Impaired Glucose Tolerance Is a Risk Factor for Cardiovascular Disease, but Not Impaired Fasting Glucose

The Funagata Diabetes Study

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OBJECTIVE — To determine whether the new category of impaired fasting glucose (IFG) recently proposed by the Expert Committee of the American Diabetes Association is a risk factor for cardiovascular disease.

RESEARCH DESIGN AND METHODS — Death certificates and residence transfer documents from the cohort population consisting of participants of the diabetes prevalence study in Funagata, Yamagata prefecture, Japan, 1990–1992, were analyzed up through the end of 1996. First, the cohort population was classified into three groups: normal glucose tolerance (NGT) (n = 2,016), impaired glucose tolerance (IGT) (n = 382), and diabetic (n = 253). Then the same population was reclassified into normal fasting glucose (NFG), IFG, and diabetic. The cumulative survival rates among the groups were compared using the classical life-table method, and age-adjusted analyses, the person-year method, and Cox's proportional hazard model were adopted.

RESULTS — At the end of seven observed years, the cumulative survival rates from cardiovascular disease of IGT and diabetes were 0.962 and 0.954, respectively, both significantly lower than that of NGT (0.988). The Cox's proportional hazard model analysis showed that the hazard ratio of IGT to NGT on death from cardiovascular disease was 2.219 (95% CI 1.076–4.577). However, the cumulative survival rate of IFG from cardiovascular disease was 0.977, not significantly lower than that of NFG (0.985). The Cox's hazard ratio of IFG to NFG on death from cardiovascular disease was 1.136 (0.345–3.734), which was not significant either.

CONCLUSIONS — IGT was a risk factor for cardiovascular disease, but IFG was not.

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Together with changes in recent years from the traditional Japanese lifestyle to a Western lifestyle, the prevalence of diabetes in Japan has increased. In addition to changes to avoid the death and/or ruin of quality of life caused by late-onset complications of diabetes, it is very important for clinical practitioners and health-providers to detect as early as possible those who are at risk for diabetes. New diagnostic criteria for diabetes have recently been proposed by the Expert Committee of the American Diabetes Association (ADA) (1) and provisionally agreed to by a World Health Organization (WHO) consultation (2). These criteria, which use fasting plasma glucose levels (FPGs), made the detection of diabetes easier and less expensive than using 2-h plasma glucose levels after a 75-g oral glucose tolerance test (OGTT). However, cardiovascular disease, separate from microvascular complications, is a health problem that might possibly occur in patients with diabetes. It has been reported repeatedly, mainly from European and American countries, that glucose intolerance, including both diabetes and impaired glucose tolerance (IGT), is one of the risk factors for cardiovascular disease (3,4). The ADA Expert Committee proposed a category that was new but similar to IGT, impaired fasting glucose (IFG), which is diagnosed when FPG falls between 110 and 125 mg/dl, although the ADA Expert Committee did not define IFG as equivalent to IGT. However, the criteria for IGT and IFG overlap in this gray zone. Our question was whether IFG would be a risk factor for cardiovascular disease, as was IGT.

To determine this, we conducted a cohort study consisting of the participants of the diabetes prevalence study in Funagata, Yamagata prefecture, Japan, in 1990–1992 (5). The first goal of the present investigation using the data collected from the Funagata cohort population was to confirm that IGT is a risk factor for death from cardiovascular disease, because in Japan only one study so far, the Hisayama study, has provided evidence to support this (6). If this hypothesis was confirmed, then the second goal of this cohort study was to determine whether IFG is a risk factor for cardiovascular disease.

RESEARCH DESIGN AND METHODS

Cohort population

Most of the inhabitants of Funagata, an agricultural area located ~400 km north of

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Abbreviations: ADA, American Diabetes Association; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; ICD-9, *International Classification of Diseases*, *Ninth Revision*; ICD-10, *International Classification of Diseases*, *Tenth Revision*; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.

