ORIGINALS

The Relationship between Diagnostic Information Obtained from Three Tests for Detecting Mild Diabetes Mellitus

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Summary. The purpose of the study was to evaluate and compare the most commonly used criteria for the interpretation of the oral (OGTT) and intravenous (IVGTT) glucose tolerance tests and the intravenous tolbutamide test (IVTT) and to establish the criteria that give the highest degree of diagnostic agreement. The highest degree of diagnostic agreement was obtained with the following limits: a) blood glucose $>$ or ≤ 120 mg/100 ml within $2\frac{1}{2}$ h after a 100 g OGTT together with b) a k-value of $>$ or ≤ 1.05 as a limit for a 25 g IVGTT and c) a 30 min blood glucose level as percentage of fasting of $>$ or ≤ 77 as limit for a 1 g IVTT. Using these criteria the three tests deemed the same subjects either diabetic or nondiabetic in about $\frac{2}{3}$ of the cases. The best correlation between the blood glucose values of the OGTT and the k-values of the IVGTT and the 30 min values

of the IVTT was obtained using the blood glucose concentrations of the last part of the OGTT. The 2 and the 3 hr values were however equal to the $2\frac{1}{2}$ hr values with regard to the degree of correlation with the values of the intravenous test. The results indicated that the diagnostic disagreement reported previously between the three tests may partly be due to the use of blood glucose values in the first part of the OGTT for the classification of the test and partly due to the screening limits chosen for interpretation of the three test.

Key words: Diabetes mellitus, oral glucose tolerance test, intravenous glucose tolerance test, intravenous tolbutamide test, diagnostic criteria, concordance between tolerance tests.

The increasing interest in discovering diabetes mellitus in its mildest and even asymptomatic forms has two main reasons. The first is that the study of the biochemical and endocrinological disturbances in this stage of the disease might give a clue to the etiology and pathogenesis of diabetes mellitus. The second is that even subjects with subclinical diabetes may require treatment, for they may also develop diabetic angiopathy [1].

The glucose intolerance of patients with mild diabetes is often so slight that more than one test is required to confirm or refute the results. The oral glucose tolerance test (OGTT) has for many years been the most commonly used test for detection of mild diabetes. The intravenous glucose (IVGTT) and the intravenous tolbutamide test (IVTT) were *inter alia* designed to circumvent intestinal absorption, which might influence the result of the oral tolerance test. At present, no objective criteria exist for establishing the superiority of one test procedure over the other in the diagnosis of diabetes mellitus. As pointed out by Lundbaek [2] glucose tolerance tests cannot be used to define diabetes mellitus, but only to define the 'degree of diabeticity'. It would, on the other hand, be desirable if the three most commonly used tests gave the same diagnostic information, i.e. judged the same individuals diabetic or nondiabetic, independently of the tests used.

It is the objective of the present study to compare the diagnostic results obtained with the oral and intra-

venous glucose tolerance tests and the intravenous tolbutamide test, in a group of elderly obese and non-obese persons without clinical symptoms of diabetes, whose fasting blood glucose was below 100 mg/100 ml. The aim of the study is, in addition, to elucidate the factors that affect the degree of concordance of the diagnostic results, and finally to establish screening limits for the tests that give the highest degree of agreement.

Methods

Fifty-six subjects (Table 1) with a fasting blood glucose less than 100 mg/100 ml were studied with an OGTT, an IVGTT and with an IVTT. The subjects were all more than 55 years old, and were divided into a non-obese and an obese group. Obesity was defined as a percentage of average body weight > 115 (Documenta Geigy, Scientific Tables, 6 ed., p. 623, 1960). All subjects consumed a standardized diet containing 300 g carbohydrate for three days before the tests. The subjects were selected from patients referred to Medical Department M, Aarhus Kommunehospital, because of various musculoskeletal disorders, psychoneurosis, bronchitis and obesity. None of the subjects received drugs known to influence glucose tolerance.

The IVGTT (25 g), OGTT (100 g) and IVTT (1 g) were performed as described earlier [3, 4].

In order to find the screening limits that give the highest degree of diagnostic agreement between the

three tests, different criteria were used to classify the tests as diabetic and non-diabetic (Table 2).

The various criteria applied to the *OGTT* are those of Fajans & Conn [5], Mosenthal and Barry [6], the UGDP criterion [7] and the criterion used by the author in earlier studies [3, 4]. These criteria will be referred to in the following as F & C, M & B, UGDP, and author's.

