Prevalence of Fasting Hyperglycemia and Known Non-Insulin-Dependent Diabetes Mellitus Classified by Plasma C-Peptide: Fredericia Survey of Subjects 60–74 Yr Old

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A Danish population of 5699 individuals (60–74 yr old) was screened by fasting blood glucose (FBG) and interviewed about known diabetes. The distribution of FBG in individuals not known to have diabetes showed no sex difference or significant variation with age. Fasting hyperglycemia (FH), defined as FBG ≥ 7 mM in subjects without a history of diabetes, was found in 1.7% of men and women. Known diabetes (KD) had a prevalence of 3.9 and 5.0% in men and women, respectively. The prevalence rates of FH and KD increased significantly with age. In the two subgroups, plasma C-peptide was measured after overnight fasting and subsequently 6 min after an intravenous injection of glucagon. Based on the distribution of the C-peptide concentrations in non-insulin-treated KD subjects, lower limits for non-insulin-dependent diabetes mellitus (NIDDM) of 0.30 pmol/ml for fasting C-peptide and 0.60 pmol/ml for stimulated C-peptide were arbitrarily chosen. According to these cutoff points, only 38.5% of KD subjects treated with insulin had insulin-dependent diabetes mellitus, corresponding to 9.3% of all KD subjects. After exclusion of these patients, the prevalence of recognized NIDDM was 3.5% in men and 4.5% in women. All FH subjects except one had C-peptide values in the NIDDM interval. A close agreement between fasting and glucagon-stimulated C-peptide was seen. In epidemiological studies with an expected high prevalence of NIDDM, we propose to use fasting C-peptide for classification of patients with insulin-treated diabetes. *Diabetes Care* 10:26–32, 1987

Only a few surveys have assessed the prevalence of diabetes mellitus among elderly people in Caucasian communities (1–3) and described the distribution of fasting blood glucose (FBG) (3). Differentiation into type of diabetes has been done only rarely (4,5) and has been based on clinical characteristics. Insulin-treated elderly diabetic patients may have insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM) treated with insulin because of otherwise unsatisfactory metabolic control (insulin requiring). In epidemiological studies including elderly age groups, an objective, convenient method, comparable with other studies of the characterization of insulin-treated diabetics would be desirable. Plasma C-peptide response after glucagon stimulation has been suggested to be of clinical value in making the distinction between IDDM and NIDDM (6–9) and to differentiate better than fasting C-peptide (8). Fasting C-peptide has been determined in a randomly selected sample of Micronesians (10) and in a Danish epidemiological study of known diabetic patients treated with oral antidiabetics or insulin (11). Until now no study has described the distribution of glucagon-stimulated C-peptide in a representative sample of elderly people with known diabetes (KD) or fasting hyperglycemia (FH) found during a population screening. Furthermore, the use of stimulated versus fasting C-peptide values in epidemiological studies has not been evaluated.

The aims of this study in an elderly population were: *1*) to record the prevalence of KD; *2*) to describe the distribution of FBG and the prevalence of occult FH defined as FBG ≥ 7.0 mM; *3*) to describe the β-cell function by plasma C-peptide concentration in the subpopulations of individuals with KD and FH; and *4*) to estimate the prevalence of NIDDM among patients with insulin-treated diabetes.

MATERIALS AND METHODS

Materials

The study was carried out in the municipality of Fredericia, which on January 1, 1981, comprised 45,859 inhabitants.

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The distribution of rural and urban districts within the municipality corresponds to that of the whole country (12). All Danes are registered in the currently updated National Register. During the study period (February 1, 1981, to October 31, 1982) 14 random test samples, each consisting of 240–480 individuals, were drawn from the updated population register of individuals 60–74 yr old living in the municipality. All subjects were numbered consecutively and invited to be examined in the order they were drawn. The total population under study included 5699 subjects within the specified age interval, of which 5292 (92.9%) were examined. Of the 407 (7.1%) nonresponders, 25 (0.4%) died before study, 360 (6.3%) did not wish to participate, and 22 (0.3%) moved or did not participate for other reasons. The procedure has been described in detail previously (13,14).

