Prevalence of Insulin Deficiency Among Initially Non-Insulin-Dependent Middle-Aged Diabetic Individuals

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The endogenous insulin secretion capacity of 171 insulin-treated middle-aged persons with diabetes (81 men, 90 women) of the Kuopio University Central Hospital district (population 250,000), East Finland, was measured by the C-peptide response to glucagon. The prevalence of insulin deficiency among initially non-insulin-dependent diabetic (NIDDM) individuals was calculated on the basis of those who were initially treated with diet or oral drugs and 3 yr or more after diagnosis had been treated with insulin and were insulin deficient in this study. The prevalence of complete insulin deficiency (postglucagon C-peptide undetectable) was among initially NIDDM individuals of the same region, 0.7% in men and 1.2% in women. Using the postglucagon C-peptide level of 0.20 nmol/L as a cut-off point, the prevalence of insulin deficiency was 2.0% in men and 1.9% in women and, on the basis of C-peptide level of 0.60 nmol/L, the prevalence of insulin deficiency was 3.5% in men and 2.7% in women. Our data suggest that the deterioration of insulin secretion capacity in NIDDM to the level that leads to insulin dependency occurs less often than has been previously suggested. DIABETES CARE 1986; 9:228–31.

It is a widely held view that in some patients with non-insulin-dependent diabetes mellitus (NIDDM) β-cell function may deteriorate with time and that this may lead to a secondary failure of treatment with oral hypoglycemic drugs and to a need for insulin therapy.[1] The frequency of this phenomenon is, however, unknown, due to a lack of prospective studies on newly diagnosed diabetic individuals who do not initially require insulin but who later become insulin dependent. Indirect information on the frequency of insulin deficiency in NIDDM can be obtained from cross-sectional studies. In this article we report the prevalence of insulin deficiency assessed by C-peptide measurements after glucagon stimulation among initially NIDDM middle-aged diabetic individuals.

STUDY POPULATION AND METHODS

Study population. The Kuopio University Central Hospital district comprises a population of 250,000. All insulin-treated patients in this district were identified on the basis of a central register of drug-treated diabetic individuals maintained by the Social Insurance Institution. A total of 218 insulin-treated patients aged 45–64 yr was found. All were asked to participate in a study to measure endogenous insulin secretion capacity; 171 patients participated (81 men, 90 women), giving a participation rate of 78%. The endogenous insulin secretion capacity was assessed by C-peptide measurements after intravenous glucagon stimulation.[2]

The estimation of the number of diabetic individuals in the Kuopio University Central Hospital district was carried out on the basis of a cross-sectional study based on all medical records of living subjects of 14 health centers, covering a total population of 151,000 inhabitants (13 rural health centers, population base 77,000; Kuopio town health center, population base 74,000). The WHO diagnostic criteria for diabetes mellitus were used.[3] The details concerning the collection of data have been previously reported.[4] On the basis of these data, 47.0% of the diabetic individuals in the age group 45–64 yr were treated with diet only, 38.8% with oral drugs, and 14.2% with insulin. The population living in the municipalities served by these 14 health centers was representative for the whole population of the Kuopio University Central Hospital district with respect to age and sex structure and other relevant demographic characteristics. Therefore, we used percentage distribution of different treatment groups from these 14 health centers to characterize the diabetic population of the Kuopio University Central Hospital district.

The prevalence estimate of insulin deficiency was based on

the observed number of diabetic subjects who initially showed a non-insulin-dependent type of the disease but in whom insulin treatment had been started ≥3 yr after diagnosis and who at the time of this study were receiving insulin and were insulin deficient on the basis of postglucagon C peptide. The details of the procedure for calculating the prevalence estimates are presented in the APPENDIX. As shown in the APPENDIX, the IDDM individuals (those diabetic patients who initially or within 3 yr after diagnosis were treated with insulin and whose C peptide after glucagon was undetectable) were excluded from final analysis.

Laboratory methods. C-peptide measurements after intravenous glucagon stimulation were assessed according to Faber and Binder.[2] C-peptide concentration was measured by radioimmunoassay (Antibody M 1230, Novo, Copenhagen, Denmark). The detection limit of C-peptide concentration was 0.017 nmol/L. In the analysis of data, the postglucagon C-peptide response was divided into three categories: postglucagon C peptide ≤0.017 nmol/L, postglucagon C peptide ≤0.20 nmol/L, and postglucagon C peptide ≤0.60 nmol/L.

Glycosylated hemoglobin A_1 ($GHbA_1$) was determined by commercial column chromatography (Quick-Sep Fast Hemoglobin Test System, Isolab, Akron, OH) after incubation in 0.9% saline solution for 12 h.

Statistical methods. The results are expressed as mean ± SEM. The differences between the groups were assessed by Student's two-tailed *t* test for independent samples.

RESULTS

Characteristics of the study population are shown in Table 1. Diabetic women were older than diabetic men and, correspondingly, their age at diagnosis of diabetes was higher than that of men. No difference in body mass index (BMI), duration of diabetes, duration of insulin treatment, or $GHbA_1$ was observed between the sexes, but the daily insulin dose was higher in men than in women.

