

The Effect of Prednisolone on Glucose Tolerance in Respect to Age and Family History of Diabetes Mellitus

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The familial tendency of diabetes mellitus has long been known. Many investigators^{1,2,6,11,12,15,16,18} have suggested that the predisposition to this disorder of metabolism is inherited as a Mendelian recessive character. Neel¹⁰ pointed out that, as well as an increased incidence of diabetes mellitus among the relatives of diabetic patients when compared with nondiabetics, there are also large numbers of abnormal glucose tolerance curves indicative of impaired carbohydrate metabolism in apparently normal relatives of diabetics. His main interest was in the possibility of detecting genetic carriers and he suggested that potentially diabetic patients might transmit the tendency to their descendants. Iannaccone and others⁷ studied hereditary factors and age of onset of diabetes and their findings appeared to confirm the hypothesis of recessive inheritance of diabetes mellitus. This theory was supported by Steinberg,¹⁴ who also pointed out that a high percentage of individuals genetically liable to diabetes are not recognized and that there is no method of predicting when such persons will become clinically diabetic. In 1955 Jackson⁸ suggested that an obscure disorder of carbohydrate metabolism is present from birth and, at a later date, this may be clinically recognized as diabetes mellitus. Conn and Fajans⁵ have made a significant contribution by comparing glucose tolerance before and after loading doses of cortisone in two groups, one showing some family history of diabetes and the other none. They found that a significant number of nondiabetic relatives of diabetic patients showed decreased glucose tolerance following cortisone, when compared with the control series of subjects with no diabetic family history. Further observation of those originally tested has suggested that diabetes occurs more frequently in the positive reactors than in those who have no decrease of carbohydrate tolerance after loading with cortisone.³ West¹⁷ performed a similar study and

confirmed Conn's finding that a significant number of nondiabetic subjects with a family history of diabetes showed a decreased carbohydrate tolerance after loading with cortisone, when compared with a group of normal controls. He also pointed out that a "positive" response to this steroid-glucose test was found more frequently in older than in younger subjects. It is well to remember that in 1924 McLean⁸ pointed out that in apparently normal individuals there was a gradual decrease in carbohydrate tolerance with increasing age. The present investigation is concerned with a modification of Conn's technic to study the effects of prednisolone on glucose tolerance in nondiabetic relatives of diabetic patients in various age groups.

SUBJECTS AND METHODS

In all, seventy-seven persons were investigated. All were ambulant and free of any symptoms or signs suggestive of metabolic disorder. They were divided into two groups, (a) one with a family history of diabetes mellitus and (b) the other with no known family history of the disease. Each of these groups was then subdivided into three groups according to age (table 1).

Group 1 (under twenty years). Fourteen controls and sixteen relatives of diabetics were studied. The mean age of the controls was seventeen years with a range of nine to nineteen years and of the diabetic relatives sixteen years with a range of eleven to nineteen years.

Group 2 (twenty to forty years). Here the twelve controls had a mean age of twenty-six years with a range from twenty-one to thirty-eight years and the eighteen relatives of diabetics a mean age of twenty-seven years with a range from twenty to thirty-nine years.

Group 3 (over forty years). In this group the mean age for the nine controls was sixty-two years with a range from fifty-one to seventy-five years and for the eight relatives of diabetics forty-eight years with a range from forty-two to fifty-three years.

The study was made under normal conditions of en-

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TABLE 1

	Total		Group 1 under 20 years		Group 2 20 to 40 years		Group 3 over 40 years	
	Controls	Diabetic relatives	Controls	Diabetic relatives	Controls	Diabetic relatives	Controls	Diabetic relatives
Number of patients	35	42	14	16	12	18	9	8
Mean age (years)	32	29	17	16	26	27	62	48
Age range (years)	9-75	11-53	9-19	11-19	21-38	20-39	51-75	42-53
Sex distribution								
Male	12	20	1	8	10	9	1	3
Female	23	22	13	8	2	9	8	5

vironment and, although no rigid dietary control was exercised, each subject was closely questioned to ensure that he or she had taken a reasonably well balanced diet with adequate carbohydrate. Two glucose tolerance tests were performed on each subject under these conditions. All were fasted for twelve hours and a sample of capillary blood was then taken. They were immediately given 1 gm. of glucose per kg. body weight in a 20 per cent aqueous solution by mouth and samples of capillary blood were taken half-hourly for the following two hours. The interval between the standard tolerance test and the prednisolone tolerance test in every instance was between three and five days. Before the second test all were given 1 mg. of prednisolone per fourteen pounds body weight twelve hours and again two hours before the test commenced. The blood glucose estimations were made by the method of Somogyi.¹³

RESULTS

The results were examined with regard to changes at each individual point of the glucose tolerance test (GTT). From this preliminary study it was decided that the only changes worthy of consideration were those observed during the second hour. A difference of more than 20 mg. per 100 ml. between the pre- and post-prednisolone blood glucose values at any two of the three points one, one and one half and two hours was arbitrarily taken to indicate a positive result. Figure 1 shows the pre- and post-prednisolone curves of negative reactors among diabetic relatives and these are seen to coincide over these points.

