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CHANGES IN THE GLUCOSE TOLERANCE OF OBESE SUBJECTS AFTER WEIGHT REDUCTION

BY ROGER S. HUBBARD AND EDGAR C. BECK

(From the Buffalo General Hospital and the University of Buffalo Medical School, Buffalo)

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In a previous publication (1) a summary of studies made upon obese subjects was presented. Included in this article was a discussion of the changes in blood sugar concentration which followed the ingestion of 100 grams of glucose by patients who were overweight. These patients showed a somewhat low tolerance for sugar, an observation which is in accord with that of a number of investigators (2, 3, 4, 5). After dietary therapy had been instituted and continued for some time the patients showed some improvement in the tolerance tests, but the change was slight and was not considered definitely significant. During the past four years the number of patients studied has increased greatly and a fair proportion has been reduced approximately to normal weight by dietary therapy. It has seemed desirable to examine the question again at this time, for in several recent papers (6, 7, 8) it has been suggested that reduction of weight has a definite effect upon the glucose tolerance.

The literature upon the glucose tolerance test is extensive. It has been reviewed recently by Herrmann (9) and by Myers and McKean (10) and will not be discussed here in detail. There are, however, a few points more or less closely connected with the subject of this communication which should be emphasized. Not only does a large number of pathological states affect the test, but certain physiological conditions may also influence it (11). Among the non-pathological causes of variations, age, the presence of various emotional states, including fatigue, and the diet taken prior to the test may be mentioned specifically. It is not strange, therefore, that Lennox (12) and others have observed rather marked irregularities in the results of repeated glucose tolerance tests upon the same subject. The occurrence of these makes it necessary, it seems to the authors, to collect data suitable for statistical analysis before valid conclusions can be drawn concerning the effect of any procedure upon glucose tolerance curves.

The existence of some relationship between obesity and diabetes seems to be quite generally accepted (13). This relationship has led many investigators to study the glucose tolerance of obese subjects. The results of these studies have been somewhat confusing. A few cases of hypoglycemia have been noted in such patients (14, 15, 16) but high blood sugar values have been observed much oftener (5). Frequently there is some other condition present, such as advanced age or hypertension, which appears to have a direct influence upon glucose metabolism. This often makes a study of the specific effect of obesity difficult (5, 17), and some authors have not found satisfactory evidence that obesity itself is closely associated with abnormalities of glucose tolerance (18). Since the results upon untreated obese subjects appear to vary markedly, it is evident that the interpretation of changes after any therapy is difficult.

There are few papers in which the effect of diet and weight reduction is so reported as to be comparable with the results obtained in this clinic. In 1931 Tyner (19) stated that the rise in blood sugar following Brill's test meal (20) was less marked after 12 patients had been on a restricted diet than it was when they were first seen. In three more recent papers (6, 7, 8) other experiments are described. In each of these later studies attention was centered upon the dietary treatment of patients selected because some abnormality of the glucose tolerance test was found in a preliminary examination. Each author shows clearly that dietary therapy, producing loss of weight, was accompanied in these subjects by an improvement in the glucose tolerance. In one of these papers (8) by Newburgh and Conn it is suggested that this improvement is directly associated with the change in weight. Since only patients with abnormal initial tests were included in these studies it is difficult to determine whether the findings are applicable to the average obese subject.