Methods

Screening. All 5699 subjects were invited by letter to come to the clinic between 0700 and 1000 h after fasting from 2100 h the previous night. At the time of the visit, blood glucose (capillary ear blood), height, and weight (without shoes and coat) were measured, and body mass index (BMI) was calculated [weight (kg)/height (m^2)]. All participants were interviewed for a possible history of diabetes and previous or present antidiabetic treatment. Blood glucose was measured in capillary whole blood with a hexokinase method (Glucoquant 245178, Boehringer-Mannheim, Mannheim, FRG). The between-batch coefficient of variation of the method was 1.9% (blood glucose <10 mM).

Diagnostic criteria. Newly diagnosed FH was defined as FBG ≥ 7.0 mM in a subject without KD, as recommended by Siperstein (15). Known diabetic patients on insulin treatment were classified as KD subjects regardless of their actual blood glucose concentration. Diabetic patients treated with diet and/or oral antidiabetics were called KD subjects if their FBG was ≥7.0 mM or further information from general practitioners and/or hospital records confirmed the diagnosis. Untreated subjects claiming a history of diabetes were only included as KD subjects if their FBG was ≥7 mM.

Evaluation of β-cell function. KD and FH subjects participated in an examination of β-cell function. They were invited to the clinic between 0800 and 0900 h after fasting from 2100 h the previous night. All FH subjects were examined within 1 wk of the screening.

Glucagon (1 mg i.v.) was administered for 3 s. Just before and 6 min after glucagon was injected, venous blood was drawn and analyzed for blood glucose and C-peptide (16–18).

The reproducibility of C-peptide determinations was 6.6% (17), whereas the average difference between two glucagon-stimulated C-peptide concentrations, measured in 30 NIDDM patients, was 11% (19).

Criterion for NIDDM. Because all diet- and tablet-treated KD subjects were nonketotic, they were regarded as representing patients with primary NIDDM. We therefore used the lower limits of the distributions of the C-peptide concentrations in diet- and tablet-treated patients to define the cutoff points between IDDM and NIDDM in insulin-treated patients and subjects with FH.

Statistical methods. The relation between BMI and FBG was estimated by a Pearson product-moment correlation. Values of both variables were transformed into $\log_e$ values to produce normally distributed data.

Variation of prevalence with sex and age was estimated by a logistic regression analysis (20) of the prevalence odds. The level of statistical significance was $P = .05$.

C-peptide values in the groups were compared by Student's t test for unpaired data after $\log_e$ transformation because of the skewed distribution to the right. Fasting and stimulated C-peptide concentrations were compared by linear regression analysis.

RESULTS

Of the 5292 (92.9%) responders, 236 had a history of diabetes. Twenty-one KD subjects and 140 without KD and blood glucose <7.0 mM admitted that they were not fasting and did not return for a second testing the next day. They are excluded from Fig. 1 and from the results comprising FBG measured at the screening procedure. In the second part of the examination, which evaluated β-cell function, 228 (96.6%) KD subjects, and 87 (98.9%) FH subjects were examined.

Fasting Blood Glucose

Figure 1 shows the FBG distribution of 5131 screenees (215 with and 4916 without KD, respectively). Bimodality was not present in our elderly population, even when data from the two graphs were pooled.

Among all individuals without KD, 98.3% had FBG <7 mM, 95% had FBG ≥4.0 mM, and 50% had FBG ≥4.7 mM. No relation between FBG and age or sex was seen in subjects without KD (Fig. 2).

The BMI was the same in nondiabetic men and women (Table 1). The association between FBG and BMI in nondiabetic subjects was statistically significant but weak (men: $r = .20$, $P < .0001$; women: $r = .23$, $P < .0001$), whereas in FH subjects the correlation between FBG and BMI was not significantly different from zero (men: $r = -.24$, $P > .10$; women: $r = .08$, $P > .60$).

