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Glucose Storage and Oxidation in Different Degrees of Human Obesity Measured by Continuous Indirect Calorimetry

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Summary. Glucose disposal of a 100 g glucose load has been determined in 26 obese compared with 10 non-obese subjects by means of a new application of continuous indirect calorimetry. The obese subjects were divided into 4 groups, according to their degree of glucose intolerance and their insulin response to the glucose load. Through this division it appeared that subjects with no glucose intolerance were moderately obese while the groups with glucose intolerance showed a higher degree of obesity, glucose intolerance increasing with age. The 10 obese subjects with no glucose intolerance (group A) presented values for glucose disposal similar to those of the control subjects. The 4 obese subjects with impaired glucose tolerance (group B) showed no significant changes in glucose storage and in basal oxidation, but a significant decrease in oxidation in response to the load (11 ± 2 g vs 19 ± 1 g in the control group, $p < 0.02$). The 6 obese subjects with overt diabetes and elevated insulin response to the glucose load (group C) showed a significant decrease in glucose storage (34 ± 6 g vs 63 ± 1 g, $p < 0.001$) but not in oxidation. The 6 obese subjects with overt diabetes and decreased insulin response (group D) showed a significant decrease in glucose storage (25 ±4 g vs 63 ± 1 g, $p < 0.001$) and oxidation (12 ± 1 g, vs 19 ± 1 g, $p < 0.005$). These observations show that in obese diabetics, glucose intolerance results primarily from decreased glucose storage and to a lesser extent from a decrease in glucose oxidation.

Key words: Diabetes, obesity, glucose storage, glucose oxidation, indirect calorimetry, oral glucose tolerance test, glucose intolerance.

The relationship between diabetes and obesity has been known for many years [1, 2, 3]. Abnormalities of carbohydrate metabolism are frequently encountered in obese subjects, with various degrees of glucose intolerance from mild impairment to overt diabetes with either maintained insulin secretion, or marked insulin deficiency.

Two major metabolic mechanisms are responsible for glucose utilization and therefore determine glucose tolerance: glucose storage and glucose oxidation. After glucose ingestion, a major part of glucose is retained in the liver where it is used for glycogen synthesis and triglyceride formation [4]. A small fraction serves to replace glucose produced by the liver in the basal state, while another rather small fraction is oxidized at the periphery in response to the glucose load.

A new application of continuous indirect calorimetry has been developed to make a quantitative estimation of glucose storage and oxidation after an oral glucose load [5, 6]. This method offers the advantage of being non invasive and is easily reproducible.

The purpose of the present study was to measure the modifications of glucose storage and oxidation in obese subjects with different degrees of glucose intolerance and to study the relationship between the changes in glucose tolerance and those of glucose disposal.

Materials and Methods

a) Subjects

Twenty-six obese subjects were studied (Table 1). Their weights were in all cases above 120% of their ideal body weight (IBW), according to the Metropolitan Life Insurance Tables (1959). The protocol was submitted to and accepted by an ethical committee. All subjects gave their informed consent before the studies.

The control group consisted of 10 normal volunteers. It is part of another study [6]. The mean age was 24 ± 1 years and the body weight was 95 ± 2% of IBW.

As some of the obese subjects were older, another group of 5 normal nonobese volunteers was added. The mean age was 55 ± 3 years and the subjects were within 105 ± 3% of their IBW.

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Table 1. Classification and characteristics of the subjects

Subjects	Sex	Age	% ideal body weight
Group A			
1	F	17	130
2	F	21	123
3	F	16	132
4	F	16	129
5	F	23	121
6	M	43	124
7	M	24	129
8	M	32	136
9	M	30	126
10	M	22	131
		24±3	128±2
Group B			
1	F	19	158
2	M	26	137
3	M	58	200
4	F	19	173
		31±9	167±13
Group C			
1	F	34	215
2	F	18	200
3	M	47	127
4	F	41	209
5	F	55	155
6	F	62	125
		43±6	172±17
Group D			
1	F	55	132
2	F	43	236
3	F	66	128
4	M	48	122
5	M	35	261
6	M	68	132
		53±5	169±26
Control group (non obese) n = 10	6 × F 4 × M	24±1	95±2
Control group (non obese older subjects) n = 5	3 × F 2 × M	55±3	105±3

The obese subjects were divided into 4 groups according to their degree of glucose intolerance and to the insulin response to the glucose load. Age and percent ideal body weight of each group are seen in Table 1.