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

Table 1—*Characteristics of the cohort population at baseline*

	NGT	IGT	Diabetes	Newly diagnosed diabetes	Known diabetes
n	2,016	382	253	136	117
Age (years)	58.8 ± 10.6	62.7 ± 9.8	65.6 ± 9.8	69.5 ± 8.6	66.9 ± 10.9
Sex (M/F)	920/1,096	140/242*	105/148	56/80	49/80
FPG levels (mg/dl)	91 ± 10	99 ± 12	130 ± 37	130 ± 37	—
2-h plasma glucose levels after 75-g OGTT (mg/dl)	101 ± 22	158 ± 17†	266 ± 79†	266 ± 79†	—

Data are means ± SEM. *Sex distribution was significantly different from the NGT group (χ^2 test), $P < 0.001$; †Mean value was significantly different from that of the NGT group (z test), $P < 0.05$.

Tokyo, who were included in the original diabetes prevalence study have not moved away, so that this community was appropriate for the cohort study. From 1990 to 1992, all the registered residents aged >40 years were subjected to a 75-g OGTT, but 344 with cerebral vascular disease or other disability were excluded. Some 117 residents who were known, by public health nurses and confirmed through contacts to outpatient clinics by one of authors (A.S.), to be suffering from diabetes were excluded from OGTT survey but were included in the cohort population. There were 2,534 residents who completed the 75-g OGTT, so that the participation rate was 74.5%. These participants, enrolled into the cohort population, were divided into three subgroups according to 1985 WHO criteria (7): normal glucose tolerance (NGT) (n = 2,016), IGT (n = 382), and diabetic (n = 136). The diabetic group, consisting of those with known diabetes and newly diagnosed diabetes, was made up of 253 subjects in all.

As shown in Table 1, the mean age (± SD) of the NGT, IGT, and diabetic groups was 58.8 ± 10.6, 62.7 ± 9.8, and 65.6 ± 9.8 years, respectively. Although there were no significant differences in age among the three groups, subjects in the IGT and diabetic groups were a little older than those in the NGT group, so that care was needed in the interpretation of the comparison of cumulative survival rates among the three groups.

Because the first OGTT survey took place in June of 1990, from that time to the end of 1996, death certificates of individuals whose address was listed as Funagata were collected with the permission of the Management and Coordination Agency of the Japanese government. The death code (*International Classification of Diseases, Ninth Revision* [ICD-9] between 1990 and 1994, *Tenth Revision* [ICD-10] between 1995 and 1996) and the date and place of the death event were inspected. During this research period, 370 residents died in Funagata. Among these were 124 people from the cohort mass. Most of the other deaths were people initially excluded from the study because of some disability, as mentioned above. On the other hand, residence transfer documents during the same period were surveyed with the permission of the Funagata Municipal Office. There were 112 residence transfers, 35 of which were from the cohort population.

Statistical methods

Life-table method. Using the classical actuarial life-table method, in which all the causes of death were first adopted as the end point, the cumulative survival rates of the NGT, IGT, and diabetic groups were calculated. Evaluation of the differences among the cumulative survival rates was done after z value conversion. If the P value was <0.05, the difference was considered to be statistically significant. Then, by limiting the causes of death to cardiovascular disease (ICD-9 codes 410–438 and equivalent ICD-10 codes), including coronary heart disease and stroke, the cumulative survival rates from cardiovascular disease were obtained.

Person-year method. For age adjustment of the three groups, the person-year method was used, in which stratification was made into 5-year age-groups by sex: 40–44, 45–49, 50–54, and so on. The observed person-years and death events in each column were counted, with the death events counted twice. First, death events from all causes were counted, and then only death events from cardiovascular disease were counted. Finally, the odds ratios of IGT to NGT and of diabetes to NGT were computed (8). The P value was calculated by Mantel-Haenszel's χ^2 test.

Cox's proportional hazard model. Using Cox's proportional hazard model, another method for adjustment of age differences among groups, the hazard ratios of age, IGT to NGT, and diabetes to NGT were analyzed. In the calculation of the latter two, one group (e.g., the diabetic group in the case of computing the ratio of IGT to NGT) was assumed not to exist. As with the person-year method, the hazard ratios were estimated twice: with all causes of death included and with death from other than cardiovascular disease excluded. Calculation was done using a personal computer with StatView software.