The data given below are based upon studies of patients who presented themselves during the past five years at the out-patient department of the Buffalo General Hospital. Among the preliminary studies was a glucose tolerance test which was carried out as follows: A specimen of venous blood was taken from the patient while he was in the post-absorptive state. He then ingested 100 grams of glucose dissolved in 250 cc. of water. Thirty minutes, one hour and two hours after the glucose was ingested specimens of venous blood were drawn. Blood sugar concentrations were determined by Myers' and Bailey's (21) modification of the picric acid method of Lewis and Benedict (22). Patients were then seen by one of the authors (E. C. B.) who prescribed the diet consisting of 80 grams of protein, 40 grams of fat and 40 grams of carbohydrate described in detail in the preceding article (1). The patients were seen at fortnightly intervals thereafter, and records were made of their weights and of changes in their symptoms. At each visit the diet was discussed and the patients were urged to carry out the treatment carefully. It is probable that the diet was not followed exactly, but the reduction in food intake must have been marked, for substantial losses in weight were shown by the majority of the patients who maintained their relationship with the clinic. When the weight had been reduced to an extent which seemed reasonably satisfactory, the glucose tolerance test was repeated.¹ The present article is based upon a study of 39 patients who were brought approximately to normal weight. No method of selection was used except that patients with diabetic symptoms were not studied. Otherwise, all patients presenting themselves at the clinic whose weight was reduced to an extent which the physician in charge (E. C. B.) considered reasonably satisfactory, and upon whom a second tolerance was obtained after weight reduction, have been included.

Of the 39 patients all but 2 were women. Their

¹ Upon only 5 of the 39 patients were tests carried out between the initial one and the studies made after weight reduction. Two patients were studied twice and 3 once during the period of treatment. Since the therapy was continued for an average period of 350 days, it seems improbable that any differences noted between the two sets of tests could be attributed to adaptation to the procedure.

ages ranged from 25 to 72 years (only one was over 70) and averaged 44 years. Their initial weights averaged 200 pounds and ranged from 151 to 265 pounds. Only 2 weighed less than 160 pounds. In comparison with the figures given in Davenport's table (23), these patients averaged 52 per cent above normal weight. The individual weights ranged from 12 to 97 per cent above normal. Only 2 were less than 25 per cent above normal. The average time during which the patients took the diet before the tests were repeated was 350 days, with extreme values of 196 and 862 days. During this period they lost between 26 and 110 pounds apiece. The average weight lost was 58 pounds. At the end of the period their weights averaged 8 per cent above normal, with a range of from 10 per cent below to 25 per cent above that figure. Only 1 was more than 20 per cent and only 4 were over 15 per cent above normal.

Before proceeding to an analysis of the data obtained upon these patients, it seemed desirable to determine whether the results of the glucose tolerance tests made upon them can be regarded as approximately representative of those of a large group of obese subjects. Table I shows that

TABLE I
Results of glucose tolerance tests made upon patients when they entered the clinic

Blood specimens analyzed	Average values		Median values		Standard deviations	
	*233 cases	†39 cases	*233 cases	†39 cases	*233 cases	†39 cases
	milligrams per 100 cc.		milligrams per 100 cc.		milligrams per 100 cc.	
Specimens were taken before glucose was given....	125±0.8	127±1.5	122±1.0	127±1.9	17±0.3	14±1.1
† hour after glucose...	182±1.4	184±4.6	179±1.7	183±5.8	32±1.0	28±2.1
1 hour after glucose...	183±2.0	191±4.2	181±2.5	186±4.3	47±1.4	39±3.0
2 hours after glucose...	149±1.9	155±3.7	143±2.4	154±4.6	43±1.3	34±2.6

* Under "233 cases" are the results of glucose tolerance tests made upon all of the obese patients who were studied when they first entered the clinic.

† Under "39 cases" are the first results obtained upon the patients who were also studied after their weights had been reduced approximately to normal.

they can be properly so considered, for the averages of the results upon these 39 patients are practically identical with those obtained upon 235 patients who were accepted for treatment by the obesity clinic.

These average initial figures were high but

were not markedly so. The results of the separate tests upon the 39 patients in the series were compared with normal values for the procedure used as given in a recent paper by McCullagh and Johnston (24). In 27, or 69 per cent of the subjects, the fasting blood sugar was higher than 120 mgm. per 100 cc., the value which these authors accept as normal. Eighty-seven per cent of the patients showed some abnormality but, in most instances, the degree of the abnormality was not marked. In 5 of the tests all four blood sugar values were within normal limits. In 9 the fasting blood sugar alone was high, and in only 7 were all four blood sugar concentrations above normal.

