

# From Policemen to Policies: What Is the Future for 2-h Glucose?

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**OBJECTIVE** — To describe the characteristics and vital prognosis of men with diabetes diagnosed by one fasting plasma glucose (FPG) concentration  $\geq 7.0$  mmol/l, with diabetes diagnosed by one isolated postchallenge hyperglycemia (IPH) (FPG  $< 7.0$  mmol/l and a 2-h plasma glucose concentration  $\geq 11.1$  mmol/l), or with impaired glucose tolerance (IGT).

**RESEARCH DESIGN AND METHODS** — This study involved a cohort of 6,881 Caucasian nondiabetic men from the Paris Prospective Study, aged 44–55 years, who were followed for cause of death for 20 years.

**RESULTS** — Diabetes was diagnosed in 4.3% of the men (1.0% diabetes diagnosed by IPH), and IGT was diagnosed in 9% of the men. At baseline, the men with diabetes diagnosed by IPH had a lower cardiovascular risk profile than those with diabetes diagnosed by FPG, as did the men with IGT and a normal fasting glucose level ( $< 6.1$  mmol/l, IGT and normal fasting glucose), compared with men with impaired fasting glucose (6.1–6.9 mmol/l, IGT and impaired fasting glucose [IFG]). At 20 years of follow-up, all-cause and cancer death rates were higher in men with diabetes diagnosed by IPH than in men with diabetes diagnosed by FPG (55 vs. 44%,  $P < 0.1$  and 31 vs. 17%,  $P < 0.01$ , respectively) but were not significantly different for coronary causes (6 vs. 11%). Men with IGT and normal fasting glucose also had significantly higher cancer death rates than men with IGT and IFG.

**CONCLUSIONS** — The most likely explanation for the high cancer and low coronary death rates is that men with diabetes diagnosed by IPH consumed alcohol; the men in this study drank 49 g of pure alcohol on average per day, equivalent to 0.6 l of wine. If these results are confirmed by other prospective studies, screening subjects for isolated postchallenge hyperglycemia may not be worthwhile.

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The currently recommended method for screening and diagnosing diabetes is based on fasting plasma glucose (FPG), measured on at least two occasions (1,2). Although subjects with hyperglycemia 2 h after undergoing standard 75-g oral glucose tolerance test are still considered to have diabetes, this test is unlikely to be performed, considering the recommendations from the American

Diabetes Association, even if the World Health Organization was less categorical about not using the oral glucose tolerance test (1,2). In fact, even though the previous recommendations for the diagnosis of diabetes were current (3), the oral glucose tolerance test was rarely performed in practice. In France, its use was limited; in 1998, for ambulatory laboratory tests, there were 17,000,000 prescriptions for

fasting glucose determinations and only 77,000 0- to 2-h oral glucose tolerance tests (4). Therefore, in subjects with normal FPG but postchallenge hyperglycemia, diabetes was often not diagnosed; in the future, there will be even less chance that diabetes will be diagnosed in these subjects.

Since the 1985 report by the World Health Organization (3), most epidemiological studies have used the oral glucose tolerance test. The reported prevalences of diabetes have often been based only on the 2-h glucose evaluation, as recommended by the World Health Organization, because the fasting status of subjects in epidemiological studies is difficult to ensure. In some studies, FPG was not determined at all.

We have very limited knowledge about the characteristics and prognosis of subjects in whom diabetes is diagnosed by an isolated elevated 2-h plasma glucose, also known as isolated postchallenge hyperglycemia (IPH) (2-h plasma glucose  $\geq 11.1$  mmol/l and FPG  $< 7.0$  mmol/l) or about subjects in whom impaired glucose tolerance (IGT) is diagnosed (2-h plasma glucose between 7.8 and 11.1 mmol/l and FPG  $< 7.0$  mmol/l).

The aim of this study was to describe the characteristics of men with diabetes diagnosed by IPH and those with IGT, with and without impaired fasting glucose (IFG) (fasting plasma glucose between 6.1 and 6.9 mmol/l), and to study their risks and causes of early death, compared with men with normal glucose tolerance without IGT and those in whom diabetes was diagnosed by FPG concentration  $\geq 7.0$  mmol/l.