The results from the complete series are shown in figure 2. It is seen that there is an elevation in the GTT following the administration of prednisolone in both controls and relatives of diabetics, but that this is more marked in the relatives when the second half of the curve is examined.

However, when these results are considered in the three age groups, it is seen that most of the significant

NEGATIVE REACTORS AMONG DIABETIC RELATIVES

a) Under 20 years - 8 Subjects b) 20-40 years - 7 Subjects

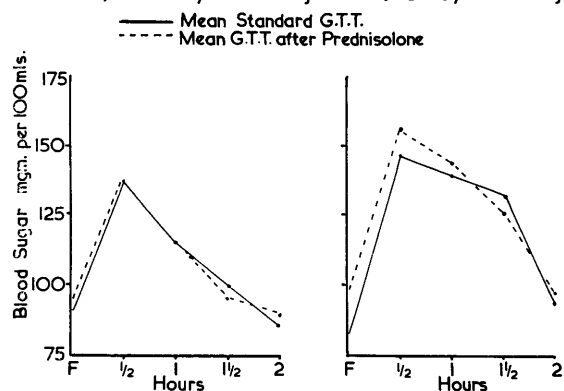


FIGURE 1

TOTAL SERIES

a) Controls - 35 Subjects b) Diabetic Relatives - 42 Subjects

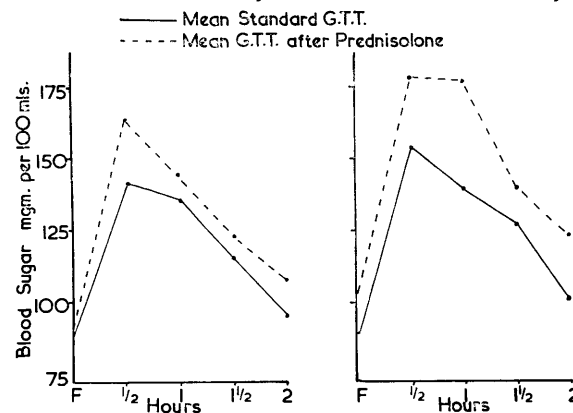


FIGURE 2

decrease in the tolerance of controls occurs because of the large number of positive reactors in the group of control patients over the age of forty years.

The results for Group 1 (under twenty years) are shown in figure 3, where there is a slight elevation in the second half of the mean prednisolone GTT in the

GROUP 1. UNDER 20YEARS

a) Controls-14 Subjects b) Diabetic Relatives-16 Subjects
 — Mean Standard G.T.T.
 - - - Mean G.T.T. after Prednisolone

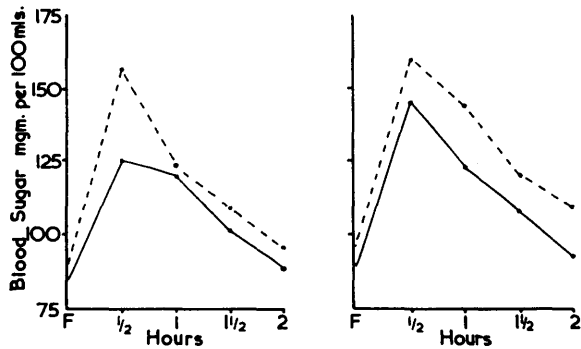


FIGURE 3

controls, among whom there was one positive reactor. By contrast there is conspicuous elevation of the mean prednisolone GTT in diabetic relatives, of whom eight of sixteen were positive reactors.

Figure 4 shows the results for Group 2 (twenty to forty years). There is an insignificant elevation of the mean GTT after prednisolone in the controls, only one of whom was a positive reactor. By contrast, the mean GTT following prednisolone in the relatives of diabetics is markedly elevated because eleven of eighteen were positive reactors.

In Group 3 (over forty years) the controls and diabetic relatives may not be truly comparable because of age differences. However, a positive reaction was given by five of nine controls compared with six of eight diabetic relatives.