It seemed desirable to determine whether a relationship between the degree of the obesity and the relatively slight abnormality shown by the glucose tolerance tests could be demonstrated. Accordingly, the correlation coefficient between the sum of the four blood sugar values and the per cent by which the patients exceeded their ideal weight was calculated. This coefficient was $+0.08 \pm 0.11$. It has been suggested by Ogilvie (5) and Newburgh and Conn (8) that the duration of the obesity indirectly affects the tolerance for glucose and that the age of the patients serves as a rough index of the time during which the patients have been overweight. The correlation coefficient between the age and the sum of the four blood sugar values was therefore calculated. It was $+0.17 \pm 0.10$. Of the 5 patients with completely normal glucose tolerance tests 3 were below and 2 above the average of the ages for the whole series. Of the 7 patients 30 years old or less only 2 showed glucose tolerance curves which were completely normal. Although no positive evidence of a correlation between either the degree or duration of the obesity and the changes in the glucose tolerance curves of these patients was demonstrated, nevertheless the authors believe that there probably is some relationship between the obesity and the changes in the tolerance test. There seems to be no other possible explanation for the occurrence of such a large number of abnormal values in patients selected as these patients were.

In Table II are given the results of glucose tolerance tests before and after weight reduction by the dietary therapy described. There is no

TABLE II
Comparison of glucose tolerance tests carried out before and after weight reduction

Blood specimens analyzed	Extreme range		Median values		Standard deviations	
	*Before weight reduction	†After weight reduction	*Before weight reduction	†After weight reduction	*Before weight reduction	†After weight reduction
Specimens were taken before glucose was given . . .	104-147	100-145	127±1.9	114±1.4	14±1.1	10±0.8
½ hour after glucose . . .	140-266	113-242	183±5.8	161±4.3	28±2.1	32±2.4
1 hour after glucose . . .	128-294	104-278	186±5.3	148±5.1	39±3.0	38±2.9
2 hours after glucose . . .	106-284	84-195	154±4.6	122±3.8	34±2.6	28±2.2

* Under "before weight reduction" are the averages of the results of glucose tolerance tests made when the 39 patients studied were first seen.

† Under "after weight reduction" are the values obtained by an identical procedure after the weights of the patients had been reduced to approximately normal values.

Average values were also computed. They were not significantly different from the median values given, and have therefore been omitted.

doubt that the values found after treatment were much lower than those obtained when the patients were first seen, *i.e.*, that an improvement in tolerance had taken place. The total improvement can be conveniently expressed by calculating the decrease in the sum of the four blood sugar values. The average and median values of this decrease were 115 ± 9 and 130 ± 11 mgm. per 100 cc.

Changes of this order of magnitude are certainly too marked to be attributed to the ordinary causes which produce fluctuations in the glucose tolerance test. They must be associated with some factor which is common to the whole series of patients. Only two such factors seem worth considering. These are the changes in the weight of the patients and the low diet which was fed during the period of therapy. It has been reported that each of these may affect the glucose tolerance test. An attempt was made to determine whether there was any evidence of an effect of either of these two factors upon the glucose tolerance test. The relationship between the change in weight and in the test can be expressed by the correlation coefficient between the per cent change in weight and the change in the sum of the four blood sugar values. This coefficient was $+0.37 \pm 0.09$.² The only possible basis for a

² The correlation coefficient between the loss of weight in pounds and the blood sugar change was $+0.33 \pm 0.10$.

calculation of the effect of diet in these studies was the rather unsatisfactory one based upon the length of time during which the diet was ingested. The correlation coefficient between the number of days on the diet and the total change in the glucose tolerance test was $+0.14 \pm 0.10$. It is clear that these calculations furnish no evidence that the diet has directly produced the improvement in the glucose tolerance test. They do suggest that this improvement may be associated with the decrease in weight.