For the *IVGTT* three different criteria have been selected, all within the traditional range. Unger and Madison [8] found during *IVTT* that a 30 min blood glucose value 77% of fasting effectively separated diabetics and non-diabetics. In the present analysis we used this level as well as one slightly higher and one slightly lower.

of 67% was, however, associated with a *different* degree of concordance in diagnosing non-diabetics (66%) and diabetics (83%). Similar concordance of the tests in diagnosing *both* diabetics *and* non-diabetics (obese and non-obese) with our criterion for the *OGTT* was obtained by a k-value of 1.05 for the *IVGTT* and a blood glucose level 30 min after tolbutamide of 77% of the pretest level for the *IVTT*. The highest agreement using the method of F & C were 47 and 58% for respectively the non-obese and the obese group. The corresponding figures for the M & B method were 60% for the obese and 54% for the non-obese group, and for the UGDP criteria 57 and 67% for the non-obese and obese groups respectively.

Table 1. *Clinical data*

	Number ♂/♀	Age years ^a	Height cm	Weight kg	Percentage of average body weight
Non-Obese Subjects	20/11	66 ± 1.9	166 ± 2.2	67 ± 2.5	96 ± 2.5
Obese Subjects	11/14	70 ± 2.0	164 ± 2.4	85 ± 2.7	126 ± 2.8

^a ± S.E.M.

All tests were performed during a hospital stay. The subjects were up and about and not at bedrest except during the night. The tests were performed in the morning after a 12 to 14 hrs fast, with the subjects in the supine position.

Antecubital venous blood was obtained from an indwelling plastic catheter and the blood samples were stored at - 20° C until analysis. Blood glucose was determined on whole blood by a glucose oxidase method in single determinations [9], and all blood samples from the same individual were determined in the same assay.

Correlations were carried out with the distribution-free Spearman's test [10] and the 5% limit was accepted as indicating significance.

Results

The *concordance* of the three tests, i.e. the sum of the cases where the diagnostic results of the three tests agreed in percentage of the total number of agreement-disagreement cases, were compared using four different criteria for the *OGTT* and three for the interpretation of the *IVGTT* and the *IVTT* (Table 3). Using the author's criterion, the best agreement (63%) was found in the *non-obese* group, when k-values of 1.05 and 1.20 were used as cut-off points in the *IVGTT* and 30 min blood glucose values 74 and 77% of fasting blood glucose values in the *IVTT*. In the *obese* the best *concordance* (67%) was found using a k-value of 1.20 and 30 min blood glucose values 74% of fasting blood glucose values in the *IVTT* as limits. In the *obese* group the agreement percentage

The concordance was not increased by using either a higher (125 mg/100 ml) or a lower (115 mg/100 ml) blood glucose concentration as screening limits for the authors criterion, and a k-value of 1.05 as limits for the *IVGTT* and a 30 min blood glucose level 77% of fasting as cut-off points for the *IVTT*.

Table 2. *Screening limits applied to the tests*

<i>OGTT</i>		
Fajans & Conn ⁵	Blood glucose	> 160 mg/100 ml at 1 hr and > 120 mg/100 ml at 2 hrs
Mosenthal & Barry ⁶	Blood glucose	> 150 mg/100 ml at 1 hr and > 100 mg/100 ml at 2 hrs
UGDP ⁷	Sum of blood glucose values at 0, 2 and 3 hrs	> 500 mg/100 ml
Author ^{3, 4}	Blood glucose	> 120 mg/100 ml within 2½ h
<i>IVGTT</i>		
Lundbaek ²	k-value	a. 0.95 b. 1.05 c. 1.20
<i>IVTT</i>		
Unger & Madison ⁸	Blood glucose as percentage of fasting value	a. 80 b. 77 c. 74

The reason why the subjects were diagnosed differently using the author's criterion and those of F & C and M & B was that the subjects judged non-diabetic or diabetic by our criterion did not fulfill the 1 hr limit of F & C's criteria and eight out of ten did

not fulfill M & B's criteria for the 1 hr blood glucose concentration.

From Table 4 it can be seen that in those cases where the use of our criterion and the criteria of F & C, M & B and of UGDP gave divergent results, the IVGTT and the IVTT in a high percentage were in

results of the non-obese and the obese group differed; while the 30 min values of the IVTT of the obese group were significantly correlated to all the post glucose values of the OGTT, only the 2½ and 3 hr values of the non-obese group were significantly correlated to the 30 min values of the IVTT. The

Table 3. Corresponding percentages of three different tolerance tests using different criteria for interpretation of the tests

		Non-obese			Obese		
		0.95	1.05	1.20	0.95	1.05	1.20
<i>OGTT</i>							
Fajans & Conn's criteria	IVTT < 74	40 ^a	43	47	50	54	54
	IVTT < 77	37	36	37	54	54	46
	IVTT < 80	27	27	27	58	58	46
Mosenthal & Barry's criteria	IVTT < 74	50	57	60	33	42	54
	IVTT < 77	47	50	60	42	42	46
	IVTT < 80	33	37	37	42	42	42
UGDP criteria	IVTT < 74	47	53	57	58	63	63
	IVTT < 77	50	53	53	63	63	54
	IVTT < 80	40	43	40	67	67	54
Author's criterion	IVTT < 74	57	63	63	54	58	67
	IVTT < 77	60	63	60	58	58	58
	IVTT < 80	50	53	50	58	58	54