Reclassification of the cohort population

The cohort population was reclassified according to the ADA recommendation, referring to only FPG, into normal fasting glucose (NFG), IFG, and diabetic groups (1). Subjects with known diabetes were included in the diabetic group. The number of subjects in the NFG, IFG, and diabetic groups was 2,307, 155, and 189, respectively, at the start of follow-up. The life-table method, the person-year method, and Cox's proportional hazard model were used for analysis.

RESULTS

IGT is a risk factor for cardiovascular disease

As shown in Fig. 1*A*, the results of the life-table analysis revealed that at the end of seven observed years, the cumulative survival rates from all the causes of death for IGT and diabetes were 0.916 and 0.898, respectively, both significantly lower than that for NGT (0.954). In the IGT and diabetic groups, these rates were significantly lower from the 6th and 3rd years, respectively. When the causes of death were limited to cardiovascular disease, as shown in Fig. 1*B*, the cumulative survival rates for IGT and diabetes were 0.962 and 0.954, respectively, again significantly lower than that for NGT (0.988). It was noted that the

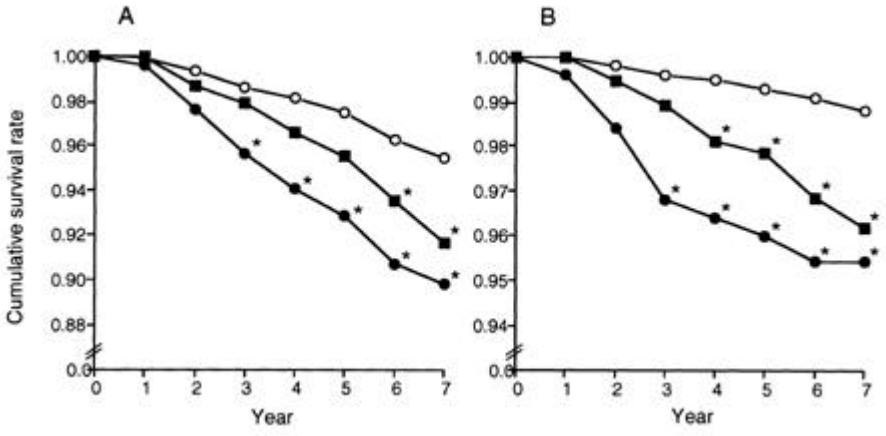

Figure 1—*Cumulative survival rate of the Funagata cohort population, classified into NGT, IGT, and diabetic groups according to the WHO criteria (1985). A: Cumulative survival rates from all causes of death, determined by the life-table method, of both the IGT (■) and the diabetic group (●) were significantly lower when compared with those of the NGT group (○). B: Cumulative survival rates from cardiovascular disease (coronary heart disease and stroke) of the IGT and diabetic groups were also significantly lower than that of the NGT group.* *$P < 0.05$.

cumulative survival rate from cardiovascular disease for IGT was significantly lower than that for NGT in the 4th year, 2 years earlier, when compared with the cumulative survival rate from all causes.

In the person-year method, odds ratios of death from all causes for IGT to NGT and diabetes to NGT were 1.429 (95% CI 0.881–2.319) and 1.743 (0.802–3.785), respectively (NS), as shown in Table 2. This meant that the differences in cumulative survival rate from all causes among the IGT, diabetic, and NGT groups were due to the age differences among these groups. However, when the cause of death was limited to cardiovascular disease, odds ratios for IGT to NGT and diabetes to NGT were 2.303 (1.022–5.188) and 3.537 (1.029–12.159), respectively, both of which were significant, as shown in Table 2.

