Modification of Response to the Triamcinolone Glucose Tolerance Test by Treatment with Oral Hypoglycemic Agents

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SUMMARY

(a) From 67 to 87 per cent of the abnormal triamcinolone glucose tolerance curves are improved after treatment with small doses of hypoglycemic drugs.

(b) As the weight reducing diet normalized only 6.6 per cent of the abnormal triamcinolone curves, it is possible to conclude that weight reduction alone is not enough to normalize this test.

(c) The incidence of obstetrical complications (macrosomias, miscarriages, stillbirths, habitual abortion, and congenital malformations) in women with an abnormal triamcinolone test decreases remarkably or disappears after normalization of this test. DIABETES *15*:726-29, October, 1966.

There is considerable evidence to indicate that in a person with a high probability for the later development of diabetes mellitus, vascular changes may be demonstrated even though a standard glucose tolerance test may yield results within normal limits, as arbitrarily defined. Furthermore, it has been postulated that severe obstetrical complications may occur in the development of the diabetic state before impairment of glucose tolerance can be demonstrated by conventional tests. Thus, if prophylactic or therapeutic measures are to be effective in preventing these complications or retarding the occurrence of overt diabetes they should be applied early in the course of the disease.

The goals of this work were: (a) To study the possible beneficial effect of small doses of hypoglycemic drugs attempting a normalization of the results of the triamcinolone test.[1] (b) To analyze in subsequent pregnancies the effects of this normalization.

MATERIAL AND METHODS

Two hundred and forty-three female subjects, with a "normal" standard glucose tolerance test and an "abnormal" triamcinolone glucose tolerance test, and with three or more of the following characteristics, were selected:

(1) Two or more abnormally large babies (4 kg. or more). (2) Sporadic glycosurias during pregnancy. (3) Polyhydramnios. (4) Infants with congenital malformations. (5) Two or more unexplained abortions. (6) Intrauterine fetal deaths. (7) Obesity (more than 15 per cent above ideal body weight). (8) Exaggerated weight increase during pregnancy or puerperium.[2]

These subjects were divided into five groups of similar age and parity (table 1).

TABLE 1

Age, parity and obesity in the groups

Treatment	Phenformin	Tolcyclamide	Tolbutamide	Glycodiazine	Diet
Obesity (15% or more)	58%	38%	37%	43%	100%
Age (years)	23 - 45	26 - 44	17 - 45	26 - 45	24 - 45
Mean age	36	33	32	33	34
Mean parity	5.6	4.5	4.8	5.0	4.7

Group I: Thirty patients treated with a reducing diet only (20 calories per kilogram of ideal weight).

Group II: Thirty-two cases with a reducing diet plus *long-acting phenformin,* in a single dose of 50 mg. daily, with the first meal.

Group III: Forty-three cases with a reducing diet plus glycodiazine (SH-717) 250 mg., in a single daily dose before breakfast.

Group IV: Twenty-eight cases with a reducing diet plus tolcyclamide (K-38), 125 mg. three times a day, before meals.

Group V: One hundred and ten cases treated with a

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reducing diet plus tolbutamide, 125 mg. three times a day, before meals.

There was no special method of selecting the patients in a determined group, except in Group II (phenformin) where 40 per cent of the patients were treated with this drug because they showed an abnormal response to the intravenous tolbutamide test. All patients included in Group I were more than 15 per cent over their ideal body weight.

To carry out the standard and the triamcinolone tests, a 3000 calorie diet containing 300 gm. of carbohydrate was prescribed for at least three days prior to the glucose tolerance tests. The glucose load was 1.75 gm. per kilogram of ideal body weight, with a maximum of 150 gm. Blood samples were taken at zero, one, two and three hours and glucose determined by the Somogyi-Nelson method. The triamcinolone test was performed by giving 8 mg. triamcinolone to subjects weighing less than 66 kg., at eleven hours and at one hour prior to the glucose load. For those in excess of this weight, two doses of 12 mg. were substituted, following the original method outlined in a previous paper.[1]

The tolbutamide test was carried out by the rapid administration of one gram of tolbutamide intravenously. Blood samples were taken at zero, fifteen, thirty, forty-five and sixty minutes.

Criteria Used in the Evaluation of the Curves

The Standard Glucose Tolerance Test (GTT)

NORMAL: Glucose levels below 100, 150, 110 and 105 mg. per 100 ml. at zero, one, two and three hours.

ABNORMAL: Two of the figures at or above normal.[1]

Tolbutamide test

NORMAL: A 33 per cent decrease in the initial serum glucose level at thirty minutes.