## RESEARCH DESIGN AND METHODS

### Subjects

This study analyzed the 6,881 Paris policemen, all Caucasians aged 44–55 years, who had no cardiovascular disease and in whom diabetes had not been diagnosed during the first annual follow-up

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**Abbreviations:** CHD, coronary heart disease; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IPH, isolated postchallenge hyperglycemia.

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



**Table 1—Characteristics at baseline for the 6,881 men studied in the Paris Prospective Study**

	IGT			Diabetes			P‡	
	Normal/IFG	IGT and non-IFG	P*	IGT and IFG	Diagnosed by IPH	P†		Diagnosed by FPG
FPG (mmol/l)	<7.0	<6.1		≥6.1 and <7.0	<7.0		≥7.0	
2-h glucose (mmol/l)	<7.8	≥7.8 and <11.1		≥7.8 and <11.1	≥11.1			
<i>n</i>	5,957	364		263	68		229	
Age (years)	48 (2)	48 (2)		49 (2)	49 (2)		49 (2)	
Family history of diabetes (%)	7.1	9.4		7.2	6.3	0.05	15.5	
Smokers (%)	42	58		51	32		43	
BMI (kg/m <sup>2</sup> )	25.7 (3.1)	25.8 (3.6)	0.001	27.7 (3.5)	24.9 (3.4)	0.0001	28.6 (3.8)	0.05
Systolic blood pressure (mmHg)	143 (20)	151 (23)	0.01	157 (24)	162 (23)		163 (29)	0.0001
Diastolic blood pressure (mmHg)	80 (12)	85 (13)		88 (13)	86 (13)		90 (16)	0.001
Fasting glucose (mmol/l)	5.5 (0.5)	5.6 (0.4)	0.001	6.4 (0.2)	5.8 (0.6)	0.0001	7.8 (1.0)	0.01
2-h glucose (mmol/l)	5.2 (1.2)	8.8 (0.9)		8.8 (0.8)	12.3 (1.2)	0.0001	10.2 (3.8)	0.0001
Fasting insulin (pmol/l)	68 (20–235)	78 (20–208)	0.001	101 (30–351)	69 (15–330)	0.0001	129 (36–461)	
2-h insulin (pmol/l)	209 (46–952)	438 (110–1,738)	0.001	582 (168–2,012)	407 (88–1,890)		397 (104–1,510)	0.0001
Cholesterol (mmol/l)	5.6 (1.1)	5.7 (1.1)		5.8 (1.1)	5.7 (1.2)		6.0 (1.2)	
Triglycerides (mmol/l)	1.2 (0.5–3.3)	1.4 (0.4–4.2)		1.5 (0.5–4.3)	1.2 (0.5–3.2)	0.0001	1.7 (0.6–5.1)	
Nonesterified fatty acids (mmol/l)	77 (34–172)	107 (45–252)		103 (44–240)	143 (58–351)	0.0001	105 (46–240)	0.0001
Mean corpuscular volume (≥ 100 fl) (%)	29	39	0.05	28	58	0.001	36	0.001

Data are means (SD), geometric means (95% CI), or %. \*IGT diagnosed by non-IFG versus IFG; †diabetes diagnosed by IPH versus FPG; ‡diabetes diagnosed by IPH versus normal/IFG.

men with normal glucose tolerance as well as IGT and IFG.