The results of Cox's proportional hazard model analysis are shown in Table 3, in which evidence for age as a strong risk factor for death from all causes was obtained again and illustrated more clearly. Although the hazard ratios of death from all causes for IGT to NGT and diabetes to NGT were 1.313 (0.837–2.059) and 1.205 (0.742–1.957), respectively, NS, the hazard ratios of death from cardiovascular disease for IGT to NGT and diabetes to NGT were both significant, 2.219 (1.076–4.577) and 2.274 (1.069–4.838), respectively. Thus, analyses using the person-year method and Cox's proportional hazard model showed that glucose intolerance, from the stage of IGT to overt diabetes, was a risk factor for death from cardiovascular disease.

IFG is not a risk factor for cardiovascular disease

As shown in Fig. 2*A*, no significant difference of cumulative survival rates death from all causes was observed between IFG (0.919) and NFG (0.951). In addition, no significant difference was observed when the analysis was limited to death from cardiovascular disease, as shown in Fig. 2*B* (0.977 for IFG vs. 0.985 for NFG). Because there was no difference in the cumulative survival rates between IFG and NFG before age adjustment, the significance of adopting the person-year method and Cox's proportional hazard model analysis was small. As shown by reference data in Tables 2 and 3, the odds ratio and Cox's hazard ratio of death from cardiovascular disease for IFG to NFG were 1.324 (0.012–140.91) and 1.136 (0.345–3.734), respectively, so that

Table 2—*Odds ratio (person-year method)*

	Observed person-years	Number of deaths	Odds ratio	(95% CI)	*P* value
WHO criteria (1985)					
Death from all causes					
NGT	11,050	75	—	—	—
IGT	2,104	26	1.429	(0.881–2.319)	0.1669
Diabetes	1,366.5	23	1.743	(0.802–3.785)	0.1799
Death from cardiovascular disease					
NGT	11,050	19	—	—	—
IGT	2,104	11	2.303	(1.022–5.188)	0.0456
Diabetes	1,366.5	11	3.537	(1.029–12.159)	0.0461
ADA recommendation (1997)					
Death from all causes					
NFG	12,690	91	—	—	—
IFG	832	10	1.246	(0.495–3.139)	0.6454
Diabetes	998.5	23	2.112	(1.304–3.423)	0.0031
Death from cardiovascular disease					
NFG	12,690	27	—	—	—
IFG	832	3	1.324	(0.012–140.91)	0.9080
Diabetes	998.5	11	3.168	(1.524–6.588)	0.0028

P values were determined using the Mantel-Haenszel method.

Table 3—*Cox's hazard model*

	Hazard ratio	(95% CI)	*P* value
WHO criteria (1985)			
Death from all causes			
Age	1.105	(1.085–1.126)	0.0001
IGT*	1.313	(0.837–2.059)	0.2360
Diabetes†	1.205	(0.742–1.957)	0.4506
Death from cardiovascular disease			
Age	1.114	(1.079–1.150)	0.0001
IGT*	2.219	(1.076–4.577)	0.0309
Diabetes†	2.274	(1.069–4.838)	0.0329
ADA recommendation (1997)			
Death from all causes			
IFG*	1.236	(0.643–2.378)	0.5255
Diabetes‡	1.706	(1.072–2.715)	0.0241
Death from cardiovascular disease			
IFG*	1.136	(0.345–3.734)	0.8342
Diabetes‡	2.484	(1.226–5.033)	0.0116

Calculation was done *without diabetic group; †without IGT group; ‡without IFG group.

IFG, unlike IGT, was not a risk factor for death from cardiovascular disease.

CONCLUSIONS — The first simple conclusion we obtained from this population-based cohort study conducted in Funagata, northern Japan, was that glucose intolerance, including IGT and diabetes, was a risk factor for death from cardiovascular disease. This was the same conclusion as that arrived at in the Hisayama study (6), the only study previously conducted among the southwestern Japanese population. It needs to be particularly emphasized that it only took 4 years from the start of observation until the differences between IGT and NGT in the cumulative survival rates from cardiovascular disease became significant.