ABNORMAL: Less than a 33 per cent decrease in serum glucose at thirty minutes.[1]

The Triamcinolone Glucose Tolerance Test (TGTT)

NORMAL: All blood levels below 115, 170, 135 and 120 mg. at zero, one, two, and three hours, respectively.

SUSPICIOUS: One figure above normal.

ABNORMAL: Two figures at or above normal.[1]

Therapeutic evaluation

The treatment period was arbitrarily established at eight months. Repeat triamcinolone tests were carried out after four months of therapy (first evaluation), and at the end of the program (final evaluation). To perform these tests, the drugs were interrupted for eight days and a hypercaloric diet was instituted three days prior to the test. Post-treatment evaluations after six months, one and two years are now in progress.

The therapeutic response was classified as EXCELLENT, GOOD or NULL.

EXCELLENT: Absolute normalization of the triamcinolone test was achieved.

GOOD: The triamcinolone test was markedly improved, but one figure remained abnormal.

NULL: The triamcinolone test remained abnormal or worsened in spite of treatment.

RESULTS

Final evaluation (eight months of treatment) showed a favorable response, in a high percentage of patients treated with hypoglycemic agents, contrasting with those treated only with a reducing diet, in which only exceptionally was it possible to normalize an abnormal triamcinolone test (figure 1).

In the first evaluation (four months of treatment) the results were the following: Diet 6.6 per cent; phenformin 48 per cent; glycodiazine 61.5 per cent; tolcyclamide 54.5 per cent; and tolbutamide 46 per cent.

Slight dizzy spells and occasional headaches attributed to hypoglycemia were observed in several women. These effects appeared in the third or fourth month of treatment and were controlled in every case by the administration of snacks. No difference in the intensity of these symptoms could be observed in any particular group.

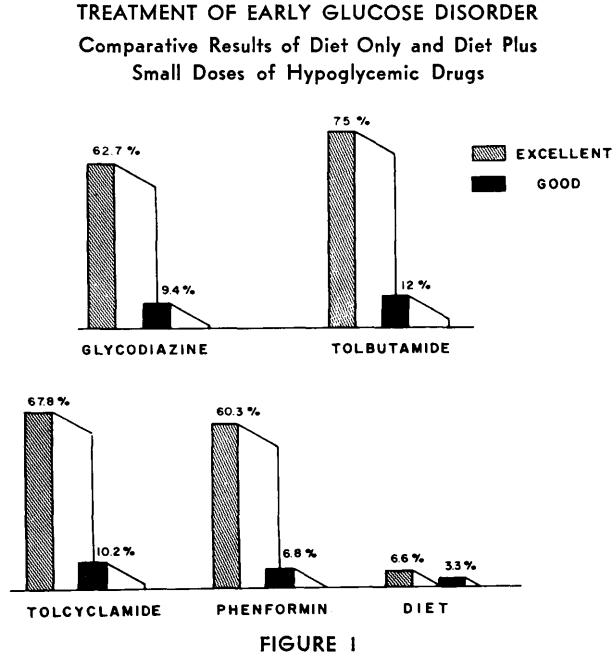

FIGURE 1

Tolerance was generally excellent and there was no need to interrupt any of the treatment programs.

SUBSEQUENT PREGNANCIES

Although it was recommended that the patients avoid pregnancy until they achieved a normal TGTT or completed the eight-months program, six women became pregnant during the last four months of treatment; all six showed a normal TGTT since the first evaluation. Between one and nine months (mean 4.6) after the program was over, sixty-three patients became pregnant. In forty-eight of these with normalization of the triamcinolone curve, there were four miscarriages, one over-size baby and forty-three normal births. In contrast, in the patients whose triamcinolone tests remained abnormal, there were seven miscarriages, three over-size babies, two stillbirths and two congenital malformations in a total of twenty-one pregnancies (table 2).

TABLE 2

New pregnancies after treatment (sixty-nine cases)

	With normal TGTT	With abnormal TGTT
Congenital malformations	0	2
Miscarriages	4	7
Over-size babies	1	3
Stillbirths	0	2
Normals	43	7
Pregnancies	48	21

Of fourteen patients with "habitual abortion," whose TGTT became normal after treatment, ten gave birth to normal children. Three patients whose TGTT remained abnormal, aborted again.

Before treatment, 80 per cent of the patients had one or more of the following findings: acroparesthesias, asthenia, dry-mouth sensation, or slight polyuria findings reported elsewhere by our group in this type of patient.[2] These symptoms disappeared in all but four of the cases where the triamcinolone curve had been normalized.

Sixty-two women complained of pruritus vulvae before treatment. Fifty-eight experienced complete relief after normalization of the triamcinolone test with no local treatment.

