging from a comparison of standardized coefficients for the regression of incidence of cardiovascular disease on specified risk factors, there is little indication that the relationship of the level of risk factors to the development of cardiovascular disease is different for individuals with and without diabetes.[8]

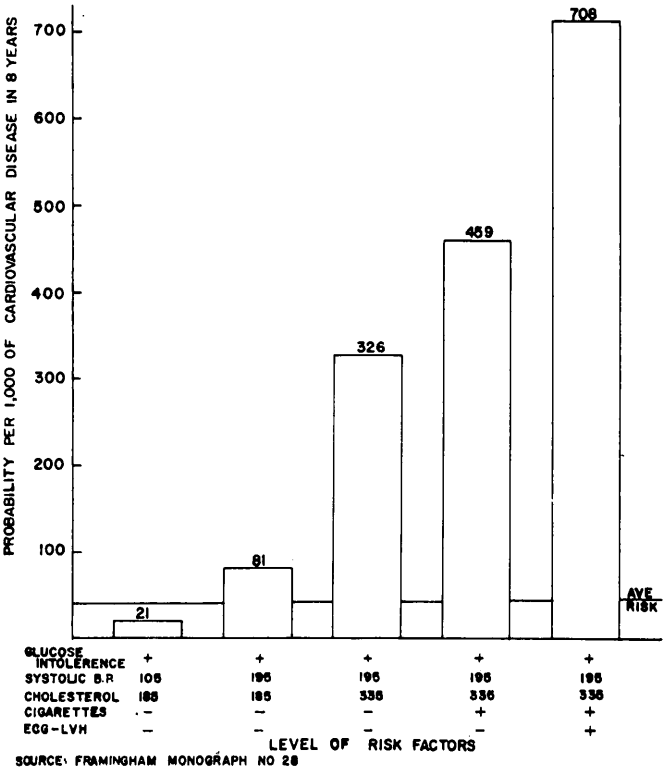

FIG. 2. Risk of cardiovascular disease with glucose intolerance according to level of other risk factors—Framingham Study, 18-year follow-up, men 40 years old.

TABLE 5
Mean level of certain characteristics in subjects with and without diabetes (Framingham Study, Exam 11)

Characteristic	Diabetes	No diabetes	
Men			
HDL cholesterol (mg/dl)	43.9 (1.28)	46.0 (0.46)	NS
LDL cholesterol (mg/dl)	135.2 (3.72)	142.4 (1.28)	NS
Triglycerides (mg/dl)	137.9 (8.00)	135.0 (3.48)	NS
Systolic blood pressure (mm Hg)	148.4 (2.26)	139.1 (0.71)	***
Relative weight (%)	125.7 (1.59)	121.5 (0.56)	*
Number	107	847	
Women			
HDL cholesterol (mg/dl)	53.5 (1.44)	57.8 (0.44)	**
LDL cholesterol (mg/dl)	157.4 (3.29)	154.5 (1.11)	NS
Triglycerides (mg/dl)	141.3 (6.73)	113.1 (1.67)	***
Systolic blood pressure (mm Hg)	150.1 (2.08)	138.8 (0.62)	***
Relative weight (%)	129.0 (1.97)	120.6 (0.56)	***
Number	143	1215	

Parenthetical entries refer to standard error of the mean. Tests for difference between means for diabetes and no diabetes indicated in margin as: *P < 0.05; **P < 0.01; ***P < 0.001; NS, P > 0.05.

PATHOGENETIC IMPLICATIONS

It is entirely possible that the cardiovascular sequelae of diabetes may differ depending on whether the diabetes is hyperinsulinemic or not, early or late in onset, caused by some known etiology, treated or not, or depending on the kind of treatment required. These possibilities have not been adequately investigated in epidemiologic studies.

The greater vulnerability of women to cardiovascular sequelae of diabetes begs explanation. Although differences in risk factors do not entirely account for the greater susceptibility of women, a low HDL cholesterol in

TABLE 6
Standardized logistic regression coefficients for CHD incidence (Framingham Study)

Characteristics†	Standardized logistic regression coefficients§			
	Univariate		Multivariate	
	Men	Women	Men	Women
HDL cholesterol	−0.488***	−0.741***	−0.610***	−0.650***
LDL cholesterol	0.288*	0.303*	0.332**	0.260*
Triglyceride	0.048	0.276**	−0.092	−0.106
Systolic blood pressure	0.323**	0.400**	0.327**	0.216
ECG-LVH	0.279***	0.207**	0.245**	0.159*
Relative weight	0.029	0.283*	−0.016	0.031
Diabetes	−0.024	0.474***	−0.114	0.390***

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
† Measured at Exam 11.
§ Estimated by method of Walker-Duncan.

the presence of diabetes appears to raise the CHD risk of women relative to that of men. In women, the triad of obesity, diabetes and low HDL cholesterol carries an especially high risk of CHD.[22]