Group A consisted of 10 obese diabetics whose glucose tolerance curve was within normal limits, after a 100 g oral glucose load. Plasma glucose was 86 ± 2 mg/dl at time 0 and 95 ± 5 mg/dl after 2 h.

Group B consisted of 4 obese diabetics with impaired glucose tolerance. Plasma glucose was 84 ± 4 mg/dl at time 0, and 159 ± 10 mg/dl after 2 h. They presented an hyperinsulinaemic response to the glucose load.

Group C consisted of 6 obese diabetics with overt diabetes and increased insulin response (in comparison to the normal group). Plasma glucose was 139 ± 17 mg/dl at time 0 and 266 ± 45 mg/dl after 2 h.

Group D consisted of 6 obese diabetics with overt diabetes but low insulin response to the oral glucose load. Plasma glucose was 271 ± 28 mg/dl at time 0 and 456 ± 25 mg/dl after 2 h.

b) Experimental Protocol

All subjects received an equilibrated diet with a minimal intake of 250 g carbohydrate a day and were not on any medication for at least 48 h prior to the study. In all cases, the test was performed after an overnight fast of at least 10 h.

The subjects were administered a 100 g oral glucose load in 400 ml lemon flavoured water. The oral glucose tolerance test was performed during continuous indirect calorimetry. Blood was withdrawn from an antecubital vein every 30 min, starting 30 min before the glucose load, for measurements of glucose, immunoreactive insulin (IRI) and non esterified fatty acids (NEFA).

Two urine samples were collected: one overnight, the other for the duration of the test. These were used to calculate urinary glucose and nitrogen.

c) Gas-exchange Measurements

Continuous indirect calorimetry was performed as previously described [6, 7, 8]. It allows determinations of both carbohydrate and lipid oxidation rates as well as calculation of the total quantity of glucose and lipid oxidized during the period of the test, the quantity of glucose oxidized at basal rate and in response to the load (suprabasal oxidation). The quantity of glucose stored during the 3 hours of the test was calculated by subtracting from the 100 g ingested glucose, the total quantity of glucose oxidized, urinary glucose loss and excess glucose remaining in the glucose space. The glucose space was considered to represent 25% of the body weight of the subjects [9]. Glucose storage, in this study, corresponds to glucose taken up by tissues without being oxidized, i. e. essentially to glycogen synthesis and deposition. The values of glucose disposal obtained in normal subjects by this method correspond well [5, 6] to those obtained by Felig et al. [10] in their study of splanchnic glucose exchange, using a method based on simultaneous measurement of glucose in hepatic venous and brachial arterial blood.

d) Analytical Procedures

Plasma and urinary glucose were measured by the hexokinase method; plasma immunoreactive insulin (IRI) according to the method described by Herbert et al. [11]; plasma non-esterified fatty acids (NEFA) according to Dole and Meinertz [12]; and urinary nitrogen by the method of Kjeldahl [13].

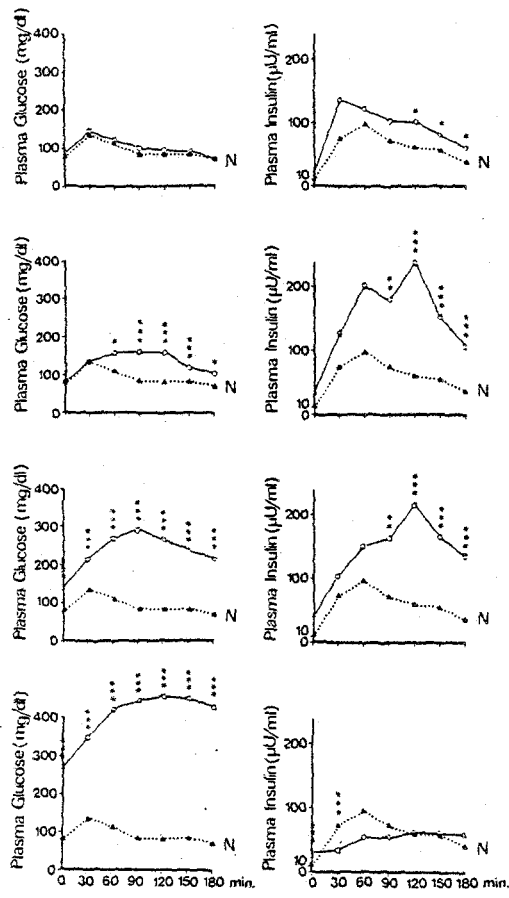
e) Statistical Methods

All data are presented as mean ± SEM. The statistical comparisons between obese and control groups were calculated by means of the unpaired t-test analyses.

