

Follow-Up of "Non-Diabetic" Relatives of Diabetics by Retesting Oral Glucose Tolerance after 5 Years

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Summary. Of 743 first degree relatives of diabetics in whom oral glucose tolerance tests had been performed in 1967 488 were re-tested in 1972. Among the original "normals" (n=353) 17.6% had developed a "subclinical" and 1.3% an "overt diabetes" within 5 years. The original "subclinical diabetics" (n=118) showed a remission to "normal" in 35.6% and a progression to "overt diabetes" in 13.6%. 3 out of the 17 formerly "overt diabetics" were found to be "normal" after 5 years and 3 were "subclinical diabetics". Thus the performance of an oral glucose tolerance test is of limited prognostic value in the individual case. In both studies a

higher prevalence of abnormal test results occurred in the older age groups and in overweight subjects. Remission or deterioration did not depend, however, on age or on weight changes. The frequency of abnormal tests was higher in males than in females, but the tendency towards the development of diabetes was more pronounced in females, in accordance with a previous observation of a higher age dependence of glucose tolerance in females.

Key words: Follow-up studies, glucose-tolerance tests, sub-clinical diabetes, remission of diabetes, genetics.

For the investigation of early stages of diabetes mellitus the oral glucose tolerance test with various modifications is the most commonly used method. The question arises as to whether disturbed glucose tolerance allows a reliable prognosis with respect to the development of overt diabetes. This question can only be answered by follow-up studies over several years.

In 1967 oral glucose tolerance tests were performed in 743 subjects reported to be non-diabetic. They were all first degree relatives of known diabetics [10]. Five years later, oral glucose tolerance tests were repeated in most of these subjects in order to get information about the prognostic value of this test. We also tried to obtain information about the influence of various factors, such as age, sex or weight change on changes of glucose tolerance.

Materials and Methods

The 743 first degree relatives of known diabetics tested in 1967 were originally reported to be "non-diabetic" and were 30 years of age or over [10]. With the exception of 18 patients who were found to have clinical diabetes with fasting blood glucose values of 160 mg/100 ml or more all subjects of the previous study were asked to attend a second investigation at the out-patient department of this hospital. Those

who did not attend the clinic and did not reply to the first letter were contacted again.

Table 1 gives the number of those who attended, those who have died, those who refused to attend for various reasons and those who did not reply to both letters. All subjects were asked to take a diet rich in carbohydrates for three days before the test and to present themselves between 7.30 and 9 a.m. after an overnight fast. Venous blood samples of 10 ml were collected before as well as 60, 120 and 180 min after the oral administration of 75 g glucose (Glukose Probetrunck, Fa. Boehringer, Mannheim). Blood glucose was estimated by the autoanalyzer (Glucose-oxidase-method). 5 years ago the glucose estimation was performed by the ferricyanide method according to Hoffmann [9]. During the tests the subjects were seated with some slight walking permitted. Two hours

Table 1. Follow-up for the 743 originally "non-diabetic" relatives of known diabetics tested in 1967

1967	1972	
743	18	not asked again, 1967 found to have fasting values > 160 mg/100 ml
	237	not retested 25 died 117 refused 95 no response
	488	retested

after glucose ingestion the urine was tested for glucose (Glucotest-tape). Height and body weight were measured in all subjects. The ideal body weight and the relative overweight were calculated according to the values of the Society of Actuaries (Geigy tables [5], page 701). A history was taken in each case with particular reference to disorders of the gastrointestinal tract, liver and endocrine organs and to recent diuretic therapy and steroid administration.

A diagnosis of a "diabetic" glucose tolerance curve was made if the sum of the 1-hr and the 2-hr levels was 300 mg/100 ml or more [11]. Among these "diabetic" results we subdivided into "sub-clinical diabetes" if the fasting value was below 120 mg/100 ml or "overt diabetes" if the fasting value was 120 mg/100 ml or more. The term "subclinical diabetes" is thereby used in the sense as proposed by the WHO [4]. It corresponds to "latent diabetes" as defined by Fajans and Conn [7], a term commonly used in medical practice. The 1967 results were re-evaluated according to these criteria.