The death rates from cancer for the men with diabetes diagnosed by IPH and

IGT and non-IFG were two to three times higher than for the men with normal/IFG ( $P < 0.05$  at 10 years and  $P < 0.0001$  at 20 years). These death rates were higher

in the men with IGT and non-IFG than in the men with IGT and IFG ( $P < 0.03$ ) and higher in the men with diabetes diagnosed by IPH than in men with diabetes

**Table 2—Death rate at 10 and 20 years of follow-up by cause, according to diabetic status, in the 6,881 men followed for vital status and causes of death in the Paris Prospective Study**

	IGT			Diabetes			P‡	
	Normal/IFG	IGT and non-IFG	P*	IGT and IFG	Diagnosed by IPH	P†		Diagnosed by FPG
FPG (mmol/l)	<7.0	<6.1		≥6.1 and <7.0	<7.0		≥7.0	
2-h glucose (mmol/l)	<7.8	≥7.8 and <11.1		≥7.8 and <11.1	≥11.1			
<i>n</i>	5,957	364		263	68		229	
10-year follow-up								
All causes	7.0 (403)	14.8 (52)	0.01	7.9 (20)	18.1 (12)		14.3 (32)	0.0001
CHD	1.4 (79)	2.7 (9)		1.6 (4)	1.5 (1)		5.1 (11)	
All cancers	3.0 (165)	7.1 (24)	0.03	2.8 (7)	8.3 (5)	0.001	1.5 (3)	0.05
Alcohol-related cancers	0.6 (34)	1.8 (6)		0.4 (1)	3.4 (2)	0.07	0.5 (1)	0.009
All alcohol-related causes of death	0.8 (43)	2.1 (7)		1.7 (4)	4.9 (3)	0.1	1.5 (3)	0.0003
20-year follow-up								
All causes	21.1 (1,188)	36.3 (127)	0.02	27.4 (69)	54.6 (36)	0.1	44.1 (98)	0.0001
CHD	4.2 (216)	8.1 (24)		6.7 (15)	5.8 (3)		11.1 (21)	
All cancers	9.9 (519)	19.1 (59)	0.03	12.0 (27)	31.3 (17)	0.01	17.0 (29)	0.0001
Alcohol-related cancers	1.9 (96)	5.6 (16)		3.8 (8)	11.5 (6)	0.06	5.3 (9)	0.0001
All alcohol-related causes of death	2.4 (123)	7.3 (21)		5.9 (13)	17.3 (9)	0.03	7.8 (14)	0.0001

Data are % (n). \*IGT diagnosed by non-IFG versus IFG; †diabetes diagnosed by IPH versus FPG; ‡diabetes diagnosed by IPH versus normal/IFG.

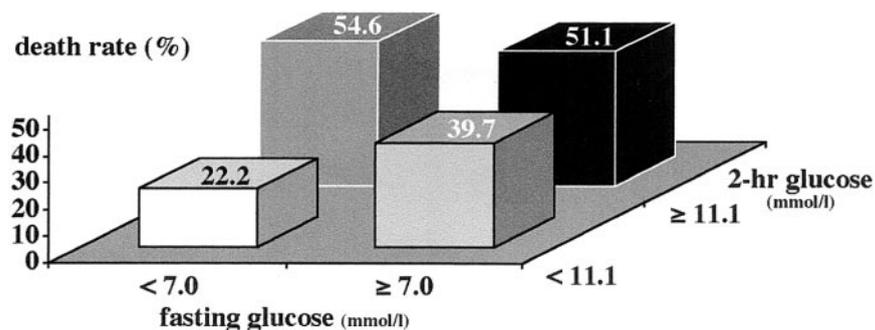
diagnosed by FPG ( $P < 0.01$  at both 10 and 20 years).

After 10 years of follow-up, the deaths rates for alcohol-related cancers were six times higher in the men with diabetes diagnosed by IPH than in the men with diabetes diagnosed by FPG or the men with normal/IFG ( $P < 0.01$  for both). At 20 years of follow-up, there was still a sixfold excess compared with the men with normal glucose tolerance ( $P < 0.0001$ ), but the excess was only twofold that in the men with diabetes diagnosed by FPG ( $P < 0.06$ ).