During the period of this cohort study, the death-code system was changed from ICD-9 to ICD-10. Since we used two code systems, a criticism might be raised in reference to this inconsistent use. However, because we considered that biases might occur if we ourselves changed the codes to get consistency from two code systems, we left the authorized code unchanged. Moreover, for example, in the ICD-9 system, if a man died with pneumonia after being bedridden for a long time from the sequelae of stroke, a possible death code was 486 (pneumonia), but the ICD-10 system would assign this case I698 (stroke), so that even in the use of a mixture of the ICD-9 and ICD-10 code systems, overestimation of cardiovascular disease as the cause of death for glucose intolerance might be denied.

Excess mortality from cardiovascular disease, not only in subjects with diabetes, but also in those with IGT, suggested that the cause of macrovascular damages, as different from microvascular complications, might not be solely due to hyperglycemia. The important lesson taken from the results of the Diabetes Control and Complications Trial (DCCT) is the complete evidence for hyperglycemia as the major cause of the development of retinopathy, nephropathy, and neuropathy as late-onset complications of diabetes (9). Because the participants of the DCCT were young patients with type 1 diabetes, we could not learn from this study whether hyperglycemia is also responsible for the occurrence of cardiovascular disease. However, fasting hyperglycemia and all-day hyperglycemia (high levels of HbA_{1c}) could also be responsible for the development of cardiovascular disease, as reported by some researchers (10–12) and by the recently published final report of the U.K. Prospective Diabetes Study (13).

For IGT, because there was already an established risk for cardiovascular disease and plasma glucose levels were not remarkably high, some factor other than hyperglycemia seemed to be related to the development of macrovascular disease. Reaven (14) proposed syndrome X including IGT to be one of the potential risk factors of cardiovascular disease, and suggested that insulin resistance is likely a causal factor of cardiovascular disease.

Taking together the results of this study and other cohort studies, we would like to emphasize that IGT, even without any symptoms, needs to be recognized as a clinical entity needing intervention to prevent the occurrence of cardiovascular disease by reducing mild hyperglycemia and insulin resistance, either through a change of lifestyle to a more desirable one or by the administration of insulin resistance–reducing agents, as hypertension and hypercholesterolemia have been already recognized. To obtain evidence that these interventions

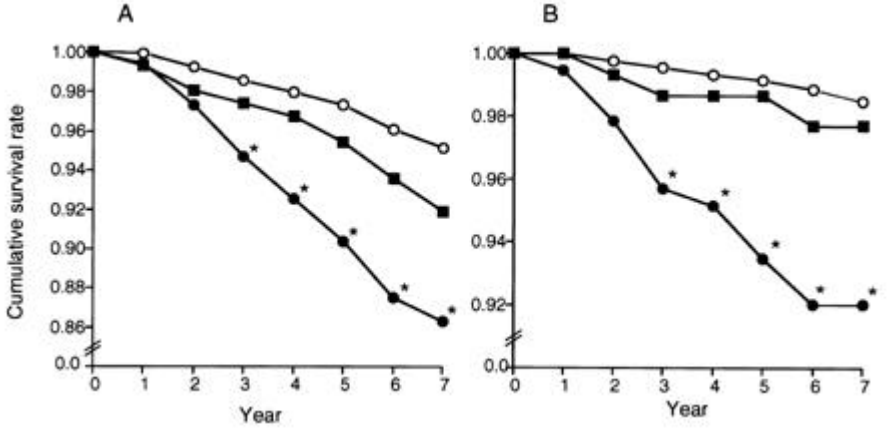

Figure 2—*Cumulative survival rate of the Funagata cohort population, classified into NFG, IFG, and diabetic groups according to the ADA recommendation (1997).* A*: The cumulative survival rate of the IFG group (■) from all causes of death was not different from that of the NFG group (○), although the cumulative survival rate of the diabetic group (●) was significantly lower than that of the NGT group.* B*: The cumulative rate of survival from cardiovascular disease in the IFG group was also not different from that of the NFG group.* *$P < 0.05$.

actually reduce the risk of cardiovascular disease, however, a randomized clinical or community trial needs to be undertaken in the future.