Results

The group of retested subjects is approximately representative of the original population. The 237 subjects not retested were classified according to the 1967 diagnosis as follows: 146 (= 61.6%) "normals", 78 (= 32.9%) "subclinical diabetics", 13 (= 5.5%) "overt diabetics". These percentages are similar to those of the retested group (72.3%, 24.2% and 3.5% resp.). The number of cases according to the three diagnoses during both tests are given in Table 2. In the whole group there has been a slight degree of deterioration. The mean sum of the 1- and 2-hr blood glucose values amounted to 264.1 ± 78.2 mg/100 ml in 1967 and to 278.4 ± 95.9 mg/100 ml in 1972. This

Table 2. Number of cases according to the given criteria in 1967 and in 1972 (percentages according to the 1967 diagnosis)

$\frac{1967}{1972}$	"normal"	"subclinical diabetic"	"overt diabetic"	sum
"normal"	287 = 81.1%	42 = 35.6%	3 = 17.7%	332 = 68.1%
"subclinical diabetic"	62 = 17.6%	60 = 50.8%	3 = 17.7%	125 = 25.6%
"overt diabetic"	4 = 1.3%	16 = 13.6%	11 = 54.6%	31 = 6.3%
sum	353 = 100%	118 = 100%	17 = 100%	488

difference is statistically significant ($p < 0.05$). The deterioration can also be seen from the prevalence of the various diagnoses: reduction of "normals" from 353 to 332 and increase of "subclinical diabetes" from 118 to 125 and "overt diabetes" from 17 to 31.

There is a surprisingly high percentage of remission to "normal" among "subclinical diabetics" of the first test (35.6%) and even among "overt diabetics" (3 out of 17). The effect of age, sex or weight changes on the frequency of remission and deterioration has also been tested.

Table 3. Mean age in years in October 1972, calculated separately for the various subgroups according to Table 2

$\frac{1967}{1972}$	"normal"	"subclinical diabetic"	"overt diabetic"
"normal"	50.1 ± 12.2	50.6 ± 12.1	52.8 ± 20.5
"subclinical diabetic"	54.6 ± 12.4	57.5 ± 11.0	57.0 ± 18.1
"overt diabetic"	62.8 ± 5.1	62.6 ± 9.7	62.1 ± 11.9

Table 4. Number of males (first figure) and females (second figure) and male to female ratio, calculated separately for the various subgroups according to Table 2

$\frac{1967}{1972}$	"normal"	"subclinical diabetic"	"overt diabetic"	sum
"normal"	130/157 0.83	23/19 1.21	1/2	154/178
"subclinical diabetic"	27/35 0.77	33/27 1.22	3/0	63/62
"overt diabetic"	1/3	9/7 1.28	5/6	15/16
sum	158/195	65/53	9/8	232/256

Table 5. Number of remissions (from "diabetic" to "normal" or from "overt" to "subclinical" diabetic) and deteriorations (from "normal" to "diabetic" or from "subclinical" to "overt diabetic") separately for males and females. Higher tendency of deterioration in females (not significant)

Change of classification 1967-1972	remission deterioration	sex	
		male	female
		27	21
		37	45
$\chi^2 = 1.50$		P = 0.11	

Influence of Age

In 1967 a positive correlation between the age of subjects and the percentage of diabetic test results had been observed. This tendency was again observed five years later. In all 3 subgroups according to the 1967 diagnosis a higher mean age was observed in those who progressed to diabetic stages compared to those who remained unchanged or showed a remission (Table 3).