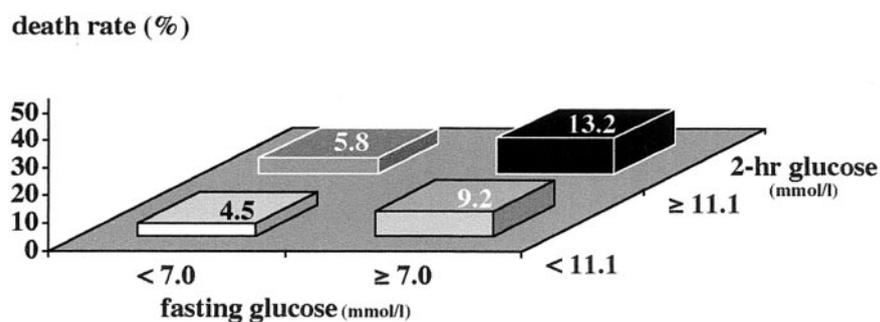
The death rates for all alcohol-related causes of death were highest in the men with diabetes diagnosed by IPH, significantly higher than in the men with normal/IFG ( $P < 0.0003$  at 10 years and  $P < 0.0001$  at 20 years), and significantly higher than in the men with diabetes diagnosed by FPG only at 20 years ( $P < 0.03$ ). In contrast, the men with IGT and IFG and men with IGT and non-IFG had similar death rates for all alcohol-related causes.

To further illustrate the causes of death in men with diabetes diagnosed by IPH and with diabetes diagnosed by FPG, we divided the latter group into the 139 men with diabetes diagnosed by an isolated fasting hyperglycemia (FPG  $\geq 7.0$  mmol/l and 2-h plasma glucose  $< 11.1$  mmol/l) and the 90 men with diabetes diagnosed by combined fasting and 2-h hyperglycemia (FPG  $\geq 7.0$  mmol/l and 2-h plasma glucose  $\geq 11.1$  mmol/l) (Fig. 1). For all causes of death, men with a 2-h plasma glucose  $\geq 11.1$  mmol/l had similar death rates that were independent of whether the fasting plasma glucose level was higher or lower than 7.0 mmol/l (54.6 and 51.1%, respectively); the rates were 20% higher than in men with diabetes diagnosed by an isolated fasting hyperglycemia (diabetes diagnosed by IPH versus diabetes diagnosed by isolated fasting hyperglycemia,  $P < 0.03$ ) and more than twofold higher than in the nondiabetic men ( $P < 0.0001$ ). In contrast, for CHD mortality, death rates in men with diabetes diagnosed by IPH were only a little higher than in the nondiabetic men (5.8 and 4.5%) and lower than in men with diabetes diagnosed by isolated fasting hyperglycemia (9.2%) and men with diabetes diagnosed by fasting and 2-h hyperglycemia (13.2%). However, for death from cancer, the death rate in men with diabetes diagnosed by IPH was very high:

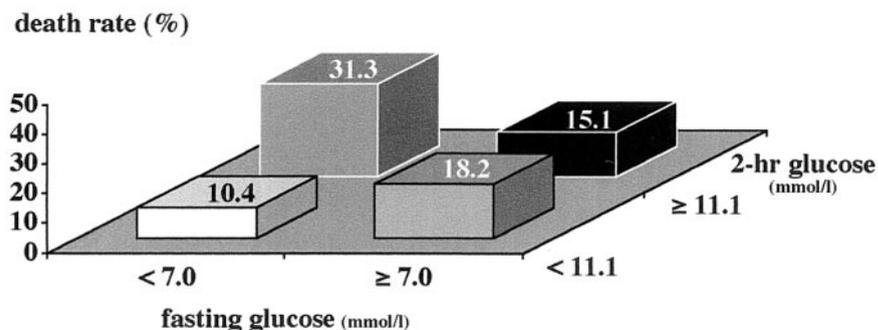
**A: ALL CAUSE DEATHS**



**B: CORONARY DEATHS**



**C: CANCER DEATHS**



**FIG. 1.**—Death rates over 20 years for all causes of death (A); deaths caused by CHD (B); and deaths caused by cancer (C), according to FPG  $< 7.0$  and  $\geq 7.0$  mmol/l and 2-h plasma glucose values  $< 11.1$  and  $\geq 11.1$  mmol/l for men aged 44–55 years in the Paris Prospective Study.

three times higher than in nondiabetic men (31.3 and 10.4%,  $P < 0.0001$ ) and two times higher than in men with diabetes diagnosed by isolated fasting hyperglycemia or diabetes diagnosed by fasting and 2-h hyperglycemia (18.2%,  $P < 0.03$  and 15.1%,  $P < 0.01$ , respectively).