Prevalence of KD and FH

Table 2 shows the age- and sex-specific prevalence of FH and KD. Known diabetes was found in 3.9% of the examined men and 5.0% of women, whereas 1.7% of both men and women had FH. Logistic regression analyses showed no significant sex difference in prevalence for FH subjects ($P > .50$) or for KD subjects ($P > .10$). A statistically significant increase with age was seen for KD ($P < .0005$) and FH ($P < .025$); the increase was higher for KD than for FH.

Treatment with insulin was reported by 54 KD subjects (23 men, 31 women), oral antidiabetic drugs by 105 (38 men, 67 women), and diet only by 68 (28 men, 40 women) patients. Nine subjects (4 men, 5 women) had been diag-

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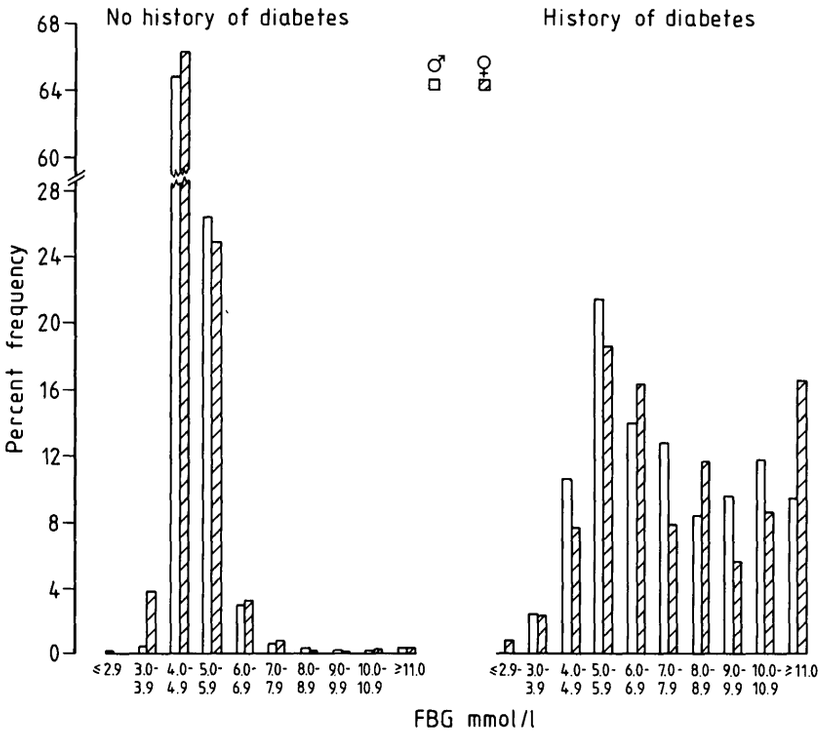

FIG. 1. Distribution of fasting blood glucose (FBG) in 4916 individuals without known diabetes (88 had FBG ≥7 mM = fasting hyperglycemia) and 215 with a history of diabetes. Of responders, 21 subjects with and 140 without known diabetes and blood glucose <7.0 mM were not fasting and therefore not included in the results. Columns to *right* represent summations of individuals with FBG ≥11 mM.

nosed as diabetic patients within the preceding 4 yr but were untreated at the time of the screening. They were included among KD subjects because their FBG was >7 mM.

Fasting and Glucagon-Stimulated C-Peptide

No difference in the distribution of C-peptide in the fasting state or after glucagon stimulation was found between men and women. The distribution of fasting and glucagon-stimulated C-peptide is therefore shown for the sexes together (Fig. 3).

Known diabetes without insulin treatment. As seen in Fig. 3, patients treated with oral drugs and patients treated with diet alone had almost identical distributions of C-peptide, whether fasting or after stimulation with glucagon.

Fasting C-peptide in all KD subjects without insulin treatment was >0.29 pmol/ml; 95% had values >0.38 pmol/ml.