Results

The values for glucose disposal together with the plasma glucose IRI curves in the two control groups of 10 young and 5 older non-obese normal subjects and the four groups of obese subjects are presented in Figure 1. NEFA levels and values of total lipid oxidation are seen in Table 2.

In the control group of younger subjects 63 ± 1 g glucose were stored during the 3 hours following the 100 g glucose load, 20 ± 2 g were oxidized in the



	Basal oxidation	Suprabasal oxidation	Changes in glucose space	Urinary loss	Glucose storage
Normal subjects n = 10	20 ± 2	19 ± 1	−2 ± 1	0	63 ± 1
Normal subjects (older group) n = 5	17 ± 1	21 ± 1	0	0	62 ± 2
Ob A n = 10	17 ± 1 NS	22 ± 2 NS	−3 ± 1 NS	0	64 ± 2 NS
Ob B n = 4	23 ± 1 NS	11 ± 2 p <0.02	+6 ± 3 p <0.01	0	60 ± 2 NS
Ob C n = 6	20 ± 2 NS	21 ± 1 NS	+21 ± 7 p <0.005	4 ± 3	34 ± 6 p <0.001
Ob D n = 6	12 ± 2 p <0.02	12 ± 1 p <0.005	+29 ± 6 p <0.001	22 ± 4	25 ± 4 p <0.001

Fig. 1. Plasma glucose and insulin levels (left) and values of disposal (g glucose ± SEM) of the 100 g oral glucose load after 180 min (right) in the four groups of obese subjects (Ob A, B, C, D) and in the two groups of non obese normal controls. Statistical significance of the differences is given in comparison with the non obese control group (n = 10). * = $p < 0.05$; ** = $p < 0.02$; *** = $p < 0.001$

basal state and 19 ± 1 g were oxidized in response to the load. A decrease of 2 ± 1 g glucose was observed in the glucose space at the end of the 3-hour period of the test. The values were not significantly different in the older group, with 17 ± 1 g for basal glucose oxidation, 21 ± 1 g for suprabasal oxidation and 62 ± 2 g for glucose storage. No urinary loss and no significant changes were observed in the glucose space.

In group A composed of 10 obese subjects with normal glucose tolerance, the glucose tolerance curve did not significantly differ from that of the non-obese control group, with a mean fasting plasma glucose level of 86 ± 2 mg/dl and a peak of 143 ± 6 mg/dl at 30 min. Mean plasma IRI levels were however, significantly higher ($p < 0.05$) at 120, 150 and 180 min. Plasma NEFA levels were 498 ± 47 μmol/l at time 0, in comparison with 460 ± 53 μmol/l in the control group (Table 2).

Glucose disposal showed no significant difference from the control group with 64 ± 2 g glucose stored over the 3 hours of the test, 17 ± 1 g glucose oxidized in the basal state and 22 ± 2 g glucose oxidized above basal oxidation. A decrease of 3 ± 1 g glucose was observed in the glucose space. There was no significant urinary loss. Total lipid oxidized during the test was 7 ± 1, compared to 5 ± 1 g in the control group (Table 2).

In group B composed of 4 obese subjects with impaired glucose tolerance, the mean fasting plasma glucose level was within normal limits at 84 ± 4 mg/dl. Glucose levels continued to increase after 30 min, to reach a plateau of 159 ± 14 and 159 ± 10 mg/dl at 60 and 120 min respectively. Mean plasma insulin levels (34 ± 2 μU/ml), already significantly higher than in the control group in the fasting state, increased markedly to reach a peak of 239 ± 42 μU/ml at 120 min. Values were significantly higher than

Table 2. Fasting plasma NEFA levels and total lipid oxidation during the oral glucose tolerance test

	n	NEFA μmol/l	Total lipid oxidation g/180 min
Control group (non obese)	10	460 ± 53	5 ± 1
Group A	10	498 ± 47	7 ± 1
		NS	NS
Group B	4	637 ± 93	12 ± 3
		$p < 0.05$	$p < 0.001$
Group C	6	458 ± 79	9 ± 1
		NS	$p < 0.001$
Group D	6	540 ± 135	12 ± 3
		NS	$p < 0.05$

Statistical differences are expressed in comparison with the non obese control group

those of the control group at 0, 90, 120, 150 and 180 min. The mean fasting plasma NEFA levels were elevated at 637 ± 93 μmol/l.