GROUP 2 - 20 40YEARS

a) Controls 12 Subjects b) Diabetic Relatives 18 Subjects
 — Mean Standard G.T.T.
 - - - Mean G.T.T. after Prednisolone

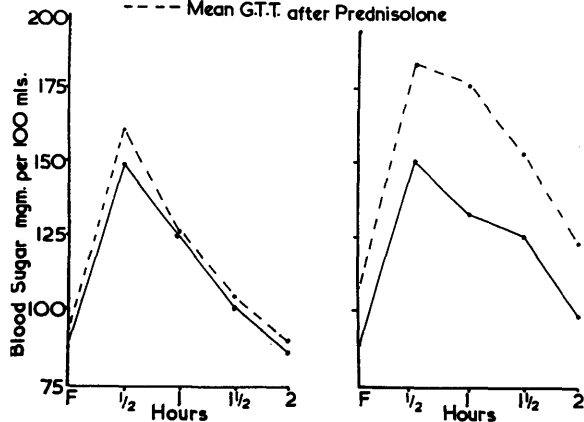


FIGURE 4

GROUP 3 - OVER 40YEARS

a) Controls 9 Subjects b) Diabetic Relatives 8 Subjects
 — Mean Standard G.T.T.
 - - - Mean G.T.T. after Prednisolone

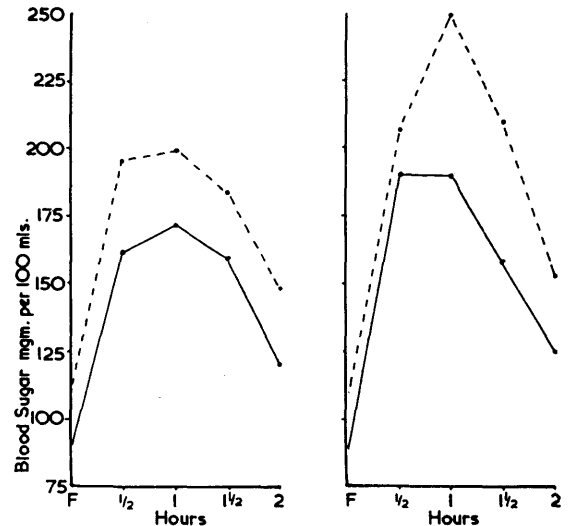


FIGURE 5

the glucose tolerance curves in this group (figure 5) shows that, although the prednisolone GTT in the controls is definitely elevated, the response in the diabetic relatives is much greater.

Table 2 shows positive reactors in diabetic relatives and controls when considered according to age and sex.

DISCUSSION

In any study where age is an unknown factor, difficulties arise in obtaining comparable results. One problem is that of obtaining suitable controls. The group investigated was one of hospital outpatients with some members of staff and some medical students. No healthy children were available for study in a public hospital. For this reason the juvenile controls consisted substantially of a group of female laboratory technicians who were at work during the tests. Another problem in the juvenile group was that a parent of a young child can develop diabetes at a later stage and hence a positive response may be obtained in a subject initially regarded as a control. However, in this series only one of the fourteen juvenile controls has shown a positive response so far.

Healthy adults in the forty to sixty age group were not readily available. To overcome this an attempt was made to use long-term orthopedic inpatients as control subjects at a period not less than three weeks after injury or operation. They showed a marked and uniform

TABLE 2
Positive reactors in relation to age and family history

	Total		Group 1 under 20 years		Group 2 20 to 40 years		Group 3 over 40 years	
	Controls	Diabetic relatives	Controls	Diabetic relatives	Controls	Diabetic relatives	Controls	Diabetic relatives
Number of patients	35	42	14	16	12	18	9	8
Positive reactors								
Number	7	25	1	8	1	11	5	6
Percentage	20	58	7	50	8	61	46	75

loss of carbohydrate tolerance and gave strongly positive reactions after prednisolone, suggesting that either injury or hospitalization may alter tolerance appreciably. The curves in many instances resembled the type observed during the feeding of a high fat diet. Such patients were considered unsuitable.

The controls in Group 3 consisted of hospital outpatients with trivial illnesses having no effect on carbohydrate metabolism. They were somewhat older than the diabetic relatives investigated. Studies in this age group were complicated because of the progressive loss of carbohydrate tolerance with increasing age (figure 6a) which is accentuated by prednisolone (figure 6b).