TABLE 1
Characteristics of study population

	Men	Women
No. of subjects	81	90
Age (yr)	54.2 ± 0.5	56.4 ± 0.6*
BMI [kg/(m)²]	25.0 ± 0.4	25.9 ± 0.4
Age at diagnosis of diabetes (yr)	39.2 ± 0.8	42.2 ± 1.0†
Duration of diabetes (yr)	15.0 ± 0.9	14.1 ± 0.7
Duration of insulin treatment (yr)	11.5 ± 1.0	9.8 ± 0.9
Insulin dose (U/day)	46 ± 2	40 ± 2†
$GHbA_1$ (%)	10.5 ± 0.2	10.9 ± 0.2

*$P < .001$, †$P < .05$.
Results are given as mean ± SEM.
Comparison between men and women by Student's two-tailed *t* test for independent samples.
BMI = body mass index [wt (kg)/ht (m)²]

TABLE 2
History of permanent insulin therapy by sex and postglucagon C-peptide response

	Number of patients	
Permanent insulin therapy	Men	Women
At diagnosis	34	27
C peptide <0.017 nmol/L	26	24
C peptide ≤0.20 nmol/L	3	2
C peptide ≤0.60 nmol/L	2	1
C peptide >0.60 nmol/L	3	0
Within 3 yr after diagnosis	14	13
C peptide <0.017 nmol/L	4	6
C peptide ≤0.20 nmol/L	5	1
C peptide ≤0.60 nmol/L	4	2
C peptide >0.60 nmol/L	1	4
After ≥3 yr after diagnosis	33	50
C peptide <0.017 nmol/L	4	7
C peptide ≤0.20 nmol/L	7	4
C peptide ≤0.60 nmol/L	8	5
C peptide >0.60 nmol/L	14	34
Total	81	90

As shown in Table 2, 61 diabetic patients (34 men, 27 women) had had insulin treatment since diagnosis of diabetes. Among these diabetic patients, postglucagon C-peptide concentration was undetectable in 26 men (76%) and in 24 women (89%). Three of the diabetic men (9%) showed very high C-peptide levels, suggesting that, although these patients were non-insulin-independent, they had been treated with insulin. In 14 diabetic men and in 13 diabetic women insulin treatment had been started within 3 yr after diagnosis, although use of insulin was not the original mode of treatment. Only one diabetic man (7%) and 4 diabetic women (31%) in this group showed high C-peptide values. Of the 83 diabetic individuals (33 men, 50 women) whose insulin treatment had begun ≥3 yr after diagnosis, 11 patients (4 men, 7 women) had no detectable C-peptide response to glucagon. The mean duration of diabetes was 12.6 yr (range 6–21 yr) and insulin treatment had begun an average of 5.7 yr after diagnosis (range 3–12 yr). Among these diabetic individuals whose insulin treatment had been started ≥3 yr after diagnosis, responder diabetic persons (postglucagon C peptide >0.017 nmol/L, $N = 72$) were older than nonresponders (56.9 yr versus 52.6 yr, $P < .05$) but no difference between these groups was observed in insulin dose, BMI, $GHbA_1$, or duration of diabetes (12.6 yr versus 12.4 yr). As expected, the proportion of diabetic individuals having a C-peptide response >0.60 nmol/L was high in the group in which insulin treatment had been started >3 yr after diagnosis (42% in men, 68% in women).

Table 3 shows the prevalence of insulin deficiency in initially non-insulin-dependent diabetic persons in both sexes. If the criterion was a complete lack of insulin secretion (postglucagon C peptide <0.017 nmol/L), then the prevalence of insulin deficiency was 0.7% in men and 1.2% in women.

TABLE 3
Prevalence of insulin-deficient patients among initially non-insulin-dependent diabetic individuals by sex and postglucagon C-peptide response

Criterion of insulin deficiency by C-peptide response	Prevalence of insulin deficiency (%)		
	Men	Women	Both sexes
C peptide <0.017 nmol/L	0.7	1.2	1.0
C peptide ≤0.20 nmol/L	2.0	1.9	1.9
C peptide ≤0.60 nmol/L	3.5	2.7	3.1

Using higher C-peptide levels as cut-off points, the prevalence increased correspondingly. If the criterion was postglucagon C-peptide level ≤0.60 nmol/L, then the prevalence of insulin deficiency was 3.5% in men and 2.7% in women.

DISCUSSION

In this study insulin deficiency was assessed by C-peptide measurements after intravenous glucagon stimulation, which is an appropriate way to measure endogenous insulin secretion capacity.[5-7] Only insulin-treated patients were studied because diabetic individuals treated with diet or oral antidiabetic drugs are non-insulin-dependent by definition. Diabetic individuals treated with diet or oral drugs who have high C-peptide values after glucagon stimulation do not develop ketoacidosis and are not truly insulin dependent, although hyperglycemia may be better controlled by insulin injections. The prevalence rate of insulin deficiency ("true secondary failure") among diabetic persons who initially showed a non-insulin-dependent type of the disease was calculated in the group of diabetic individuals in whom insulin treatment had been started ≥3 yr after diagnosis to exclude patients with slowly developing IDDM. The calculation of prevalence rate of insulin deficiency among initially NIDDM individuals was not dependent on the proportion of insulin-treated patients, as shown in the APPENDIX. Therefore, the mode of treatment had no influence on our prevalence estimates.