Influence of Sex

A slightly higher prevalence of diabetes in males and a higher age dependence of glucose tolerance in females compared to males has been described [10]. Thus it might be expected that more females would develop diabetes within the 5 years. The number of males and females in the various subgroups is given in Table 4. In 1967 there were 74 "diabetic" males and 61 "diabetic" females. In 1972, however, these figures were, equally, 78. A remission from "overt" to "subclinical" diabetic or from "diabetic" to "normal" occurred in 27 males and in 21 females (Table 5). Deterioration, however, occurred in 37 males and 45 females. Thus the tendency towards the development of diabetes within the 5 years was more pronounced in females than in males, although this difference is not statistically significant. Comparing the changes of summed blood glucose values in males and females the same tendency, again not statistically significant, can be seen (Table 6).

Influence of Weight

The mean weight in the various subgroups in 1967 and in 1972 is given in Table 7. In both test periods the mean weight was higher in "diabetic" subjects compared to "normals". In all but two subgroups a slight weight reduction was observed. This weight reduction was more pronounced in those who were "subclinical diabetic" in 1967 (a weight reduction had been recommended to these subjects) and even more in those with "overt diabetes".

There was no correlation between weight changes and remission or progression of glucose intolerance in any of the subgroups. This was also checked by the χ^2 -test (Table 8), dividing the whole group of subjects into subgroups according to weight gain or loss and according to increase or decrease of summed blood glucose levels. The χ^2 was 0.529, which is not significant. Similar results were obtained if relative over- or underweight values were taken instead of the absolute values of weight. Again the weight changes within the 5 years did not correlate with changes of glucose tolerance.

Table 6. Number of cases with increase and decrease of the summed glucose levels (1- and 2-h values) separately for males and females. Higher tendency of deterioration in females (not significant)

		sex	
		male	female
Sum of blood glucose levels during oral glucose tolerance test 1967-1972	increased	128	156
	decreased	104	100
$\chi^2 = 1.53$		P = 0.10	

Table 7. Mean weight in 1967 (first figure) and in 1972 (second figure) and average weight change, separately for the various subgroups according to Table 2

1967 \ 1972	"normal"	"subclinical diabetic"	"overt diabetic"
"normal"	75.5-75.2 - 0.3	79.3-77.7 - 1.6	71.5-67.5 - 4.0
"subclinical diabetic"	79.4-80.0 + 0.6	82.5-80.5 - 2.0	84.0-79.0 - 5.0
"overt diabetic"	67.0-67.3 + 0.3	82.2-79.4 - 2.8	81.7-77.2 - 4.5

Table 8. Lack of correlation between weight changes and changes of summed blood glucose values within 5 years

		weight change	
		gain	loss
Sum of blood glucose levels during oral glucose tolerance test 1967-1972	increased	107	146
	decreased	83	130
$\chi^2 = 0.53$		P = 0.46	

Remission to "Normal"

The spontaneous remission of diabetes without treatment is not uncommon, but still regarded as an unusual situation. The detailed results of the 3 patients with remission of what was called "overt diabetes" to "normal" (patient number 84/5, 301/2 and 818/1) and 8 instructive examples of subjects with "subclinical diabetes" in 1967 but normal results in 1972 are therefore given (Table 9). Weight gain was observed in 6 patients. In spite of a weight gain of 7 kg

and an overweight of 23% (compared to 14% in 1967) patient No. 262/2 showed a striking improvement in the glucose tolerance test. Patient No. 885/2 gained 17 kg, became 44% overweight, but also improved strikingly in glucose tolerance.

Progression to "Diabetic" Stages

A progression towards "diabetic" stages (from "normal" to "subclinical diabetic" or from "subclinical" to "overt" diabetic) was to be expected and this

Table 9. 3 persons with remission from "overt diabetes" to "normal" and 8 examples of persons with remission from "subclinical diabetes" to "normal". Test results in 1967 and 1972 and relative overweight and weight change