PATHOGENESIS

The pathogenesis of cardiovascular disease in diabetes is poorly understood and appears to be uninfluenced by hypoglycemic agents.[8,16] The large vessel lesion does not appear to differ substantially from atherosclerosis found in the nondiabetic population. It is evidently more a late manifestation of long standing diabetes than a product of its severity. On the other hand, the microvascular disease leading to nephropathy, retinopathy, and neuropathy are unique to diabetes, more closely linked to the hyperglycemia and less commonly in adult than early onset diabetes.[23,24]

In addition to some unique effect on small blood vessels, diabetes seems to damage the heart muscle.[24–26] Interstitial accumulations of PAS-staining material possibly

TABLE 7
Age-adjusted average annual rate of specified events/1000 at risk among women according to specified characteristics

	Diabetes	Smokers >20 cigarettes daily
Cardiovascular disease (CVD)	27.2	12.1
CVD death	17.0	6.4
Congestive heart failure	11.4	4.4
Intermittent claudication	8.4	2.9
Atherothrombotic brain infarction	6.2	2.0
Coronary heart disease	17.8	7.1

responsible for a diminished diastolic compliance, interstitial fibrosis, and conduction disturbances have been noted. Arteriolar sclerosis and proliferative lesions are also more common both in arterioles and venules.[27] Since the effect of diabetes on the incidence of cardiac failure cannot be accounted for by accompanying atherogenic traits, or interim CHD, and because it is seen predominantly in insulin-treated diabetes, it seems reasonable to hypothesize the existence of a diabetic cardiomyopathy.[5]

PREVENTIVE IMPLICATIONS

Present evidence suggests that there is more to be gained by a multifactorial risk factor intervention in diabetes than by attention confined to early detection and control of hyperglycemia alone. Reliance solely on correction of hyperglycemia to reduce the cardiovascular sequelae would appear imprudent.[28,29] Alleviation of associated cardiovascular risk factors would appear to offer more hope. Correction of hypertension and lipid abnormalities, reduction of overweight, and avoidance of cigarettes should substantially reduce the cardiovascular risk of diabetic persons. Because the impact of risk factors is the same in those with and those without diabetes, we could expect for example, that on giving up cigarettes diabetic individuals might have only half the risk of those who continue to smoke (Table 8).[30]

Interventions against diabetes itself can be expected to be

TABLE 8
Regression of cardiovascular disease on specified risk factors: diabetes vs. no diabetes

	Average standardized univariate logistic coefficients							
	Systolic pressure		Serum cholesterol		Cigarettes daily		Relative weight	
	Men	Women	Men	Women	Men	Women	Men	Women
Diabetes	0.216	0.410	0.312	0.213	0.186	0.016	−0.078	0.135
No diabetes	0.414	0.464	0.240	0.244	0.206	0.049	0.159	0.198

Men and women ages 45–74 yr. Framingham Study, 20 yr follow-up.

TABLE 9
Relative and attributable risk in 2 yr of cardiovascular disease for specified risk factors (men and women ages 45–74 yr; Framingham Study, 20-yr follow-up)

Risk factor	Men		Women	
	Relative risk	Attributable risk (%)	Relative risk	Attributable risk (%)
Cigarettes	1.5	20.6	1.1	2.8
ECG-LVH	2.7	6.2	3.5	6.8
Diabetes	2.0	3.9	2.7	5.0
Hypertension	2.2	37.7	3.2	54.6

Cigarettes = smokers vs. nonsmokers; ECG-LVH = possible or definite; Hypertension = possible (BHBP) or definite.
Relative risk: R1/R2, where R1 = average annual age-adjusted incidence for those with risk factor, and R2 = for those without risk factor.
Attributable risk: (R − R2)/R, where R = average annual rate for total population, and R2 = those without risk factor.

fruitful only when the pathogenetic mechanisms involved are more precisely delineated. Only then can specific corrective measures be properly conceived. It is difficult to judge whether screening solely for asymptomatic hyperglycemia is justified. It is not known whether treatment of mild or moderate hyperglycemia alone will prevent heart, brain, kidney, or eye damage. There is a continuing debate about whether close control of hyperglycemia is helpful in avoiding the macroangiopathy of diabetes.[8,16,28,29,31]

Although there is room for argument as to whether or not oral hypoglycemic agents actually hasten the demise of the diabetic patient, there is less uncertainty about the lack of efficacy of these agents in reducing the incidence of cardiovascular sequelae.[16]

Examination of the attributable risks for the various cardiovascular risk factors, which takes into account not only its strength as a risk factor, but its prevalence as well, indicates a minor impact of diabetes in men (Table 9). In women the community effect is greater than for the cigarette habit. In short, very little of the high incidence of cardiovascular disease in men can be attributed to diabetes and hence a major campaign based on this alone seems unwarranted even if there were proven efficacy in controlling the diabetes found.

It would thus seem more appropriate to consider diabetes as one ingredient of a cardiovascular risk profile to select highly vulnerable subgroups of the general population for preventive maintenance. Improvement in the lot of individuals with adult-onset diabetes would appear to require reduction of the cardiovascular sequelae. This requires a more careful selection of the potential candidate and control not only of the blood sugar but of the blood pressure, of the cigarette habit, blood lipids (LDL and HDL), and overweight. This broader concept of control would seem to provide a more optimistic outlook.

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