Regarding the second goal of this study, it was found that IFG, a new category proposed by the ADA, was not a risk factor for cardiovascular disease. FPG levels in the IGT group did not distribute exactly in the region of IFG (between 110 and 125 mg/dl), but were widely spread between 80 and 130 mg/dl (data not shown). Speaking at least in terms of the present study, it is a fact that IGT and IFG were different, and this difference could be an outcome of the difference between the two categories in coexisting established risk factors. Comparison of baseline data, including BMI, waist-to-hip ratio, blood pressure level, fasting plasma insulin level, serum lipids level, etc. from the IGT group with those of the IFG group will need to be done in the near future.

We conducted the diabetes prevalence study from 1990 to 1992 in Funagata, and repeated the same study from 1995 to 1997. From these data, the incidence of diabetes in subjects who were not found to have diabetes in the first tests can be estimated. The incidence rate of the subjects with mild fasting hyperglycemia corresponding to the IFG category at the time of the first tests was 44.0/1,000 person-years, significantly higher than the 2.5/1,000 person-years for subjects with NFG ($P < 0.001$) (M.T., H.E., K.I., unpublished observations). Consequently, there is only one risk for IFG: worsening of metabolic derangement progressing to overt diabetes; with IGT there are two risks, however: a risk for conversion to diabetes and a risk for development of cardiovascular disease.

The enterprising recommendation proposed by the ADA will be accepted because a diagnosis of and the detection of a risk for progression to diabetes can be made without carrying out an OGTT. However, from the standpoint of detection of a mild metabolic abnormality with a risk for cardiovascular disease, diagnoses using only FPG, without OGTT, can be said to be insufficient.

In conclusion, IGT, but not IFG, was a risk factor for death from cardiovascular disease; therefore, the two diagnostic criteria (WHO 1985 and ADA 1997) with and without OGTT should be used as routine clinical practices for the purposes of diagnosing overt diabetes or detecting risk factors for cardiovascular disease.

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References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
2. Alberti KGMM, Zimmet PZ, for the WHO consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1. diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998
3. Meigs JB, Nathan DM, Wilson PWF, Cupples LA, Singer DE: Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance: the Framingham offspring study. *Ann Intern Med* 128:524–533, 1998
4. Rodriguez BL, Curb JD, Burchfiel CM, Huang B, Sharp DS, Lu GY, Fujimoto W, Yano K: Impaired glucose tolerance, diabetes and cardiovascular disease risk factor profiles in the elderly. *Diabetes Care* 19:587–590, 1996
5. Sekikawa A, Tominaga M, Takahashi K, Eguchi H, Igarashi M, Ohnuma H, Sugiyama K, Manaka H, Sasaki H, Fukuyama H, Miyazawa K: Prevalence of diabetes and impaired glucose tolerance in Funagata Area, Japan. *Diabetes Care* 16:570–574, 1993
6. Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Yoshitake T: Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes* (Suppl. 3):S14–S16, 1996
7. World Health Organization: *Diabetes Mellitus*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
8. Kleinbaum DG, Kupper LL, Morgenstern H: Stratified Analysis. In *Epidemiologic Research*. Kleinbaum DG, Kupper LL, Morgenstern H, Eds. New York, Van Nostrand Reinhold Company, 1971, p. 320–376
9. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
10. Charles MA, Balkau B, Vauzelle-Kervoeden F, Thibult N, Eshwege E: Revision of diagnostic criteria for diabetes (Letter). *Lancet* 348:1657–1658, 1996
11. Lowe LP, Liu K, Greenland P, Metzger BE, Dyer AR, Stamler J: Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men: the Chicago Heart Association Detection Project in Industry Study. *Diabetes Care* 20:163–169, 1997
12. Barret-Connor E, Ferrara A: Isolated postchallenge hyperglycemia and the risk of fatal cardiovascular disease in older women and men: the Rancho Bernardo Study. *Diabetes Care* 21:1236–1239, 1998
13. U.K. Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
14. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988