Acta Dermatovener (Stockholm) 50: 440–444, 1970

GRANULOMA ANNULARE

Cortisone-glucose Tolerance Test in a Non-diabetic Group

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Abstract. Thirty patients with localized granuloma annulare, three with disseminated granuloma annulare and nine with non-diabetic necrobiosis lipoidica have been studied once with the cortisone-glucose tolerance test. One-third of the necrobiosis cases proved to be latent diabetics, which is the expected frequency from the literature. No connection was found between granuloma annulare and latent diabetes.

It has long been discussed if there is a relation between diabetes mellitus and granuloma annulare (GA) because of the histologic similarity between granuloma annulare and necrobiosis lipoidica (NL) (21), which in turn is strongly connected with diabetes (2, 8, 12). Rhodes and her colleagues have recently found that 10 out of 30 non-diabetic patients with GA had a pathologic prednisone-glycosuria test indicating a stage of latent diabetes (15). Stimulated by this study we have examined carbohydrate metabolism in patients with common superficial GA, disseminated GA and non-diabetic NL.

MATERIAL AND METHODS

Patients. The series comprises: 30 patients with the usual superficial GA, 3 patients with disseminated GA and 9 patients with NL. All patients were examined by at least two experienced dermatologists. Most patients were biopsied. No patient had earlier known diabetes. They all had normal fasting blood sugar; urinary tests for glucose were negative. Of the 30 patients with localized GA, 8 had a family history of diabetes in a first- or second-order relative. The investigations were made at the hospital. No patient had been operated upon or had had an infection during the last 3 months before the study. No woman was pregnant. Among the GA patients, one woman was hypertensive and was taking a thiazide, an another woman had been operated on earlier because of thyreo-toxicosis and was now taking thyroxine; both of them, however, had normal tests. In the necrobiosis group no patients were taking drugs known to affect carbohydrate metabolism or had endocrine diseases. For further details, see Table I.

Control subjects. This group comprised 15 non-obese hospital in-patients with non-endocrinological conditions, e.g. eczema, drug eruptions, leg ulcers, etc. They had not suffered recent operations or infections and had not been treated with drugs known to affect carbohydrate metabolism. None were known diabetics. They all had normal fasting blood sugar and urinary tests for sugar were negative. For further details, see Table I.

Psoriatics were not included in the study as control subjects, as a recent study indicates that 3 out of 10 psoriatics have a pathological prednisone-glycosuria test (14).

Oral glucose tolerance test (GTT). After 3 days of high carbohydrate diet, the patients (fasting) were in the morning given 1 gram glucose/kg body weight with a maximum dose of 70 g. No smoking was allowed for several hours before, or during the test. During the test they were in bed. Blood glucose was determined every 15 min for 3 hours in capillary blood by a glucose-oxidase method (13). The oral GTT was considered diabetic if the glucose two-hour value was greater than 130 mg/100 ml (1), equivocal if between 110 and 130 mg/100 ml, and normal if lower than 110 mg/100 ml.

Cortisone-glucose tolerance test (CGTT). This test was performed the day after the GTT and was done according to Conn & Fajans (4). The patient was twice given 50 mg cortisone acetate orally, $8\,^1/_2$ hours before and 2 hours before the oral GTT started. Those patients whose body weight exceeded 72.5 kg, were given 62.5 mg cortisone acetate instead with the same time intervals. The CGTT was considered diabetic if the blood sugar level was 150 mg/100 ml or higher 2 hours after the glucose ingestion (1).

RESULTS

Glucose tolerance test. (Fig. 1). Only 1 of the 30 patients with the usual superficial GA had a

Table I. *Clinical data of patients and control subjects*

	Localized granuloma annulare	Disseminated granuloma annulare	Necrobiosis lipoidica	Control subjects
Males/ Females	5/25	1/2	0/9	4/11
Age				
<20 yrs	9			2
20–39 yrs	4	2	2	7
40–59 yrs	15	1	6	5
>60 yrs	2		1	1
Duration				
<1 year	16	1		
1–3 yrs	8		5	
>3 yrs	6	2	4	
Localization				
Hands only	12			
Feet only	10			
Other region	3		9 (lower legs)	
Multiple sites	5	3		
Recurrences				
1 rec.	6			
2–3 rec.				
⩾4 rec.	2			

clearly pathologic GTT (obese woman, 32 years old; 2 hr value: 140 mg/100 ml) and two had an equivocal curve (obese woman, 51 years old; 2 hr value: 125 mg/100 ml) (man, 42 years old; 2 hr value: 115 mg/100 ml). Of our 3 patients with disseminated GA, one had a diabetic curve (man, 22 years old; 2 hr value: 145 mg/100 ml) and another an equivocal curve (woman, 48 years old; 2 hr value: 120 mg/100 ml). In the necrobiosis group, 1 patient was by mistake not submitted to GTT and of the rest, only one had an equivocal result (woman, 39 years old; 2 hr value: 110 mg/100 ml).

