

## EARLY INSULIN RESPONSE TO GLUCOSE INJECTED INTRAVENOUSLY IN PATIENTS WITH LOCALIZED GRANULOMA ANNULARE

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**Abstract.** The early insulin response to, and the glucose disappearance rate following, glucose injection was studied in 19 patients with localized granuloma annulare. The results were compared with data from a reference group of 50-year-old women randomly selected from the population. No association was found between granuloma annulare and a decreased tolerance to glucose or a decreased early insulin response.

In a preceding paper evidence was presented of patients with granuloma annulare (GA) in localized form having normal glucose tolerance, as judged by the oral glucose tolerance and the cortisone-glucose tolerance tests (21). This agrees with recent findings by Meier-Ewert & Allenby (20), Williamson & Dykes (36) and Haim et al. (11). On the other hand, Rhodes et al. (27) and Hammond et al. (14) found an association between GA and glucose intolerance.

The lack of association between GA and decreased tolerance to glucose, as found in our previous study, does not preclude that GA is associated with the diabetic state. It is generally accepted that genetic factors may play an important role in the development of diabetes mellitus. The time elapsed between conception and the appearance of a decreased tolerance to glucose is called the "prediabetic period" (35). Prediabetic subjects are supposed to be characterized by a decreased and delayed early insulin response to glucose injected intravenously (6). In this report we describe the glucose disappearance rate and the early insulin response to glucose injected intravenously in patients with localized GA as compared with a sample of the female population.

### MATERIALS

**Patients.** The study was made in 19 consecutive out-patients with localized GA collected during one year. All patients were examined by at least two experienced dermatologists and most were biopsied. The mean duration of lesions was

3½ years (range 1/2-17 years). All patients had lesions at the time of the study. The sites of the lesions were hands (11 cases), arms (4 cases), legs (1 case) and feet (3 cases). Three patients were aware of diabetes in parents and/or sibs, and another 7 in other relatives. Further data are given in Table I.

**Reference group.** A population study of women was performed in Göteborg, Sweden, 1968-69 (2). The women were selected at random from the Revenue Office Register. A total of 355 women, aged 50, were studied with an intravenous glucose tolerance test and the early insulin response was measured simultaneously (3, 4).

Three women with fasting hyperglycemia were disclosed in the population group (one of them previously unknown), and the reference group in this study then consisted of 352 women, corresponding to 85% of the population sample.

19.6% of the women in the reference group were aware of manifest diabetes in parents and/or sibs, and another 12.8% in other relatives. Further data are presented in Table I.

### METHODS

During the 3 days immediately preceding the intravenous glucose tolerance test the subjects were prescribed a diet containing 300 g carbohydrates. The subjects reported to the hospital in the morning after 12 hours of fasting. No smoking was allowed in the morning. The test was carried out between 8 and 9 a.m. with the subject recumbent during the whole period. After 15 min rest, glucose 0.5 g/kg body-weight in a 50% aqueous solution was injected during 2.5-3 min. Zero time was set at the start of the injection. Immediately before and at 4, 6 and 8 minutes after the start of the injection, venous blood samples were taken for blood glucose and serum insulin determinations. Venous blood samples were taken every 5 min from 25 to 60 min for glucose determinations. Glucose was determined with a glucose oxidase method (18). The glucose disappearance rate (*K*-value) was calculated from the slope of total blood glucose on a logarithmic scale between 25 and 60 min (13). The best fit of the straight line was determined using the method of least squares. Blood glucose values 10 mg/100 ml or less above the fasting level were excluded because values approximating the fasting level often deviate from linearity.

Serum insulin was determined with a double antibody method originally described by Hales & Randle (12) using a

Table I. Comparison of patients and reference group

	Granuloma annulare	Reference group
Number	19	352
Sex, male/female	2/17	0/352
Age, yrs, mean (range)	37 (15-57)	50
< 20	1	
20-29	6	
30-39	4	
40-49	3	
50-59	5	
Relative weight %, mean (range)	101 (77-133)	109 (76-170)
≤ 100	10 (52.7%)	111 (31.5%)
101-110	7 (36.8%)	106 (30.1%)
111-120	0	70 (19.9%)
≥ 121	2 (10.5%)	65 (18.5%)

commercial radioimmuno-assay kit (The Radiochemical Centre, Amersham, U.K.).

The early insulin response (ER) was calculated according to Thorell et al. (31) using serum insulin values before, and 4, 6 and 8 min after the start of the glucose injection. ER is an expression of the total early insulin response and is the sum of measured serum insulin increase at 8 min and the insulin calculated to have disappeared by then (31).

Relative body weight was expressed as a percentage of the ideal weight (19).