There is no doubt that diabetic individuals showing no C-peptide concentration after glucagon stimulation are insulin dependent. Postglucagon C-peptide values under the limit of 0.20 nmol/L have been shown to correlate with the occurrence of ketoacidosis in insulin-treated patients.[8] These diabetic individuals having C-peptide concentration <0.20 nmol/L are also strictly insulin dependent. Thus, in our study the prevalence of true secondary failure among diabetic persons who had initially been non-insulin-dependent was about 2.0% in both sexes. Madsbad et al.[9] have, in addition, shown that insulin treatment can be stopped in those diabetic individuals whose postglucagon C-peptide concentration exceeds 0.60 nmol/L. We have also tried to stop insulin treatment in diabetic persons with high postglucagon C peptide who participated in this study and our experience confirms the data of Madsbad et al.,[9] although in our patients the lower limit of postglucagon C peptide in those who could be successfully treated without insulin seemed to be somewhat higher (Laakso et al., unpublished results). The prevalence of true secondary failure would have been even higher if a cut-off point of 0.60 nmol/L had been used for postglucagon C peptide (3.5% in men, 2.7% in women). These figures are, however, substantially lower than prevalence estimates for secondary drug failure in NIDDM in former studies ranging from 10 to 30%.[10] The higher prevalence rates in previously published studies are at least partly explained by the use of blood glucose levels as criteria for secondary failure. The degree of hyperglycemia is not, however, a reliable indicator of insulin deficiency. In addition, blood glucose levels for the definition of secondary failure have been variable between different studies.[10] The estimation has not been based on C-peptide measurements in any published studies.

The calculation of prevalence estimates was based on the assumption that there was no difference in the C-peptide response between those insulin-treated patients who participated in this study and those who did not. The participation rate in our series was as high as 78%. Because the diagnosis of insulin deficiency in our study was based on C-peptide measurements after glucagon stimulation, we do not have that information in nonparticipants. The clinical characteristics of participants and nonparticipants were similar, however, and it therefore appears unlikely that nonparticipants would have introduced any major bias in our study.

The natural course of slowly developing but truly insulin-dependent diabetes in older age groups is largely unknown. We assumed in our study that in the age group of 45–64 yr the manifestation of diabetes that is of truly insulin-dependent type would lead to the need for insulin treatment within 3 yr. One cannot, however, exclude definitely even more slowly developing insulin-dependent diabetic patients in our series. In such cases, it is not possible to differentiate between NIDDM and IDDM diabetes on the basis of C-peptide measurements.

In conclusion, our data suggest that the deterioration of insulin secretion capacity in NIDDM to the level that leads to insulin dependency is relatively rare. Prospective studies are, however, needed to confirm this finding.

APPENDIX

Calculation of the prevalence of insulin deficiency among initially non-insulin-dependent diabetic individuals. On the basis of a cross-sectional study published earlier, the proportion of diabetic persons in different treatment groups in 14 health centers in the Kuopio University Hospital district was as follows:[4]

Treatment	Men	Women
Diet	47.0%	46.9%
Oral drugs	39.1%	38.6%
Insulin	13.9%	14.5%

The actual number of diabetic individuals in different treatment groups in the Kuopio University Central Hospital dis-

trict can be evaluated on the basis of insulin-treated patients studied (81 men, 90 women). For example, the number of diet-treated men is (47.0/13.9) × 81 = 274. Similar estimates calculated for the other treatment groups were:

Treatment	Men	Women
Diet	274	291
Oral drugs	228	240
Insulin	81	90
Total	583	621

The prevalence of insulin deficiency (P_{ID}) is calculated from the formula:

$$P_{ID} = ID/NIDD$$

where ID is the actual number of insulin-deficient patients among initally non-insulin-dependent diabetic patients; NIDD is the number of non-insulin-dependent patients.

The number of the non-insulin-dependent patients can be calculated as follows:

$$NIDD = NIDD\ (d) + NIDD\ (o) + NIDD\ (i)$$

where NIDD (d) is diet-treated NIDD; NIDD (o) is oral drug-treated NIDD; and NIDD (i) is insulin-treated NIDD. The number of NIDD (i) depends on the criterion of insulin deficiency that was based on the postglucagon C peptide:

$$NIDD\ (i) = DM\ (i) - IDD$$

where DM (i) is all insulin-treated patients, and IDD is insulin-dependent diabetics. If, for example, the criterion for insulin deficiency is the total absence of C-peptide response, P_{ID} in men is calculated as follows (see Table 2):

$$P_{ID} = 4/(274 + 228 + 81 - 30) = 0.7\%$$

Similarly, the P_{ID} values were calculated in both sexes when different criteria of insulin deficiency were used.

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