^a the number of tests where the diagnostic results of the three tests agreed in percentage of the total number of agreement-disagreement cases

Table 4. Disagreement between the three kinds of tests using different criteria for interpretation of the OGTT

Author's criterion	Fajans & Conn's criteria	Mosenthal & Barry's criteria	UGDP's criterion
Of 20 non-diabetics: 5/20 had diabetic IVGTT and 4/20 had diabetic IVTT	Of 7 diabetics ^a : 6/7 had non-diabetic IVGTT and 7/7 had non-diabetic IVTT	Of 13 diabetics ^a : 10/13 had non-diabetic IVGTT and 11/13 had non-diabetic IVTT	Of 2 diabetics ^a : 2/2 had non-diabetic IVGTT and 2/2 had non-diabetic IVTT
Of 36 diabetics: 8/35 had non-diabetic IVGTT and 13/35 had non-diabetic IVTT	Of 10 non-diabetics ^b : 8/10 had diabetic IVGTT and 5/10 had diabetic IVTT	0 non-diabetics	Of 7 non-diabetics ^b : 4/7 had diabetic IVGTT and 3/7 had diabetic IVTT

^a Of the 20 non-diabetics according to the authors criterion.

^b Of the 36 diabetics according to the authors criterion.

Limit for k-value = 1.05 and for IVTT₃₀ = 77%

accordance with the judgements of the OGTT using our criterion.

Table 5 shows the degree of correlation between the k-values of the IVGTT and the blood glucose values of the OGTT at different times. The k-values showed the closest correlation to the blood glucose values during the last 1½ hr of the OGTT. There was no correlation between the k-values and the 1 hr values of the OGTT. The relationship between the OGTT and the IVTT is also seen in Table 5. The

k-values of the IVGTT were significantly correlated with the 20-, 30-, 40-, and 50-min values of the IVTT (expressed as percentage of fasting values) in the non-obese group, but only with the 30-, 40-, and 50-min values of the obese group.

Discussion

The present report compares the three most commonly used tests for diagnosing diabetes mellitus, and adapted the criteria for the classification of the tests

in order to get the highest degree of concordance between the results of the tests in diagnosing both non-diabetics and diabetics. The study showed that a high frequency of diagnostic agreement can be obtained between the three tests, provided appropriate criteria are used.

The reason why the use of the criteria of F & C, M & B and of UGDP for the OGTT in nearly every instance showed a lower degree of diagnostic agreement with the intravenous tests than the author's criterion (Table 5), may be that the criteria of these three groups include the blood glucose values during the first part of the OGTT. We found that *the blood*

suggest that the first part of the OGTT is mainly determined by intestinal absorption rather than glucose clearing factors.

A high incidence of diagnostic disparity between the OGTT and the IVGTT has been reported by several workers. This discordance may partly be due to the *inclusion of blood glucose in the first part of the OGTT* in the classification of the tests, and partly due to the *screening limits chosen*.

Dyck and Moorhouse [17] found a good accord between the OGTT and the IVGTT in diagnosing diabetics: 20 out of 21 subjects with an abnormal OGTT had an abnormal IVGTT (95%). On the other hand,

Table 5. Correlations between K-values and blood glucose values during OGTT and IVTT

		Non-obese		Obese	
		R	p	R	p
K-value versus OGTT	-30 ^a	- 0.023	N.S.	- 0.384	N.S.
	- 60	- 0.074	N.S.	- 0.377	N.S.
	- 90	- 0.413	0.05	- 0.414	N.S.
	- 120	- 0.500	0.01	- 0.484	0.05
	- 150	- 0.385	0.05	- 0.382	N.S.
	- 180	- 0.309	N.S.	- 0.413	0.05
IVTT-30 versus OGTT	-30	- 0.186	N.S.	+ 0.533	0.01
	- 60	- 0.203	N.S.	+ 0.514	0.02
	- 90	+ 0.147	N.S.	+ 0.664	0.01
	- 120	+ 0.273	N.S.	+ 0.501	0.02
	- 150	+ 0.473	0.02	+ 0.450	0.05
	- 180	+ 0.398	0.05	+ 0.443	0.05
K-value versus IVTT	-10 ^b	- 0.255	N.S.	- 0.293	N.S.
	- 20	- 0.553	0.01	- 0.396	N.S.
	- 30	- 0.682	0.001	- 0.603	0.01
	- 40	- 0.777	0.001	- 0.585	0.01
	- 50	- 0.580	0.01	- 0.524	0.02
	- 60	- 0.091	N.S.	- 0.396	N.S.

^a Blood glucose concentration 30 min after the oral glucose load.