Conventional statistical methods were used for calculation of mean value, standard deviation (S.D.) and coefficient of correlation. Significance of difference between means was studied by Student's *t*-test (two-tailed test) and the hypothesis of differences in frequencies between groups was tested by the chi-square test (n.s. = not significant).

## RESULTS

**Glucose tolerance test.** The mean *K*-value in the patients with GA differed significantly from that in the reference group (Table II). None in the GA

Glucose mg/100 ml  
Insulin mU/l

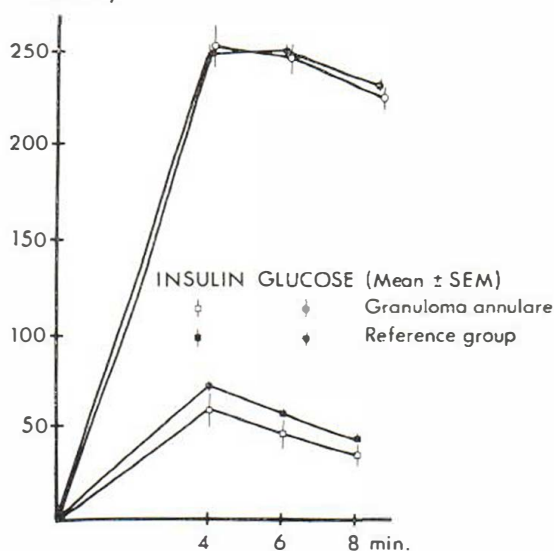


Fig. 1. Serum insulin and glucose values following intravenous injection of glucose.

group had a clearly pathological *K*-value ( $< 0.90$ ) as compared with 6% in the reference group. Two women (aged 15 and 55) and one man (aged 46) had borderline *K*-values (0.99, 1.06, 0.99, respectively) as compared with 11% in the reference group (n.s.). 58% of the patients with GA had *K*-values above 2.0 as compared with 29% in the reference group.

**Insulin studies.** The mean fasting serum insulin level was 10.1 mU/l in the GA group which was significantly different from that in the reference group (Table II). Glucose injection increased the serum insulin in all patients with GA (Table II, Fig. 1). The increase was highest at 4 min in all

Table II. *K*-value, fasting insulin, insulin values after glucose injection and early insulin response (ER) in patients with granuloma annulare and in a reference group of women aged 50

	Granuloma annulare (n = 19)			Reference group (n = 352)			Significance of difference
	Mean	S.D.	Range	Mean	S.D.	Range	
<i>K</i> -value	2.77	1.94	0.99-7.20	1.88	1.10	0.59-9.90	$p < 0.01$
Insulin							
0 min	10.1	3.8	5-19	13.9	5.3	3-47	$p < 0.001$
4 min	70.0	40.0	29-150	86.7	46.8	12-390	n.s.
6 min	59.3	35.6	21-142	72.6	45.6	14-495	n.s.
8 min	46.5	27.8	14-115	60.9	37.4	14-380	$p < 0.01$
ER	68.1	45.3	16-174	85.4	60.4	0-559	n.s.

but one of the GA patients as compared with 86% in the reference group. The variation in the insulin increment was considerable in both groups. The range of peak increase was 18–131 mU/l in the GA group compared with 0–448 mU/l in the reference group.

The mean ER, calculated from the serum insulin values at 0, 4, 6 and 8 min, was 68.1 mU/l in the GA group as compared with 85.4 mU/l in the reference group (n.s.) (Table II). Three patients with GA had a low ER as defined as an ER  $\leq 30$  mU/l (16, 18 and 29 mU/l respectively). In the reference group, 10% had an ER  $\leq 30$  mU/l (n.s.).

ER of the GA patients aged 15–39 was  $74.8 \pm 41.1$  mU/l as compared with  $58.8 \pm 51.5$  mU/l in those aged 40–57 (n.s.). The latter group of 8 patients was heterogeneous as 2 of them had borderline *K*-values and low ER and another the highest ER in the whole GA group. The correlation coefficient between age and ER in the GA group was  $-0.37$ .

ER of 10 GA patients with a relative weight of 77–100% was  $69.5 \pm 45.7$  mU/l. In the reference group the corresponding ER was  $69.6 \pm 38.0$  mU/l (n.s.). The correlation coefficient between relative weight and ER in the GA group was 0.27. One patient in the lean GA group had an ER  $\leq 30$  mU/l as compared with 6.3% of the lean women in the reference group (n.s.).

The glucose stimulation, as measured at 4, 6 and 8 min after glucose injection, was the same in the GA group as in the reference group (Fig. 1).