**CONCLUSIONS**— Should we try to find subjects with diabetes diagnosed by

IPH? First, these men were 1% of the total population, and although this is not a large percentage, it was 23% of the subjects diagnosed with diabetes at baseline. Second, the cardiovascular risk profile was higher in the men with diabetes diagnosed by FPG than those with diabetes diagnosed by IPH, which was, in turn, higher than that in men with normal/IFG. Therefore, it is not surprising that their

coronary death rate at 20 years of follow-up showed a decreasing trend over these three groups, even though the differences were not statistically significant. Thirdly, death by cancer, by alcohol-associated cancer, and by all alcohol-related diseases was significantly higher in men with diabetes diagnosed by IPH than in men with normal/IFG or diabetes diagnosed by FPG. In this population, we would implicate a heavy alcohol intake as the main reason for the high death rates in men with diabetes diagnosed by IPH; treatment to lower the blood glucose level is unlikely to change the prognosis in these patients.

Both death rate and conversion to diabetes are known to be higher in subjects with IGT than in those with normal/IFG (3). In this study, 9% of the men had IGT, 4% had IGT and non-IFG, and 5% had IGT and IFG. The group with IGT and non-IFG was metabolically close to the men with normal/IFG, but the risk of death in those with IGT and non-IFG was almost two times higher, which was largely due to cancer mortality. The group with IGT and IFG had more factors associated with insulin resistance, but their vital prognosis was very similar to that in the men with normal/IFG.

To our knowledge, no study has analyzed subjects with an IGT, and few studies have analyzed subjects with diabetes diagnosed by IPH. The first was the Rancho-Bernardo Study of 1,858 subjects (average age 70 years); in this study, diabetes was diagnosed by IPH in 72% of the diabetic women and 48% of the diabetic men (8). However, in the DECODE Study of 29,108 subjects (average age 53 years), this percentage was 35% (9), and in the subgroup of 3,991 men and 2,149 women aged 60–90 years, diabetes was diagnosed by IPH in 34% of men and 37% of women (10). In the elderly subjects from the Cardiovascular Health Survey, diabetes was diagnosed by IPH in 52% of diabetic subjects (11). In younger populations (average age 36–43 years) from Mauritius, Fiji, and Nauru, diabetes was diagnosed by IPH in 22, 20, and 8%, respectively, of the patients with newly diagnosed diabetes (12). The most recent information comes from the Third National Health and Nutrition Examination Survey of men and women aged 40–74 years (13); diabetes was diagnosed by IPH in 41% of the diabetic subjects, and this percentage increased with age. Diabetes

was diagnosed by IPH in 36% of patients aged 45–54 years (age-group of our study) and in 54% of patients aged 70–74 years. These percentages differ widely and depend on the age, sex, community, and ethnic group of the subjects, and perhaps more importantly, on the frequency of routine screening in the population and the number of subjects in the population in whom diabetes has already been diagnosed.

The first publication on the mortality of subjects with diabetes diagnosed by IPH was from the Rancho-Bernardo Study (8). Compared with nondiabetic men, the men had a relative risk of cardiovascular death of 0.7 (0.3–1.6), after adjustment for cardiovascular risk factors. In contrast, the women had a significantly increased risk compared with nondiabetic women; the relative risk was 2.6 (1.4–4.7). The risk was slightly higher for ischemic heart disease mortality. No information is given in this study about other causes of death or of the risk of death by all causes. The second study published was in the subgroup of elderly men and women aged 60–80 years from the DECODE Study (10); men and women with diabetes diagnosed by IPH had a significantly higher death rate, relative risk 1.6 (1.1–2.3), for a follow-up of  $\leq 10$  years. The most complete study comes from the islands of Mauritius, Fiji, and Nauru, which included more than 8,000 men and women in whom diabetes had not been previously diagnosed; most subjects were from Mauritius (12). The relative risk of death by cardiovascular disease was significantly higher in the men and women with diabetes diagnosed by IPH than in the nondiabetic subjects: 2.3 (1.2–4.2) and 2.6 (1.3–5.1), respectively. However, in concordance with our study, the relative risk of death from cancer was high, with a risk ratio of 8.0 (3.6–17.9) in men and 2.2 (0.8–6.5) in women.