^b Blood glucose concentration 10 min after the intravenous tolbutamide injection

glucose values during the first hour of the OGTT were not correlated with either the k-values of the obese and the non-obese group, or the 30 min blood glucose values of the IVTT in the non-obese subjects (Table 5). There was a much better correlation between the 2, 2½ and 3 hr values than between the ½, 1 and 1½ hr values of the OGTT and the k-values and the 30 min values of the IVTT. This indicates that if the three tests are to be mutually compared, the blood glucose values of the first hour of the OGTT should not be included in the criteria for interpretation of the tests.

The fact that the incremental changes in glucose load particularly influence blood glucose relatively late in the glucose tolerance test [11, 12, 13, 14, 15],

of 40 subjects with normal OGTT, only 25 had a normal IVGTT (63%). The overall agreement was 74%. If Dyck and Moorhouse had chosen a k-value of 1.30 instead of 1.50 they would have obtained the same overall agreement between the two tests (74%). However, the agreement of the two tests in diagnosing diabetics would have been 15/21 (71%) and in diagnosing non-diabetics 29/40 (73%). In other words, the balance between the two tests in diagnosing *both* diabetics and non-diabetics is much better with a k-value of 1.30 than with 1.50.

Benjamin & Casper [18] found good agreement between the OGTT and the IVGTT in diagnosing non-diabetics but not in diagnosing diabetics. A higher

screening limit for either the OGTT or the IVGTT might have given a better concordance. Kahn *et al.* [19] found that significantly more OGTTs than IVGTTs were abnormal in offspring of two diabetic parents. Either a higher screening limit for the IVGTT or for the OGTT might have given a better concordance between the two tests. Olefsky *et al.* [16] also found a high degree of disagreement between the OGTT and the IVGTT. When the OGTT was either normal or abnormal, then the chance of having a normal or an abnormal IVGTT was 60%. If the IVGTT, on the other hand, was abnormal, then the OGTT was abnormal in only 42% of the cases, and when the IVGTT was normal, the OGTT was normal in 75%.

O'Sullivan and Mahan [20] tried to evaluate the validity of the criteria of M & B, F & C, and the United States Public Health Service (USPHS) criteria, in a large group of young patients with subclinical diabetes, by determination of their accuracy in predicting the subsequent development of overt diabetes. The investigators found over a 10 year period that 52% of patients diagnosed by the USPHS criteria became diabetic, while the more sensitive criteria of F & C and of M & C only showed 32 and 21% decompensation. This kind of evaluation of the validity of a certain criterion is based on the assumption that the natural history of diabetes is characterized by a progression of diabetes from a mild, asymptomatic state to the overt clinical state of diabetes mellitus. It is, however, well known that many patients with mild diabetes continue to have mild diabetes for the rest of their lives. Criteria based on the assumption that the glucose intolerance progressively deteriorates will exclude the permanently mild diabetic subject.

Reports comparing the IVTT with the two glucose tolerance tests are scarce. Unger & Madison designed the IVTT and compared the test with the OGTT in a large group of normal and mildly diabetic subjects [8]. They found that the blood glucose concentration at 20 and 30 min, expressed as percent of pretest level, correctly (i.e., were in accordance with the diagnostic results of the OGTT) segregated diabetic patients from non-diabetics in approximately 95% of cases. Kaplan [21] also found a high degree of concordance between the IVTT and the OGTT. 54 of 55 patients (98%) with overt diabetes had an abnormal IVGTT. Of 73 subjects with subclinical diabetes and abnormal OGTT, 51 had an abnormal IVTT (70%). Pote & Poucher [22], however, found a bad concordance between the IVTT and the OGTT.

This discrepancy previously reported between the diagnostic information obtained by different tests may be explained partly by the screening limits used, and partly by the use of the blood glucose levels in the

first part of the OGTT in the screening limits. Our findings show that by using the criteria shown in Table 6, the overall concordance, i.e., the sum of concordance cases of all *three* tests, as a percentage of all concordance-discordance cases was about 60%. At the same time, the mutual concordance between *two*

Table 6. Screening limits for the tolerance tests

OGTT ^a	Blood glucose fallen or not fallen to ≤ 120 mg/100 ml within 2½ h
IVGTT	k-value $>$ or ≤ 1.05
IVTT	30 min blood glucose in per cent of fasting $>$ or ≤ 77

^a For description of procedure see Methods

tests was about 75% and was similar in diagnosing diabetics and non-diabetics. This does not mean that the criteria in Table 6 are superior to other screening limits, as they are all arbitrary. It does, however, mean that the concordance-discordance frequency in judging the same individuals diabetic or non-diabetic is higher using the screening limits in Table 6 than with the other criteria. The remaining discordance between two tests in about ¼ of the subjects may be attributed to intrinsic variability of the test.

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