patient-number	year	glucose tolerance test				urinary glucose	relative weight	weight change
		fasting	60'	120'	180'			
301/2	1967	120	248	172	68	++	- 2%	- 10 kg
	1972	90	115	125	65	Ø		
84/5	1967	132	188	152	112	+	+ 7%	+ 2 kg
	1972	95	117	85	75	(+)		
818/1	1967	128	276	136	80	++	- 20%	+ 2 kg
	1972	108	150	127	60	+		
00/4	1967	90	214	140	90	++	+ 9%	- 1 kg
	1972	85	140	110	70	Ø		
50/3	1967	104	210	130	72	++	+ 37%	+ 1,5 kg
	1972	95	150	95	78	Ø		
73/2	1967	104	206	156	86	++	+ 42%	- 3 kg
	1972	95	163	85	60	Ø		
262/2	1967	92	246	206	54	++	+ 14%	+ 7 kg
	1972	90	150	138	70	Ø		
267/1	1967	70	204	154	70	++	+ 6%	- 9 kg
	1972	90	145	125	75	Ø		
301/4	1967	108	204	148	72	++	- 19%	+ 3,5 kg
	1972	95	115	67	50	Ø		
419/1	1967	104	250	100	50	++	+ 4%	- 1,5 kg
	1972	89	150	80	94	Ø		
885/2	1967	112	220	176	80	++	+ 19%	+ 17 kg
	1972	102	175	118	57	Ø		

Table 10. 4 patients with progression to "overt diabetes" from "normal" and 5 patients with normal tests in 1967 and treatment for diabetes in 1972. Test results and relative overweight and weight changes

patient	year	glucose tolerance test				urinary glucose	relative weight	weight change
		fasting	60'	120'	180'			
271/3	1967	98	144	114	54	Ø	+ 34%	- 7 kg
	1972	122	220	193	97	+		
384/3	1967	98	208	84	72	+	+ 11%	+ 2,5 kg
	1972	120	235	120	80	+		
477/3	1967	96	96	76	72	Ø	0	- 2 kg
	1972	133	220	105	65	(+)		
567/1	1967	114	132	106	90	Ø	+ 10%	+ 2 kg
	1972	120	157	160	105	Ø		
87/5	1967	84	104	100	100	Ø	+ 35%	- 5 kg
153/3	1967	88	138	80	84	Ø	- 14%	unchanged
531/2	1967	92	140	152	152	(+)	- 5%	- 1,5 kg
558/2	1967	106	126	132	96	+	+ 133%	unknown
956/1	1967	96	118	106	76	Ø	+ 10%	- 2 kg

observation is trivial. Only 4 cases were observed with a development of "overt diabetes" from a "normal" state within 5 years (No. 271/3, 384/3, 477/3 and 567/1). These are given in Table 10. 5 patients with "normal" test results in 1967 have developed diabetes which was diagnosed and treated by the local physician. These patients have refused to be retested. 3 of these patients (No. 87/5, 153/3 and 956/1) are treated with oral antidiabetic agents, one (No. 531/2) by diet alone and one (No. 558/2) by unknown means, but not with insulin.

Discussion

The diagnosis of "diabetic" or "non-diabetic" by oral glucose tolerance test is to be considered with caution for several reasons: a) There is no general agreement about the test conditions, for instance the amount of glucose to be administered. b) The criteria of classification are arbitrary and different methods of evaluation do not indicate the same subjects as being diabetic [3, 11, 13]. c) The reproducibility of the test is rather low [12, 17]. d) There is a certain fluctuation from "normal" to "diabetic" and vice versa.

To avoid some of these difficulties test results obtained under similar conditions were compared. Also the criteria used are the same. All criteria are arbitrary, but the summing of the 1- and 2-hr values [11] has turned out to be a very useful index. The terms "normal" and "diabetic" have only been used with quotation marks in this paper in order to demonstrate that this only refers to the given criteria. The same applies to the diagnosis of "subclinical" and "overt" diabetes according to the fasting blood glucose values. "Overt" does not imply any clinical symptoms of diabetes.