After stimulation with glucagon only one diet-treated and one tablet-treated KD subject had a C-peptide value <0.60 pmol/ml (0.54 and 0.57 pmol/ml). Of KD subjects without insulin treatment, 95% had stimulated C-peptide values >0.72 pmol/ml.

Known diabetes with insulin treatment. Insulin-treated KD subjects had a wide range of fasting and stimulated C-peptide values (Fig. 3). Fasting C-peptide >0.30 pmol/ml was found in 32 (61.5% of insulin-treated KD) patients (Table 3); 95% of the values were >0.06 pmol/ml. Stimulated C-peptide values in KD subjects treated with insulin were ≥0.60 pmol/ml in 32 individuals corresponding to 61.5% of insulin-treated patients (Table 3). Of insulin-treated KD subjects, 95% had values >0.06 pmol/ml.

Fasting hyperglycemia. Fasting C-peptide was >0.30 pmol/ml in all FH subjects except one (0.26 pmol/ml); 95% of fasting C-peptide values in FH subjects were ≥0.42 pmol/ml. Stimulated C-peptide values were >0.60 pmol/ml in all FH subjects except one (0.42 pmol/ml); 95% had values >0.75 pmol/ml.

Prevalence of NIDDM among insulin-treated patients. Of 52 KD subjects treated with insulin, only 20 (8 men, 12 women) had C-peptide values in the IDDM range. Two insulin-treated patients did not want to participate in the β-cell function test and were unclassifiable. If they are included among patients with IDDM, 22 (9.3% of all KD subjects)

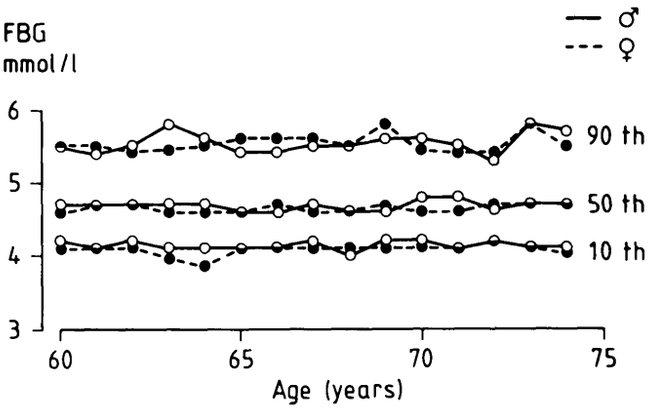

FIG. 2. Ninetieth, 50th, and 10th percentiles for fasting blood glucose (FBG) in 2254 men and 2662 women without known diabetes.

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TABLE 1
Body mass index in nondiabetic subjects and subjects with fasting hyperglycemia and known diabetes

	Men			Women		
	N	Mean	SE	*N*	Mean	SE
Nondiabetics	2258	25.4	0.07	2637	25.4	0.09
Fasting hyperglycemia	39	27.7	0.57	48	29.1	0.75
Known diabetes	91	26.3	0.36	135	28.3	0.48

All examined subjects are included, regardless of whether fasting when examined.

have IDDM. After the prevalence of NIDDM among insulin-treated patients is estimated, a reevaluation of the total prevalence of recognized NIDDM amounts to 84 (3.5%) men and 130 (4.5%) women.

Comparison of fasting and glucagon-stimulated C-peptide. The distributions of fasting and glucagon-stimulated C-peptide values are similar in shape, but the stimulated C-peptide concentrations are shifted to the right compared with the fasting values. In a linear regression analysis, close correlations between fasting and stimulated C-peptide values were found for insulin-treated KD subjects (r = .89), non-insulin-treated KD subjects (r = .80), and FH subjects (r = .79). Regardless of whether fasting or stimulated C-peptide values were considered, the same individuals were classified as having NIDDM and IDDM when the chosen cutoff points were applied (Table 3).