## DISCUSSION

The histopathological similarity between GA and necrobiosis lipoidica (37) and the close association between necrobiosis lipoidica and diabetes (23) suggest an association between GA and the diabetic state. However, the frequency of manifest diabetes in patients with GA is not considered to be increased (34). The problem has therefore been approached by studying the prevalence of glucose intolerance in non-diabetic GA subjects. When studying glucose tolerance some difficulties in the interpretation of the results must be considered. The prevalence of decreased glucose tolerance is high in the general population, especially in elderly and obese subjects. The selection of patients and reference group is thus extremely important for the outcome of the study. The GA patients in the present study were selected

consecutively from three outpatient clinics of dermatology in Göteborg and were considered to be all patients with newly detected GA in this area. The women in the reference group were randomly selected from the total population of 50-year-old women in the same town. The implication of the differences in age and relative weight between the GA patients and the reference group will be discussed in detail later on.

Other factors which may be responsible for the nonconformity in the results reported on glucose tolerance in patients with GA (11, 14, 20, 21, 27, 36) are low reproducibility and difference in test procedures, methods for glucose determination and criteria for interpretation of the glucose tolerance curve.

In the present study the mean *K*-value in the GA patients was higher than that in the reference group. This may be explained by the lower mean age in the GA group, since the tolerance to glucose decreases with age (8, 33). The frequency of low or borderline *K*-values in the GA group did not exceed the frequency in the reference group. Our results support the view that no association exists between localized GA and a decreased glucose tolerance.

The glucose-stimulated secretion of insulin is considered to be biphasic, with an early and a late phase (9, 24). The early phase is almost instantaneous and the peak value in peripheral blood is reached within 3–5 min from the start of the glucose injection (4, 31). The early phase lasts only a few minutes and the  $T_{\frac{1}{2}}$  for insulin is calculated to be about 7 min (31). If the early phase of the insulin secretion has to be measured it is obvious that blood samples must be taken repeatedly during the first 10 min, with the first sample not later than 3–5 min.

The early insulin response is very low or almost lacking in juvenile (32) as well as in maturity-onset diabetes (5, 32). Since very low early insulin response has been found in subjects with normal glucose tolerance, it has been suggested that a low early phase also is characteristic of the prediabetic state (6). In the general population of 50-year-old women, as judged from the reference group, the frequency of very low early insulin response is below 1% in subjects with normal glucose tolerance (4). The total morbidity risk and the life table expectancy in women for clinically manifest diabetes have, in Sweden, been estimated to 13 and 10.3% respectively (10). The balance of evidence indicates that many women with early insulin response higher than that

found in maturity-onset diabetes will in due course develop manifest diabetes.

The range in early insulin response was considerable in the GA patients as well as in the reference group. No GA patients had as low ER as maturity-onset diabetics (5). The mean ER and the frequency of low ER in the GA group were not significantly different from what would be expected in the general population, as judged from the reference group. No high ER ( $>180$  mU/l) was noted in the GA group, as compared with 5% in the reference group (4).

The influence of age on the early insulin response has been discussed in a few papers. Cerasi & Luft (7) found as high prevalence of low insulin responders in children as in adults and suggested that a low insulin response is genetically determined and does not change with age. Sterky & Thorell (30) found no association between age and ER in subjects aged 12–26. Crockford (8) and Barbagallo-Sangiorgi et al. (1) in small groups of subjects found lower early response in old than in young people.

In the present study the range in ER was considerable both in young and middle-aged GA patients. The number of GA patients was too small for general conclusions about the association between age and early insulin response. It would seem that the discrepancy in age between the GA group and the reference group cannot in a major degree influence the interpretation of the results.

It is generally accepted that obesity is associated with an increased secretion of insulin (17). The insulin response measured in this and other studies was mainly related to the late phase of insulin secretion, as glucose loads were given orally. On the other hand the early insulin response has not been associated with obesity (15, 30). In the reference group of the present study the variance in ER was significantly different in lean women ( $\leq 100\%$ ) from that in women above 100% relative weight, indicating that groups of subjects must be carefully matched as to degree of obesity when ER is compared (4).

As a higher frequency of lean subjects was present in the GA group than in the reference group, these two groups cannot be compared as a whole. When studying lean women only, the ERs were almost identical in the GA patients and the reference group. The discrepancy in relative weight may thus be responsible for the lower mean ER in the GA group.

If the hypothesis is accepted, that a decreased early

insulin response is the basic pathogenic factor in the development of all stages of diabetes including the prediabetic state (6), this study has not disclosed any association between localized GA and the diabetic syndrome. This hypothesis is, however, still unproven and has not been fully accepted, since normal early insulin response has been reported in patients with impaired glucose tolerance (16, 25).

A rare variant of GA, called generalized GA, has been associated with the diabetic state (11, 26, 28) and it has been reported (22, 29) that GA in diabetic subjects often presents with atypical or unusual forms. It is attractive to speculate that all stages of the diabetic syndrome, including the prediabetic state, may cause the GA to become generalized or atypical. Further investigations of this hypothesis are required.

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