Glucose disposal showed no significant change in glucose storage (60 ± 2 g) in comparison with the control group, during the 3 hours of the test. Glucose oxidation in response to the load, however, was significantly decreased (11 ± 2 g) while basal glucose oxidation (23 ± 1 g) was within normal limits. A minimal amount of glucose was in excess in the glucose space at the end of the 3 hours. There was no significant urinary loss. Total lipid oxidation during the test was significantly increased (12 ± 3 g) (Table 2).

In group C, 6 obese subjects with overt diabetes and increased insulin response, all the values of the glucose curve were significantly higher than those of the control group. Fasting plasma insulin levels (42 ± 6 μU/ml) were significantly higher than in the control group. A peak of 215 ± 43 μU/ml was reached at 120 min. IRI values were significantly elevated in comparison with the control group, at 0, 90, 120, 150 and 180 min. Fasting plasma NEFA (458 ± 79 μmol/l) were not significantly different from those of the control group.

Calculation of glucose disposal showed a significant decrease in the quantity of glucose stored (34 ± 6 g). Glucose oxidation in the basal state (20 ± 2 g) and in response to the load (21 ± 1 g) was not different from the oxidation in the control group. At the end of the 3-hour period 21 ± 7 g glucose were in excess in the glucose space and 4 ± 3 g were lost in the urine. Total lipid oxidation during the 3 hours of the test was increased to 9 ± 1 g (Table 2).

In group D, the 6 obese subjects with overt diabetes and decreased insulin response to the glucose load, plasma glucose levels were significantly elevated in every sample of the glucose curve. Fasting plasma insulin (34 ± 4 μU/ml) was higher than in the control group. However, the response to the load was significantly decreased at 30 min (35 ± 5 μU/ml) in comparison with the control response, and plasma IRI levels were maintained as a plateau between 50 and 60 μU/ml from 60 to 180 min. Fasting plasma NEFA levels were not significantly increased (540 ± 135 μmol/l).

Calculation of glucose disposal showed a significant decrease in the glucose stored (25 ± 4 g), oxidized at basal rate (12 ± 2 g) and in response to the load (12 ± 1 g). Excess glucose in the glucose space was 29 ± 6 g and urinary loss 22 ± 4 g. The total amount of lipid oxidation during the test period was increased to 12 ± 3 g (Table 2).

Discussion

The values for glucose disposal in the control group were almost identical to those previously reported [5], confirming the reproducibility of the method in estimating glucose oxidation and storage.

Measurement of glucose disposal in obese subjects with different degrees of glucose intolerance shows that deficiency of either glucose oxidation or glucose storage, or of both simultaneously, is involved in the impairment of glucose utilization. The division of the obese subjects into 4 groups, from normal glucose tolerance to impaired glucose tolerance, overt diabetes with high and low insulin response to the glucose load, corresponds to differences in the severity of the disease. Although the number of obese subjects included in the present study is rather small, it appears that subjects withouth glucose intolerance (group A) were mildly obese and younger than those with a higher degree of obesity. Furthermore, glucose intolerance was increased with increasing age (groups B, C and D).

In group A, the patients with normal glucose tolerance, plasma insulin levels were already significantly elevated at 0, 120, 150 and 180 min. This group did not present any alteration of glucose storage and oxidation, in comparison with the normal non-obese group.

Patients from group B, obese subjects with impaired glucose tolerance, presented increased plasma insulin and NEFA levels. Study of glucose disposal showed no change in glucose storage, but a significant decrease in glucose oxidation in response to the load. This observation suggests that the elevated plasma glucose levels in the second part of the glucose curve probably result from this defect. Deficiency in glucose oxidation in response to the load is indeed expected to affect mostly the late phase of the glucose tolerance curve as oxidation is normally low at the beginning of the test and gradually increases to reach its maximum after 90 to 150 min [8, 14].