One possible explanation for our observation that diabetes diagnosed by IPH (or even in men with IGT and non-IFG) is associated with death from cancer is that the accompanying hyperinsulinemia promotes growth of cancer (14). However, this does not seem to be the explanation in the Paris Prospective Study, in which the men with diabetes diagnosed by IPH who died of cancer had lower fasting and 2-h insulin concentrations at baseline

than the men who did not die because of cancer.

The men with diabetes diagnosed by IPH or the men with IGT and non-IFG had the two highest levels of nonesterified fatty acids, which could be a cancer promoter, an early catabolic effect of cancer, or a marker of alcohol and tobacco consumption. A recent study of this cohort showed that nonesterified fatty acids were an independent risk factor for alcohol- and smoking-related cancer mortality but not for CHD mortality (15). The most likely explanation for our results is that the men with diabetes diagnosed by IPH or the men with IGT and non-IFG had a high alcohol intake and subsequently died from diseases associated with excessive alcohol consumption rather than from coronary causes. The frequency of men with a higher mean corpuscular volume in these groups supports this hypothesis. However, surprisingly, although the men with IGT and non-IFG had higher alcohol-related cancer death rates than the men with IGT and IFG, death rates were similar in these two groups for all alcohol-related diseases. Alcohol has been associated with diabetes in other studies. In the Rancho-Bernardo Study, during a 14-year follow-up, the subjects in whom diabetes developed (FPG  $\geq 7.8$  mmol/l or 2-h plasma glucose  $\geq 11.1$  mmol/l) had a mean daily alcohol intake of 31 g/day compared with 19 g/day in the other subjects (16). In the Paris Prospective Study, we have already reported that diabetic subjects (FPG  $\geq 7.8$  mmol/l or 2-h plasma glucose  $\geq 11.1$  mmol/l) had a high death rate from alcohol-related causes (17). Based on a dietary survey, the average daily alcohol intake was 49 g of pure alcohol (equivalent to 0.6 l of wine per day) in a subgroup of 446 of these men; 3% of the men with an alcohol intake  $\geq 20$  g/day had diabetes (FPG  $\geq 7.8$  mmol/l or 2-h plasma glucose  $\geq 11.1$  mmol/l), whereas none of the 82 men with a lower alcohol intake had diabetes (18). In contrast, among the subjects from Mauritius, alcohol intake was not associated significantly with diabetes (2-h plasma glucose  $\geq 11.1$  mmol/l) in either men or women, even though the alcohol intake was not low: 39% of the men had three or more drinks per day (19). A recent study in the U.S. showed that the incidence of diabetes (FPG  $\geq 7.0$  mmol/l) increased above the median intake of 17 g/day of alcohol (20). From these various

studies, we have no information about the alcohol consumption in subjects with diabetes diagnosed by IPH or subjects with IGT and non-IFG, and the dietary survey in the Paris Prospective Study comprised too few subjects.

Studies of causes of death in subjects with diabetes diagnosed by IPH and subjects with IGT and non-IFG are required in other populations to determine whether deaths caused by cancer and deaths caused by CHD are common and whether the subjects in whom diabetes was diagnosed based on isolated elevated 2-h postload glucose concentrations are similar to those in whom diabetes was diagnosed by fasting glucose concentrations. If subjects with high 2-h plasma glucose concentrations die principally because of cancer, screening for diabetes and subsequent treatment for hyperglycemia would not seem to be of any benefit for increasing the longevity of these individuals.

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