The individual glucose tolerance curves obtained after treatment were also examined to determine whether many of them were markedly abnormal. In 30 of the 39 patients all of the blood sugar values in such a test were within the normal limits given by McCullagh and Johnston (24). In only 3, or 8 per cent, were the fasting blood sugar concentrations greater than 120 mgm. per 100 cc. Only 3 patients showed high values in more than one of the four blood specimens. Of these 3 only 1 gave high values in all specimens. In the tests upon 4 of the patients a value which was slightly (5 mgm. per 100 cc. or less) below the normal was found in a single specimen. It is evident that the tests upon most of the patients after dietary therapy should be considered normal.

Not only the actual values found in the final tests, but also the differences between the initial and final tests were studied. Only 4 of the patients failed to show a decrease in the sum of the four blood sugar values. These 4 included the 3 patients referred to in the preceding paragraph, who had high blood sugar values in more than one specimen. An examination of the clinical histories of these 4 patients was made to determine whether any explanation could be found for the failure of these tests to respond during treatment as did those of 90 per cent of the subjects studied. The results of this examination were suggestive, but no entirely satisfactory explanation of the failure was found. Three of the 4 patients showed hypertension with retinal signs of arterial damage, findings often associated with abnormal glucose tolerance curves (25), but this clinical condition did not seem to be more marked in these 3 patients than in others in the series. One of these 3 patients was the only subject over 70 years old included, and her advanced

age may have directly affected the glucose tolerance test (26, 27). The fourth patient in the group was suffering from arthritis, and it has been repeatedly reported (28, 29, 30) that most of the patients with this disease have abnormal glucose tolerance curves. However, 3 other patients with arthritis showed an improvement in tolerance following the period of therapy, and it is probably not proper to place great emphasis upon the presence of this disease as an explanation of the failure in this instance.

Since most of the authors who have studied changes in the glucose tolerance test during weight reduction (6, 7, 8) have chosen as subjects persons with distinctly high initial tests, and since the patients discussed in the present paper were not selected in this way, the data were studied to see first, whether there was any correlation between the initial tests and the changes observed after treatment, and, second, whether the patients with tests which were approximately normal showed changes similar to those noted in the majority of the subjects. The correlation coefficient between the sum of the initial four blood sugar concentrations and the change in that value after treatment was $+0.32 \pm 0.10$, probably denoting a significant but not a very marked correlation. Of the 5 patients with all of the four initial blood sugar values within normal limits, 2 showed decreases which were probably within the limit of error of the technical method used, but 2 others showed changes which were greater than the average of the whole series of patients. One of these 5 patients had a concentration of sugar in the specimen drawn 0.5 hours after the ingestion of glucose which was slightly (5 mgm. per cent) below the normal value given by McCullagh and Johnston. All the other values were within the rather wide normal range given by those authors. These results, while they show that the most marked improvement in the glucose tolerance occurs in patients with the most markedly abnormal initial values, show also that the response of practically all obese subjects to weight reduction through dietary therapy is probably essentially the same.

Before proceeding further with a discussion of the results, a somewhat detailed consideration of the known effect of diet upon the glucose tolerance test is necessary. Diets low in food value

are known to influence such tests in two distinct ways. Starvation (31) and prolonged undernutrition (32) frequently produce a lowering of the fasting blood sugar. On the other hand fasting (33) and the ingestion of diets low in carbohydrate (34) cause an increase in the rise of blood sugar which follows the ingestion of a test dose of glucose. To determine the significance of the changes shown in Table II it is therefore necessary to see whether the changes in the fasting blood sugar, in the rise which follows the ingestion of a test dose of glucose, or in both, are significant. The median change in the fasting blood sugar was 17 ± 1.6 mgm. per 100 cc.; all patients but 4 showed some decrease. The decrease in the total rise after glucose ingestion (the sum of the differences between the blood sugar concentration and the value found in the fasting blood) was 93 ± 9.4 mgm. per 100 cc.; all but 4 patients showed some decrease. The median decrease in the maximum rise above the fasting blood sugar level was 36 ± 5.1 mgm. per 100 cc.; only 6 patients failed to show this decrease. It is evident that a large proportion of the 39 patients showed decreases both in the fasting blood sugar and in the rise following the ingestion of the test dose of glucose, and that both changes were significant. Examination of the data available in other reports (6, 7, 8) shows that such findings are usual when reduction in the weight of obese subjects is brought about by dietary therapy.