DISCUSSION

It is difficult to compare the different drugs, since we cannot ensure that the dosages utilized were really equivalent. Another point which renders a difficult comparison in the particular case of Group II, treated with phenformin, is that 40 per cent of these patients were treated with this drug precisely because no response was obtained previously with the intravenous tolbutamide test. The splitting of the insulin-protein complexes discovered by Antoniades[4] with small doses of tolbutamide may be a factor towards explaining our results with the sulfonylureas.

A high percentage of the patients achieved an excellent or good response in the triamcinolone curve with the different hypoglycemic agents. Reports exist showing the improvement that can be achieved in a standard glucose tolerance test by weight reduction[3]; this has also been observed by us in other trials. Nevertheless, the triamcinolone test showed no such improvement with only a reducing diet.

The incidence of 11.7 per cent of congenital malformations, recorded in this type of patient in our hospital,[5] was reduced to zero. Torres et al.[6] observed similar results in overt diabetic patients with adequate control.

It is difficult to explain the relief of symptoms such as asthenia, acroparesthesias, pruritus vulvae, etc., as it is difficult to understand why they were present before an abnormal GTT.

What is the meaning of the normalization of a triamcinolone glucose tolerance test? Does it mean that the patient has achieved a balance in his intermediate metabolism sufficiently effective to ensure that overt diabetes will not develop in the future? Or does it mean that a temporary normalization has been reached, which may last for months or perhaps years, and which may eventually become altered once again? If this is so, would these patients with an abnormal triamcinolone glucose tolerance test respond once more to the same or different drugs? How long are we going to arrest the progress of the disease? These questions are difficult to answer at short range, and years of observation will be needed in order to gain a clearer view of the future outlook for the patient who has normalized a triamcinolone test after the use of hypoglycemic drugs at low doses.

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Human Red Blood Cell Lipids and Dietary Fat

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of any body weight changes.

Red cell fatty acids of blood samples, taken after eight days on the basal diet, were compared to those taken after the eight-day test period. The milk fat diets caused a large increase in the per cent palmitic acid present in cholesterol esters and phospholipids. Only a slight change in the palmitic acid content of the glyceride portion was observed. This diet containing milk fat also caused an increase in the per cent oleic acid present in phospholipid esters. Only slight differences were reported in the per cent of stearic and linoleic acids in the cholesterol esters, phospholipids, and glycerides.

The corn oil diet caused expected increases in the linoleic acid present in the cholesterol esters and phospholipids, but only a very slight increase occurred in the amount of linoleic acid in the glyceride fraction. There were no other remarkable changes in any of the fractions, though the percentage of palmitic acid decreased slightly in the phospholipid fraction. The phospholipid fraction was the most susceptible to change in the eight-day test period, and the glyceride fraction the least affected by the different fats in the test diets. These results are similar to those reported in rats by Walker and Kummerow.

The relationship between fat and cholesterol in red cells and diet was studied in two groups of twenty-seven and one of eleven males given the basal diet for sixteen days. Serum and red cell cholesterol content was determined at the start of the test period, and after eight and sixteen days.

The red cell cholesterol content of all groups remained remarkably constant during the entire period. Plasma cholesterol decreased in all groups; the average value dropped 56 mg. per 100 ml. for the men and over 40 mg. per 100 ml. in the women after sixteen days.

When the group of men was given the basal diet for eight days and then the corn oil diet for eight additional days, red cell cholesterol again remained constant, but an even greater drop in the average plasma cholesterol occurred (74 mg. per 100 ml.).

Phospholipid levels remained constant during the sixteen-day test period, but the fatty acid present did change. Subjects who ate either the corn oil or milk fat diet for sixteen days had identical red cell concentration of phospholipid phosphorus.

The fat-containing diets caused a slight increase in the cholesterol ester concentration of the red cells. The corn oil diet led to a reduction in an unidentified lipid fraction which the authors suggest might be a glycolipid. The addition of 1,000 mg. of sitosterol to the milk fat diet per 150 calories did not change the lipid composition of the red cells in respect to that found with the milk fat diet alone.

The authors have demonstrated that extreme diet changes for up to sixteen days do not affect red cell lipids. This study confirms that dietary fats have a very slight influence on the composition of lipids in red cells. However, dietary programs designed to reduce serum cholesterol levels are intended for long, perhaps lifetime, use.

It would be of interest to have data similar to those reported in this study from subjects who have been on fat modified diets containing large amounts of polyunsaturated fatty acid for extremely long periods of time, particularly the individuals who show a marked lowering of serum cholesterol levels. It would also be of interest to have similar data on serum and red cell lipids when drugs such as nicotinic acid are used to reduce serum cholesterol levels.

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