It has been shown by several authors [12, 17] that there is a distinct variation in glucose tolerance if tested a few days apart. The causes of this short term variation, usually called "low reproducibility", are unknown (e.g. gastric emptying, sympathetic innervation). Part of this variation, however, may be due to spontaneous fluctuation of glucose assimilation. It is evident that the variation observed within 5 years is to a certain extent also due to "low reproducibility". Since in the present study no short term controls have been performed it is not possible to discriminate between "low reproducibility" and true long term variation. Unfortunately there is one more difficulty which could not be eliminated: the glucose estimations were performed by the glucose oxidase method in 1972 and by the ferricyanide method in 1967. The latter gives about 10% higher values and an even greater deviation

in the higher range. As the values have not been corrected, the absolute values must therefore not be directly compared. All these difficulties may be neglected if subgroups are compared, e.g. the influence of age, sex or weight changes investigated.

In the whole group there is a certain degree of progression towards a more abnormal glucose tolerance. This was observed in spite of the change in the method of glucose estimation giving lower values in 1972. The degree of overall deterioration does not mean very much for the individual cases. A surprisingly high degree of fluctuation, with progression in 82 cases and remission in 48 cases has been observed. 358 subjects were classified with the same diagnosis in both tests. The frequently observed remissions are in accordance with the results of Fajans [6], who stated: "Progression to diabetes may not occur, may occur very slowly or very rapidly, and regression to an earlier stage of abnormality may also occur". O'Sullivan and Hurwitz [13] observed that 27% of young women with grossly abnormal glucose tolerance tests reverted to normal glucose tolerance. A similar degree of variability of diagnoses within several years has previously been described [1, 15, 18], but, for several reasons, these studies cannot be compared directly with the results given in this report.

We tried to correlate the progression or remission with various factors. Although a higher prevalence of glucose tolerance was observed in the older age groups in 1967 and 1972, it was not possible to find a correlation between the tendency to develop diabetes and either age or weight. A significantly higher frequency of abnormal results in the higher weight groups [10] has been observed. This was found again in 1972. But the weight changes within the 5 years did not correlate with changes of glucose tolerance. This is in contrast to what most doctors would predict from their personal experience. No explanation can be given for this surprising result. A similar tendency has also been described by Strauss and Hales [16]. Possibly a long history of overweight is more important for the development of diabetic glucose tolerance than the actual weight at the time of testing.

Berger and coworkers [2], on the other hand, observed a slight but significant correlation between weight reduction and improvement of glucose tolerance among 70 randomly selected obese patients, with subclinical diabetes, within 5 years. The correlation has only been observed in patients younger than 50 years and with less than 100% overweight. The divergence between the observations by Berger and co-workers and the present study may be explained by differences in the composition of the populations. Among the group of relatives of diabetics "genetic"

factors might outweigh "environmental" factors, such as obesity, in the aetiology and pathogenesis of diabetes.

In 1967 [10], in males there was only a slight increase in the percentage of abnormal test results with increasing age. In females, on the other hand, the frequency was much lower in the younger age groups, increased with increasing age and showed a similar frequency as in the males in the older age groups. It would have been expected that after an interval of 5 years the frequency of abnormal results would increase more in females than in males. This was observed, thus confirming the previous results of a high age dependence of glucose tolerance in females but a low age dependence in males. It was speculated that this might depend on the hormonal changes in females around the menopause. Other factors besides age, sex and weight which might influence the glucose tolerance, such as pregnancies, bacterial infections, hyperlipidemia or physical activity, have not been investigated. The numbers of individuals in all these subgroups would be too small for statistical analysis.

The results of the present paper indicate that the performance of an oral glucose tolerance test is of only limited prognostic value in the individual case. Instructive cases of remission to "normal" are given in Table 9. A person with a "normal" glucose tolerance test has an 81.1% chance of not developing a pathologic glucose tolerance within 5 years. The chance of not becoming "overt diabetic" during this time is 98.7%. None of the original cases, including those with "overt diabetes" in the first test, required insulin treatment during the 5 years. Insulin requirement was also not reported from the non-retested subjects.

Considering the high degree of fluctuation, especially the not uncommon remission of "diabetic" glucose tolerance test to "normal", the question as to which are the best criteria for the evaluation of the test is of minor importance. The 11 cases given in Table 9 would have been classified as "diabetic" in 1967 and as "normal" in 1972 according to virtually all proposed criteria.

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