It seemed desirable to determine whether these changes persisted when a diet more liberal than the one used in the therapy was ingested. The following experiment was devised to investigate this question. After the degree of weight reduction was considered fairly satisfactory, some of the patients were urged to eat a more liberal diet and the amount of food prescribed was increased by the addition of 200 to 250 grams of carbohydrate. After they had taken these improved diets for about two months 25 of the patients returned to the hospital for another glucose tolerance test. They had gained very little weight during this period. The results of all the tests upon these 25 patients are given in Table III. It is evident that there was no apparent decrease in the tolerance following the increase in the diet. Instead there seems to have been a slight further

TABLE III

The apparent effect of weight reduction and diet upon the glucose tolerance tests of 25 patients

Blood specimens analyzed	Median values			Standard deviations		
	*Before weight reduction	†After weight reduction (low diet)	‡After weight reduction (liberal diet)	*Before weight reduction	†After weight reduction (low diet)	‡After weight reduction (liberal diet)
	milligrams per 100 cc.			milligrams per 100 cc.		
Specimens were taken before glucose was given.....	132±2.6	113±1.9	110±1.9	16±1.5	11±1.0	11±1.0
½ hour after glucose....	183±5.8	163±4.6	153±5.5	30±2.7	27±2.6	31±2.9
1 hour after glucose....	189±6.4	160±6.5	153±5.9	38±3.6	33±3.6	35±3.3
2 hours after glucose..	154±6.4	135±4.8	122±3.9	33±3.6	28±2.7	23±2.2

These results were obtained upon 25 patients who were studied three times.

* Under "before weight reduction" are the figures obtained upon these patients when they were first seen.

† Under "after weight reduction—low diet" are the figures when they had been reduced approximately to normal weight while taking the diet first prescribed.

‡ Under "after weight reduction—liberal diet" are the results found when they had been upon a more liberal diet for between one and two months as described in the text.

Averages were also computed. They were not significantly different from the median values given, and have therefore been omitted.

improvement. The median fall in the sum of the four blood sugar values was 34 ± 14 mgm. per 100 cc. This change was largely or wholly due to a change in the rise of blood sugar after the ingestion of glucose, for the median fall in the fasting blood sugar was 2 ± 2.4 mgm. per 100 cc., and that of the decrease in the total rise after the ingestion of glucose was 26 ± 13.1 mgm. per 100 cc. The latter change may correspond to the normal response shown by glucose tolerance tests when an increased amount of carbohydrate is ingested prior to the examination, but it is probably so slight as to deserve no emphasis. The change in the fasting blood sugar certainly is of no significance.

It seems to the authors that only two explanations can be offered for the significant changes produced in the glucose tolerance tests of these 39 patients. The first is a direct effect of diet upon the test. It is possible that when diets low in carbohydrate are ingested for long periods of time they do not cause the usual increase in the blood sugar rise after a test dose of glucose but instead cause a decrease. This seems improbable, but not perhaps wholly impossible. On the basis of such an explanation for the findings, an interpretation of the results obtained after the im-

provement in the diet is very difficult. Statistical analysis afforded no evidence favoring such an explanation. A second possible cause of the results is some direct or indirect effect of weight reduction upon the metabolism of glucose. Such an explanation avoids the difficulty in interpreting the change in the rise of blood sugar after the test dose of glucose. It affords an adequate explanation of the persistence of the improvement when the more liberal diets were ingested. It is supported to some extent by the existence of some degree of parallelism between the change in weight and the improvement in the glucose tolerance. The authors believe that some effect of the change in weight upon the glucose tolerance is probably the correct explanation of the findings presented.³