DISCUSSION

The high response rate (92.9%) allows us to describe the total prevalence of known diabetes in this elderly population very precisely. We did not use an oral glucose tolerance test because of the unsolved problems related to the interpretation of the decrease in glucose tolerance with age (21) and were not able to estimate the prevalence of previously unknown diabetics in accordance with the recommendations from the World Health Organization (22) or the National Diabetes Data Group (23). We chose to describe the distribution of FBG in elderly subjects without KD and estimated the prevalence of subjects with FH defined as individuals with FBG ≥ 7 mM.

Distribution of FBG

As in the Rancho Bernardo study (24), FBG did not increase with age from 60 to 74 yr in either sex without KD (Fig. 2).

The FBG did not differ between nondiabetic men and women. This is in agreement with a Danish epidemiological study of heart diseases (25) but in contrast to two American surveys (24,26). In both studies FBG was higher in men than in women even if the difference was less in elderly age groups. In the study by Barrett-Connor (24), corrections were made for obesity, yet the sex difference was seen. Californian men were more obese than women (BMI calculated from Fig. 2 in ref. 24 was 25.3 in men and 23.9 kg/m^2 in women). No sex difference in BMI was found in our study (Table 1). Both sexes in our study were as obese as the Californian men. The discrepancies in the sex ratio in FBG between American and Danish studies may be partly explained by differences in BMI but may also be due to differences in environmental (exercise, dietary habits, hormone treatment) or genetic backgrounds.

Prevalence of KD and FH

The prevalence of KD (4.5%) and FH (1.7%) found in this study differed from the prevalence for similar age groups in the Rancho Bernardo study (KD, 5.9%; newly diagnosed diabetes, 3.2%), even if the diagnostic criterion was almost the same (fasting plasma glucose ≥ 140 mg/dl, ≃ FBG ≥ 6.8 mM) (3). Ascertainment in a national health system does not explain these differences as an overall lower prevalence was found in Denmark. Bias from nonresponders in our study was most likely unimportant, because the response rate was high in the Fredericia survey (92.9%), and the percentage of KD among nonresponders (3.4%) did not differ significantly from that among the group examined (4.5%) (χ^2 = .937, $P > .30$).

The higher total prevalence in Rancho Bernardo than in Fredericia was due to a higher prevalence in men only. In Rancho Bernardo, 7.1% of men >60 yr old had KD, and 3.7% had newly diagnosed diabetes. The prevalence of diabetes in women only showed a tendency to be higher in Rancho Bernardo, because 4.1% had KD and 2.8% had newly diagnosed diabetes (3). This may be explained by differences in life-style and exercise, because our men mainly belong to the working class, whereas Californian men were

TABLE 2
Number of examined individuals with fasting hyperglycemia and known diabetes classified according to sex and age

	Men			Women		
Age (yr)	*N* examined (%)	*N* fasting hyperglycemia (%)	*N* known diabetes (%)	*N* examined (%)	*N* fasting hyperglycemia (%)	*N* known diabetes (%)
60–64	1103 (93.7)	18 (1.6)	27 (2.5)	1191 (93.3)	13 (1.1)	38 (3.2)
65–69	755 (93.4)	8 (1.1)	30 (4.0)	884 (93.1)	16 (1.8)	48 (5.4)
70–74	560 (91.7)	14 (2.5)	36 (6.4)	799 (91.1)	19 (2.4)	57 (7.1)
Total	2418 (93.1)	40 (1.7)	93 (3.9)	2874 (92.6)	48 (1.7)	143 (5.0)