The results of this investigation confirm the findings of Conn and Fajans⁵ in that the relatives of diabetics as a group show a greater decrease in carbohydrate tolerance following the administration of a glucogenic steroid when compared with a control group (figure 2). This decrease is mainly shown during the second hour of the test, a fact also noted by Conn.⁴

The decrease in glucose tolerance in the second hour of the test following prednisolone is seen in all groups

of diabetic relatives. The change is not so marked in the juvenile group as in Group 2 (figures 2 and 3). This supports the finding of West¹⁷ who considered the response to this test increased with age. The older group (over forty years) show an even larger response to prednisolone but also show some loss of standard glucose tolerance (figure 5b).

Similarly, the older control group show a greater response to prednisolone and a greater number of positive reactors (46 per cent) than any of the other control groups. Since no preselection according to preliminary GTT was employed in this investigation, this group is not comparable to the results reported by Conn and Fajans.⁵

Thus, the test under these conditions can be considered reliable up to the age of forty years, although beyond this age it becomes less reliable. This is due in part to the marked loss of glucose tolerance with advancing age (figure 6). Also, the relatives of diabetics in this age group are often siblings of those who have already developed diabetes and who may well represent the genetic type not liable to the disease.

It is of interest that, in two sets of identical twins studied, both nondiabetic twins fit these criteria in showing a tendency towards diabetes. The first were twin boys aged fourteen years with a direct paternal family history of diabetes. When one twin developed diabetes, a prednisolone GTT was performed on the other. He showed a marked positive response and less than twelve months later developed frank diabetes requiring insulin.

The second pair of twins were girls with no family history of diabetes. One presented with diabetes mellitus in July 1952. At this time, and in 1955, standard GTT's performed on her twin sister were quite normal but in 1957 she showed a positive reaction to a prednisolone GTT. However, she has not shown any sign of diabetes as yet. It is of interest to note the absence of any other family history in her case and its presence in the previous one.

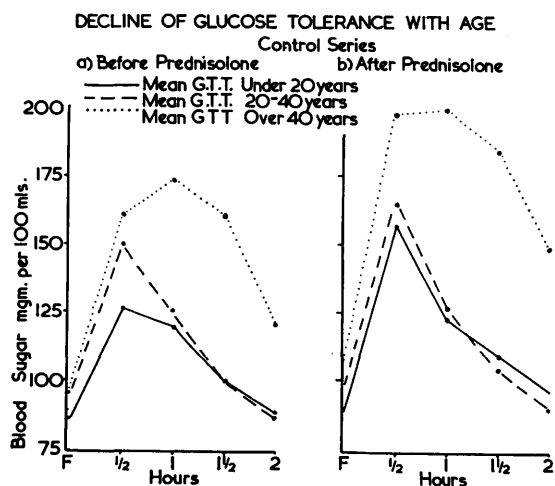


FIGURE 6

Altogether three subjects studied have developed diabetes since the tests were done. All three were positive reactors under the age of forty years.

It has been observed that in both the control and experimental series the administration of prednisolone resulted in a significant increase in blood glucose of similar magnitude at thirty minutes. No explanation can be offered for this finding. It is possibly due to a more rapid absorption of glucose produced by the action of the steroid.

Consideration of the results obtained emphasizes the necessity of proper selection of controls and the fallacy of the use of a control group within narrow age limits (such as students) for this type of study. Also, MacLean's⁹ finding of decreasing glucose tolerance with increasing age is too often forgotten.

Only a prolonged follow-up can show whether those diabetic relatives giving a negative response to the test are less prone to develop the disease than their fellows with a positive response, and thus give a final evaluation of the test.

SUMMARY

The effect of prednisolone on glucose tolerance has been studied with respect to age in forty-two subjects with a diabetic family history and compared with a control group of thirty-five subjects with no diabetic family history.

It has been found that prednisolone produces a greater impairment of glucose tolerance in the relatives of diabetics than in the control series. The significant changes in the prednisolone GTT are found in the second hour. The test appears reliable up to the age of forty years. The possible significance of the findings is discussed.

SUMMARIO IN INTERLINGUA

Le Effecto de Prednisolona Super le Tolerantia pro Glucosa, con Respecto al Etate e al Historia Familial de Diabete Mellite

Le effecto de prednisolona super le tolerantia pro glucosa esseva studiate con respecto al etate in quarantaduo subjectos con historias familial de diabete e compare con un gruppo de controlo de trenta-cinque subjectos sin historia familial de diabete.

Esseva trovate que prednisolona produce un plus marcate disturbance del tolerantia pro glucosa in consanguineos de diabeticos que in le subjectos de controlo. Le alterationes significative in le test de tolerantia pro glucosa a prednisolona se incontra in le secunde hora. Le test pare esser digne de confidentia usque al etate de

quaranta annos. Le signification possibile del constatationes es discutite.

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