It is difficult to decide by what mechanism the change in weight may have affected the glucose tolerance. Certain theories have been advanced by investigators who have discussed the rather extreme cases which sometimes simulate diabetes mellitus. Sherrill (35) has suggested that there may be a deficiency of insulin production in obese glycosuric patients. Since Newburgh and Conn (8) showed that such subjects burn glucose as readily as do normal persons, this explanation cannot be considered wholly satisfactory. However, it seems possible that the amount of insulin formed by these subjects does not completely meet the needs of the patients when their weight is maximal but does so after the weight has been reduced. Newburgh and Conn (8) believe that the deposition of fat in the liver prevents that organ from removing glucose from the circulating blood as readily as it normally does. This theory seems adequate to account for the initial abnormality of the blood sugar rise after glucose ingestion, and for the improvement in that rise after weight reduction. It is not quite so clear how the frequent high values of the fasting blood

³ Further evidence favoring the existence of a relationship between variations in weight and in the glucose tolerance test is afforded by the results upon the case of recurrent obesity reported by Newburgh and Conn (8). This patient showed abnormal glucose tolerance curves on two occasions when she was overweight, and normal tests upon two occasions when her weight had been brought to normal by dietary therapy. One of the authors of the present communication (E. C. B.) has 2 patients under observation at the present time who are apparently showing similar variations, but the studies upon them have not been completed.

sugar of obese subjects can be explained by it. This criticism is probably not an insurmountable one, but it does make the authors hesitate to accept the thesis without reservations. It seems best merely to state that in obese subjects the metabolism of glucose is very frequently somewhat different from that of the average normal person, and that when the weight is reduced the degree of this abnormality is very often decreased.

A comparison of previous studies with the present one shows one thing quite clearly. There was no significant qualitative difference between the responses in the group of experiments reported here and those which have been described by other investigators. The quantitative differences, however, were marked. These differences were largely or wholly due to the methods used in selecting the patients. In work previously presented, only patients with markedly abnormal glucose tolerance curves, frequently simulating clinical diabetes (8), were intensively studied. The material for the present study was chosen differently. The admitting office of the out-patient department did not refer patients thought to have diabetes to the obesity clinic. When obese patients with symptoms of diabetes were admitted to the clinic they were referred elsewhere as soon as their condition was recognized, although not more than 3 subjects were rejected during the period covered by the present paper. Such methods of selection must to some extent have weighted the series in favor of patients with little impairment of carbohydrate metabolism. The authors believe the results obtained demonstrate the presence of a mild impairment of carbohydrate metabolism in these patients and a response to therapy which was essentially the same as that shown by subjects with more marked degrees of abnormality. They believe that the following conclusions are justified. Most, although probably not all (6, 14, 15, 16) patients with obesity, show some abnormality in the tolerance for glucose. This abnormality can usually be markedly improved by weight reduction through dietary therapy.

CONCLUSIONS

A study of 39 obese subjects who were selected in such a way as to exclude patients with marked abnormalities in glucose metabolism is presented. The proportion of these patients who showed ab-

normal glucose tolerance tests was high (87 per cent) but the degree of abnormality was not marked. After weight reduction had been produced by dietary therapy, 90 per cent of the patients showed some improvement in the test and only 23 per cent showed any abnormality demonstrable by the methods used. The improvement in tolerance appeared to be due to the weight reduction rather than directly to the diet, for (1) the change in the curve persisted when the amount of carbohydrate fed was increased, (2) was of a type which could not readily be explained by the ingestion of diets low in food value, and (3) paralleled roughly the changes in weight.

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