Cortisone-glucose tolerance test (Fig. 1). In 30 patients with the usual superficial GA, abnormal curves were obtained in the obese woman with the diabetic GTT (2 hr value: 150 mg/100 ml), and in 2 other patients (woman, 58 years old; 2 hr value: 160 mg/100 ml), (woman, 19 years old; 2 hr value: 165 mg/100 ml). Of the 3 patients with disseminated GA, only the man with abnormal GTT had a pathological CGTT (2 hr value: 165 mg/100 ml). In the necrobiosis group, the woman with an equivocal result in the GTT had an abnormal CGTT (2 hr value: 190 mg/100 ml) and so had 2 other patients (woman, 26 years old; 2 hr value: 155 mg/100 ml), (woman, 46 years old; 2 hr value: 150 mg/100 ml). None of these 3 patients with NL was obese.

In the control subjects one woman had abnormal CGTT (44 years old; 2 hr value: 180 mg/100 ml).

Definitions

The stages in the development of diabetes have been defined and named in many ways by workers in this field. We have used the definitions of Luft & Cerasi (10). *Manifest diabetes:* Glycosuria and/or fasting hyperglycemia. *Latent diabetes:* Reduced glucose tolerance; normal fasting blood sugar and no glycosuria. *Prediabetes:* An inherited condition, where the carbohydrate metabolism seems normal when conventional glucose tolerance tests, even during steroid stress, are performed. Possibly, this condition can be detected if blood insulin is determined during an intravenous glucose load: prediabetics seem to have a slower and weaker insulin response in this situation (10).

DISCUSSION

The etiology of GA is still unknown. Jacobi, in the chapter on GA in Jadassohn's Hand Book (1931), among other causes of GA, briefly mentions the possibility of a metabolic disturbance. During recent years, the discussion of the pathogenesis of GA has focused on its relation to diabetes mellitus, instead of the earlier hypothesis of a tuberculous etiology.

In a study of 115 GA patients, Wells & Smith (20) found 3 (2.6%) with manifest diabetes. This figure lies close to the expected diabetes frequency in total populations. Conversely, the GA incidence in large groups of diabetics, has to the best of our knowledge not been studied with special regard to GA, but according to diabetes specialists it is presumed to be very low. The combination of GA and manifest diabetes in the same patient was first published in 1919 (18) and 1939 Boldt had collected 20 cases from the literature (3). But most of them were so clinically and microscopically atypical that Boldt thought they were necrobiosis lipoidica lesions. He concludes that the combination of GA and manifest diabetes in the same patient is a coincidence. The clinical impression of some that GA in diabetics is clinically different with atypical or unusual forms (11, 18)

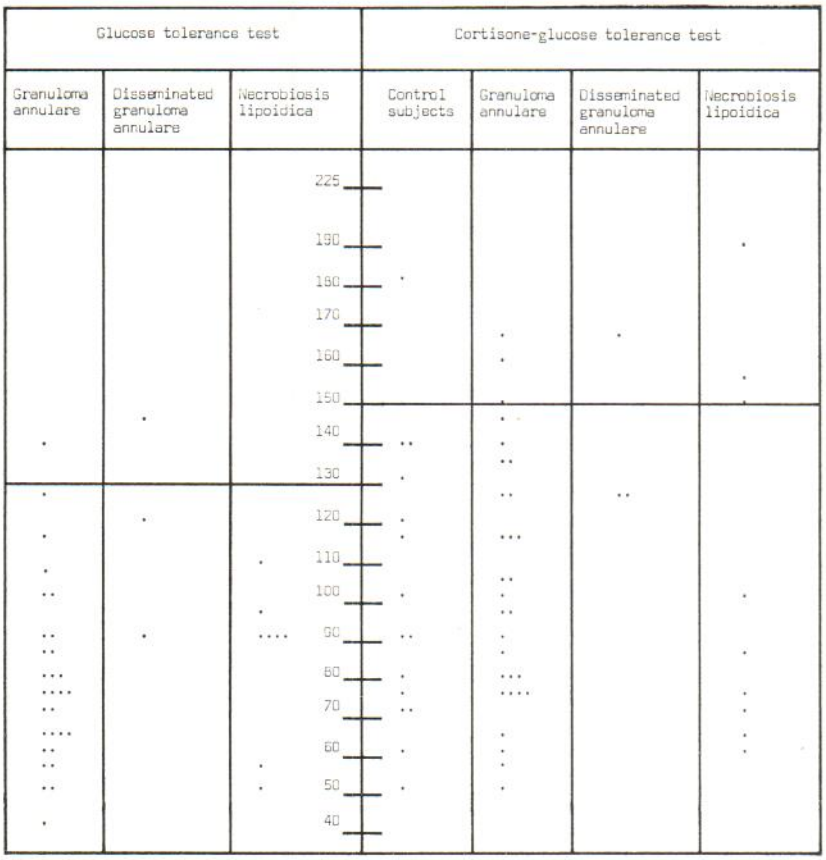

Fig. 1. Results of Glucose tolerance test and Cortisone-glucose tolerance test in mg glucose/100 ml two hours after glucose ingestion.

may be an unspecific phenomenon, as many diseases are worsened in dyshormonal situations. If GA is related to latent diabetes it would be most interesting to make a follow-up study of GA patients, say 30–40 years after GA was diagnosed and register the diabetes frequency in comparison with the expected frequency in total populations. No such study seems to have been made.