In group C made up of obese hyperinsulinaemic subjects with overt diabetes, study of glucose disposal showed a significant decrease in glucose storage, while glucose oxidation was within the normal range. The marked insulin resistance demonstrated by glucose intolerance together with high plasma insulin levels was, therefore, not associated with an alteration in glucose oxidation, but with a deficiency in glucose storage. It is not surprising that glucose oxidation was not decreased, since elevation of plasma glucose levels together with the absence of any significant increase in fasting plasma NEFA levels should favour glucose oxidation. Chevaux et al. [15] have indeed demonstrated that elevation of glucose levels at constant insulin levels causes the carbohydrate oxidation to increase.

In the last group (group D) of obese diabetics with low insulin response to the glucose load, glucose intolerance was increased more even than in the preceding groups. The patients showed a decrease in both glucose storage and oxidation. Glucose storage deficiency was definitely a consequence of the decrease in insulin secretion, although insulin resistance is not excluded as an additional factor. The moderate decrease in glucose oxidation might be related both to impaired insulin secretion (which could cause a decrease glucose uptake by the peripheral tissues) and to an increase in lipid oxidation (12 g vs 5 g in the control group during the 3 hours of the test).

It appears from these different observations that alteration of either glucose oxidation or glucose storage may affect glucose tolerance in obesity. In some cases of obesity with glucose intolerance (group B), the latter may result only from decreased glucose oxidation as a result of preferential lipid oxidation which is a consequence of the increased plasma FFA levels. As shown by Flatt [16], the increase in NEFA levels in obesity, in spite of hyperinsulinism is a direct consequence of the extensive increase in the adipose tissue mass. It does not have to be the result of a reduced sensitivity of the fat cells to insulin. In group B, the decrease in glucose oxidation in response to the load corresponds to an increase in total lipid oxidation, from 5 g in the control group to 12 g during the 3 hours of the test in the obese group. This observation is in line with the glucose fatty-acid cycle concept proposed by Randle et al. [17] and further investigated in humans by others [7, 18, 19, 20].

It appears evident that deficiency in glucose oxidation in response to the load should only affect glucose tolerance to a limited extent since, as suggested by Felig et al. [10], only a small portion of the ingested glucose is available for disposal by the peripheral tissues as increased (above basal) glucose utilization.

Cases of overt diabetes both with high or decreased insulin response to the glucose load, show a marked reduction in glucose storage. Deficiency in glucose storage is expected to affect glucose tolerance to a greater extent than deficiency in glucose oxidation. The importance of the liver in glucose disposal was first demonstrated by Scow and Cornfield [21] and Perley and Kipnis [22]. Felig and Wahren [23] confirmed the major role of the liver in glucose uptake by means of direct measurements of splanchnic glucose output in normal subjects. They reported that 55 to 60 g [4] of a 100 g oral glucose load were stored in the liver after 3 hours.

A defect in glucose storage after carbohydrate ingestion is expected to cause glucose intolerance. In physiological conditions, a large fraction of absorbed glucose is stored within 3 hours as liver glycogen which serves as a "reservoir" for glucose. Deficiency in the capacity of this reservoir results in a long lasting increase in glucose in the plasma and the extracellular space. During the 3 hours of observation used in the present study, which correspond to the conventional oral glucose tolerance test, an impaired storage of ingested glucose appears therefore to be a major cause of severe glucose intolerance.

Calculation of glucose disposal in obese diabetics of group D confirms the effect of insulin deficiency on decreased glucose storage. However, insulin deficiency does not appear to be the only cause for decreased glucose storage. Obese diabetics of group C did not lack insulin, as shown by their high insulin response to the glucose load. Their defect in glucose storage is probably due to a decrease in the capacity of the liver to store glucose, knowing the important role played by this organ in glucose uptake. This decreased capacity of the liver to store glucose in the presence of increased insulin secretion suggests that the liver is probably the main focus of insulin resistance in these patients as previously proposed by Felig and Wahren [23].

Decrease in insulin binding to receptors may certainly play a role in insulin resistance in animal and human obesity [24, 25, 26, 27, 28]. Evidence is, however, given both in animals [29] and in humans [30, 31] that decrease in the number of insulin receptors is secondary to hyperinsulinism and is not the primary cause of insulin resistance in obesity. In most patients it appears to be caused by a metabolic abnormality beyond the receptor levels [32, 33].

The application of continuous indirect calorimetry to the study of glucose disposal shows that glucose intolerance results, in the obese diabetic, both from decreased glucose oxidation, which plays a minor role, and decreased glucose storage. Defect in glucose storage can result from insulin deficiency, but probably also from an insulin-independent decreased capacity of the liver to store glucose.

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