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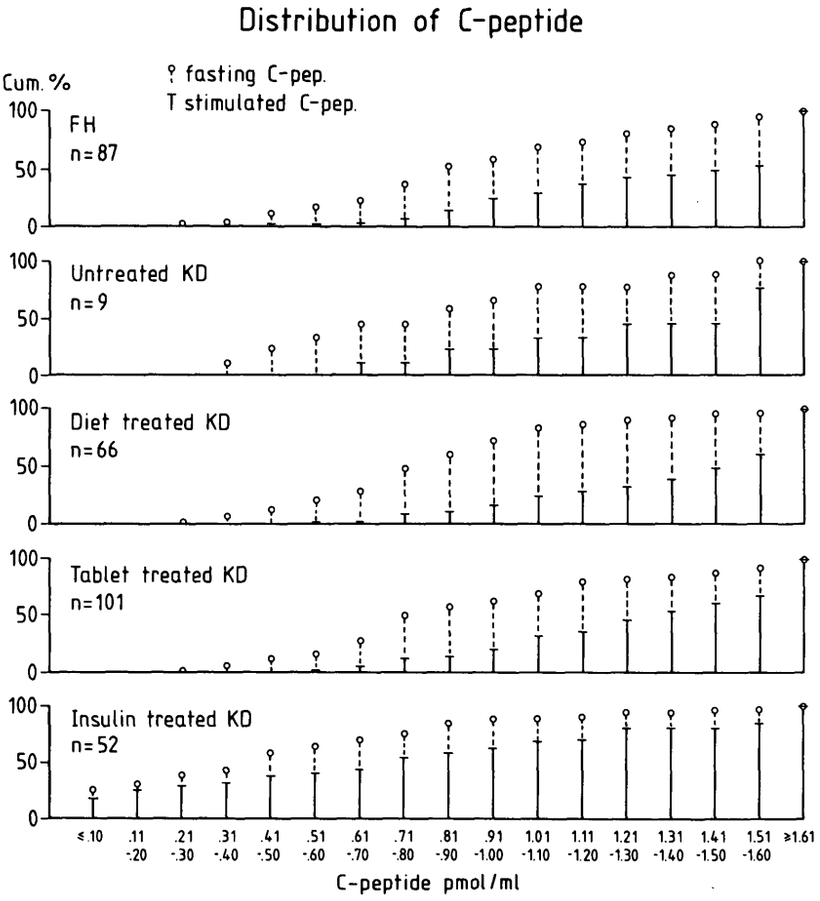

FIG. 3. Cumulated distributions of C-peptide measured after overnight fasting and 6 min after stimulation with glucagon. Both signatures should be measured from line zero. Individuals are classified as subjects with newly diagnosed fasting hyperglycemia (FH) and known diabetes (KD) subdivided according to treatment. Results are shown for 87 FH and 228 KD participating in 2nd testing of β-cell function.

predominantly upper middle class (3). It may also be explained by different genetic factors.

Evaluation of β-Cell Function

Evaluation of β-cell function by C-peptide has been proposed as a method to classify diabetes as NIDDM and IDDM (6–11,27–32). C-peptide was measured in the fasting state (8–11,29,30), after oral glucose intake (27,28), after stimulation with glucagon (6–9,32), or after intravenous glibenclamid-glucose load (31). With two exceptions (10,11), these studies were carried out in selected groups of patients. We measured fasting and glucagon-stimulated C-peptide in an unselected group of patients with KD and newly diagnosed FH.

Known Diabetes Without Insulin Treatment

Distribution of fasting C-peptide values. These showed that 95% of all KD subjects treated without insulin had values >0.38 pmol/ml. This agrees with the results of Garcia-Webb et al. (10) in Micronesians, who have almost exclusively NIDDM. We found that the distribution of fasting C-peptide was similar in untreated patients, in patients treated with diet alone, or in those treated with oral antidiabetics. This suggests that in our study, treatment with oral drugs did not affect the level of fasting C-peptide significantly or only elevated subnormal values of fasting C-peptide to the same level as diet-treated diabetic subjects.

Distribution of stimulated C-peptide values. Stimulated C-peptide values were similar to the fasting values, because 95% of all patients not treated with insulin had values >0.72 pmol/ml.

TABLE 3
Number of subjects with fasting hyperglycemia and known diabetes treated with and without insulin classified by fasting C-peptide and C-peptide after stimulation with glucagon

	Fasting C-peptide value			
	≤0.20	0.21–0.30	0.31–0.40	>0.40
Fasting hyperglycemia				
Stimulated C-peptide <0.60	0	1	0	0
Stimulated C-peptide ≥0.60	0	0	1	85
Known diabetes (non–insulin treated)				
Stimulated C-peptide <0.60	0	0	2	0
Stimulated C-peptide ≥0.60	0	2	7	176
Known diabetes (insulin treated)				
Stimulated C-peptide <0.60	16(15)*	4	0	0
Stimulated C-peptide ≥0.60	0	0	2	30

All C-peptide values in pmol/ml.
*One stimulated C-peptide value was missing; fasting C-peptide value in that patient was <0.06 pmol/ml.