In 1942, Ellis & Kirby-Smith drew attention to the histologic similarity between GA and NL (6), which recently was stressed by Wood & Beerman (21). In a clinical study at the Mayo Clinic, 111 (65%) of 171 NL patients had manifest diabetes, and of 19 re-examined patients with NL who were not previously known to have diabetes 8 (42%) had a carbohydrate abnormality when tested with GTT and CGTT (12). This strongly suggests a relation between NL and diabetes. The histologic similarity between GA and NL, and NL's relation to diabetes makes one expect combinations of GA and NL in the same patients. These diseases, however, are very seldom combined in the same person (7).

Disseminated (generalized) GA has also been connected with diabetes in the literature. Romaine et al. describe 3 cases with widespread papular GA and previously undetected diabetes who were considered diabetic because of abnormal GTT or prednisone-GTT (17). Stankler & Leslie describe 1 case of their own and review all cases with disseminated GA they can find in the literature, totalling 47 patients, but only 1 seems to have manifest diabetes (19). Probably, none of them were submitted to CGTT. Dicken and colleagues in a recent report from the Mayo Clinic survey 26 patients with generalized GA (5). In their series, 2 patients were diabetic and 2 more had mildly elevated levels of fasting blood glucose, which is higher than the usual expectancy. Our result with 1 patient having an abnormal CGTT out of 3 with disseminated GA is too small a series to permit any conclusions.

Localized GA has been studied in 30 patients with the prednisone-glucosuria test by Rhodes et al. (15). They found that one-third of them were latent diabetics. As many workers (i.e. 12) have shown that also in non-diabetic NL approximately one-third of the patients have latent diabetes, this seems to fit with regard to the histologic similarity between GA and NL. Rhodes has stressed the possible role of a glycoprotein, which is found throughout the vascular tree of diabetics, their kidneys and pancreas, in the development of the vascular complications in diabetes. This substance, with staining properties of a neutral glycoprotein, is also found in the lesions of GA and NL (review in 16).

In our study of localized GA in 30 cases, 3 women had a pathologic CGTT. Except obesity in 2 of them, we have in the third found no probable cause to disturbed glucose tolerance other than a stage of latent diabetes. None of them had diabetic relatives. Clinically, these 3 patients do not differ significantly from the other patients with superficial GA with regard to number, size, localization and duration of lesions or frequency of recurrences. A comparison of the results of CGTT between the group of control subjects and the group with localized GA does not speak for a relation between localized GA and latent diabetes. Our results are not in accordance with those of Rhodes et al. (15). The reason for these discrepant data is unknown, but various technical factors may have influenced them. We do not think that the differences between our study and that of Rhodes et al. in the patients' sex ratio and age is of such importance that it can explain our divergent results. To test the reliability of the CGTT we have also made CGTT determinations in 9 patients with non-diabetic NL. We found that one-third of them behaved like latent diabetics, which is in accordance with the results of several investigators using both the CGTT (12) and the prednisone-glucosuria test (8). This means that the CGTT, as we have used it, is suitable to detect latent diabetes in NL, and one can therefore expect it to be suitable for the same purpose in GA.

The CGTT was introduced by Fajans & Conn in 1954 as a test capable of detecting pancreatic islet beta cell fatigue earlier than could be detected by the standard glucose tolerance test. In their 7 year follow up, Fajans & Conn reported that diabetes or "probable diabetes" had developed in 35 % of originally non-diabetic relatives of diabetic patients with an initial pathologic CGTT but in only 2 % of those who, 7 years previously, had had a normal CGTT (4). The prednisone-glycosuria test used by Rhodes et al. was introduced by Joplin et al. in 1961 (9). Time and regular follow-ups are needed to assess the value of both methods in detecting latent diabetes.

We have thus not been able to confirm that there is a connection between GA and manifest or latent diabetes mellitus. However, we do not want to exclude the possibility that GA is associated with the earliest phase in the development of diabetes, i.e. pre-diabetes, as it has been defined by Luft et al. (10). In pre-diabetes, all tests of carbohydrate metabolism are normal. At present, the only way to diagnose pre-diabetes seems to be insulin determinations during a standardized glucose infusion test (10). Such studies are now in progress to try to decide finally whether GA is related to the diabetic disease.

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Received April 8, 1970

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