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Thus, our results in an unselected group of individuals with KD confirm the results of studies including selected groups of patients from hospital clinics (7–9,27,30–32).

From the distributions of fasting and stimulated C-peptide values in KD subjects treated with diet and oral antidiabetics, lower limits for NIDDM of 0.30 pmol/ml for fasting C-peptide and 0.60 pmol/ml for stimulated C-peptide seem reliable. Only two patients had C-peptide values below the limits (Table 3). Welborn et al. (30) proposed almost the same cutoff point for fasting C-peptide (0.32 pmol/ml) in hospital clinic patients. Results of other studies (6–9,32) support the cutoff point for stimulated C-peptide. Madsbad et al. (8) reevaluated the therapy of patients treated with insulin and patients treated with diet and oral antidiabetics during hospitalization. Patients with fasting C-peptide ≥0.40 pmol/ml or glucagon-stimulated C-peptide ≥0.60 pmol/ml were well controlled (FBG < 8 mM) without insulin treatment. An overlap between NIDDM and IDDM was observed for fasting C-peptide in the interval 0.20–0.40 pmol/ml.

Known Diabetes With Insulin Treatment

Insulin-treated KD subjects had values for fasting C-peptide scattered over the whole range, confirming previous results from studies of selected groups of diabetic patients from hospital clinics (8,9,30). If we apply the cutoff point of 0.30 pmol/ml for fasting C-peptide concentration, 32 (61.5%) of the insulin-treated KD subjects will be classified as NIDDM.

The stimulated C-peptide concentration and a lower limit for NIDDM of 0.60 pmol/ml used as above classified the same patients as individuals with NIDDM as fasting C-peptide did (Table 3).

Fasting Hyperglycemia

Subjects with newly diagnosed FH had fasting C-peptide values slightly shifted to the right compared with those of KD subjects, in agreement with the study in Micronesians (10). We found that the shape of the distributions of glucagon-stimulated C-peptide closely agreed with the fasting values but shifted to the right (Fig. 3). If the cutoff point of 0.60 pmol/ml had been used, all but one would have been classified as NIDDM. This agrees with the results of Laakso and Pyorala (5), who used clinical criteria, and brings solid evidence to the general impression that most individuals in older age groups with newly diagnosed diabetes without symptoms have NIDDM. Furthermore, it shows that β-cell secretion of insulin is increased compared with KD before clinical symptoms of diabetes become evident.

Reevaluation of Prevalence of NIDDM

We classified 20 (8.5%) of all KD subjects as IDDM by an objective measurement of the cell function, a much higher percentage than the 1% value of individuals >55 yr old found in Finland (5) with clinical criteria. The prevalence of recognized NIDDM in the elderly population in our study then amounts to 3.5% for men and 4.5% for women.

Comparison of Fasting and Glucagon-Stimulated C-Peptide

A close correlation between fasting and glucagon-stimulated C-peptide exists. When the cutoff points based on the lower limits of the distributions of the C-peptide concentrations in non-insulin-treated KD subjects were applied to the insulin-treated KD and FH subjects, all patients were classified in the same way.

The plasma C-peptide concentration after stimulation with glucagon has been proposed to discriminate better than fasting C-peptide when used to decide whether patients with NIDDM require insulin to be well controlled (8). The high level of agreement between fasting and glucagon-stimulated C-peptide in this cross-sectional epidemiological study implies that C-peptide measured in the fasting state is an objective, easy test to use for characterizing the mixed group of insulin-treated elderly patients with IDDM and NIDDM and that the more time-consuming stimulation with glucagon is unnecessary in population-based studies.

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