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Effect of oral and intravenous calcium load on glucose-induced insulin secretion in obese children

D Molnár, Helen Dober

Department of Paediatrics, University Medical School, Pécs, Hungary

The effect of intravenous (IV) (10 ml of 10% calcium gluconate) and oral (3 g calcium) calcium on plasma immunoreactive insulin (IRI) and blood glucose levels was investigated during intravenous (0.5 g/kg bwt. glucose) and oral (1.75 g/kg bwt. glucose) glucose tolerance test in 21 control (body fat 14.0 ± 0.5%) and 34 obese (body fat 36.1 ± 0.7%) children. Calcium given before IV glucose tolerance test and IV or oral calcium by itself did not alter blood glucose and plasma IRI concentrations in either group. Oral calcium load significantly increased the glucose-induced IRI response and decreased the blood glucose levels in obese children with impaired glucose tolerance (n = 7) compared to the levels without calcium. Since IV calcium did not alter the plasma IRI concentration, it has been assumed that oral calcium exerts its effect by influencing the secretion of an insulin secretogogue gastrointestinal factor (gastric inhibitory polypeptide ?). This effect, however, was observed only in obese children with impaired glucose tolerance.

The important role of calcium in cell activities, especially hormone secretion, has been widely recognized and numerous hormones were shown to require calcium for their secretion [6, 15, 20]. In vitro [5, 11, 13] and in vivo [9, 10, 23] studies have demonstrated that calcium is an essential requirement for insulin secretion induced by various stimuli. The present study was planned to investigate the effect of oral and intravenous calcium load on glucose-induced insulin secretion in obese children.

Materials and Methods

The investigations were carried out after an overnight fast in 21 non-obese and 34 obese children with body weights more than 20% in excess of the ideal body weight. Anthropometric measurements and the calculation of relative body weight and body fat were done as described earlier [17]. The relevant data of the children are given in Table I.

Oral load of 1.75 g/kg body wt. glucose was given with and without an oral load of 3 g calcium (calcium carbonate and calcium lactogluconate) in 18 obese and 6 lean children. In the second part of the study 0.5 g/kg body wt. glucose was administered intravenously with and without the intravenous injection of 10 ml 10% calcium gluconate in 6 obese and 5 control children. In addition, 5 overweight and 5 control children received a similar oral or intravenous calcium load without glucose. Capillary blood samples were taken by fingerprick for the measurement of blood glucose, plasma immunoreactive insulin (IRI) and plasma calcium concentration. Blood glucose was determined with the glucose oxidase method, plasma calcium with flame photometry. Plasma IRI levels

TABLE I

Physical characteristics of the investigated children (mean ±SE)

	Age, year	Height, cm	Weight, kg	Relative weight, per cent	Body fat, per cent
Control n = 21	11.9 ±0.5	150.5 ±2.6	42.4 ±2.2	99.5 ±1.6	14.0 ±0.5
Obese n = 34	11.8 ±0.5	153.7 ±3.0	68.7 ±3.6	150.1 ±3.7	36.1 ±0.7

were measured by radioimmunoassay, using commercially available kits (Isotope Institute of the Hungarian Academy of Sciences, Budapest). Normal (NGT) and impaired (IGT) glucose tolerance were defined according to the criteria of Guthrie et al. [12]. Statistical analysis was performed by paired and unpaired Student's *t* test.

RESULTS

Fasting blood glucose and plasma calcium levels were similar, but fasting plasma IRI concentrations were elevated in obese children as compared to controls (Fig 1).

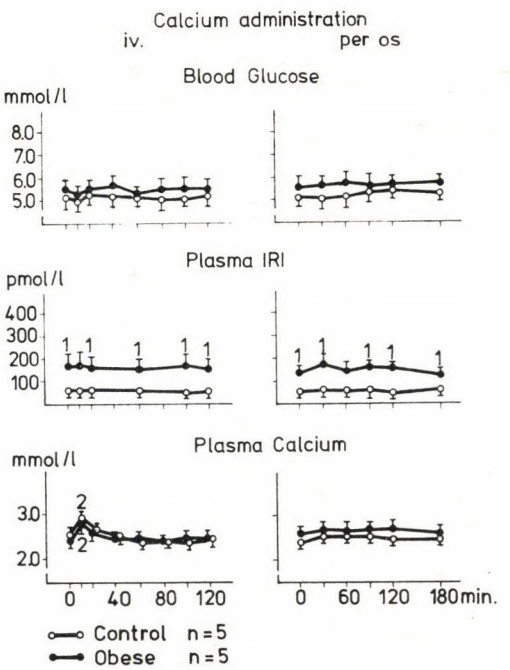

FIG. 1. Effect of intravenous (IV) and oral calcium load on blood glucose, plasma IRI and calcium levels (mean ±SE). 1 $p < 0.05$ Control vs Obese; 2 $p < 0.05$ Preload vs Postload values

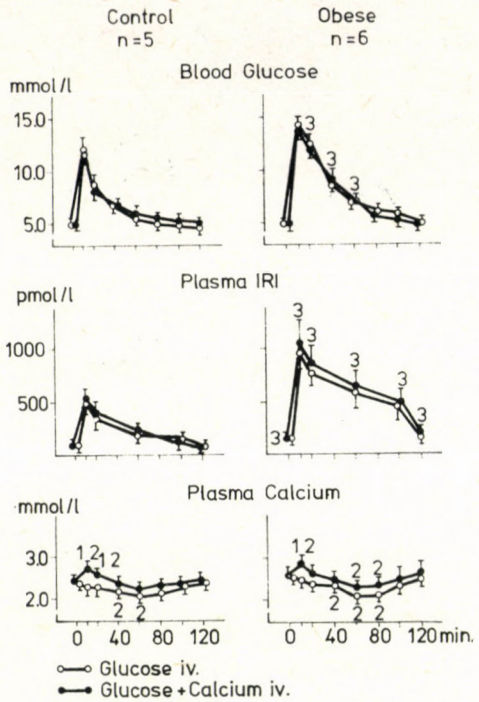

FIG. 2. Effect of intravenous glucose and intravenous glucose + calcium on blood glucose, plasma IRI and calcium levels (mean ±SE). 1 $p < 0.05$ Glucose vs Glucose + — calcium; 2 $p < 0.05$ Preload vs Postload value; 3 $p < 0.05$ Control vs Obese

Intravenous (IV) or oral calcium load did not alter blood glucose or IRI levels in either group. Plasma calcium rose significantly 10 min after IV administration of calcium while it was not affected by oral calcium load in overweight and lean children (Fig 1).

Blood glucose levels of obese children were significantly higher 20, 40 and 60 min following IV glucose injection and IRI concentrations were higher throughout the test than in controls (Fig 2). These two parameters, however, were not altered by the simultaneous IV injection of calcium in both obese and control children (Fig 2). IV glucose load decreased plasma calcium at 40, 60 and 40, and 60 and 80 min in the control and obese groups, respectively. When glucose and calcium were injected together, a transient rise of plasma calcium concentration was observed at 10 and 20 min in the controls and at 10 min in the obese children (Fig 2).

The glucose-induced increase of plasma IRI concentration was significantly higher at 30 and 60 min in the obese children when oral calcium was given, compared to the levels without calcium, whereas the comparison of blood glucose values revealed a significant decrease at 30, 60, 90 and 120 min in the group with

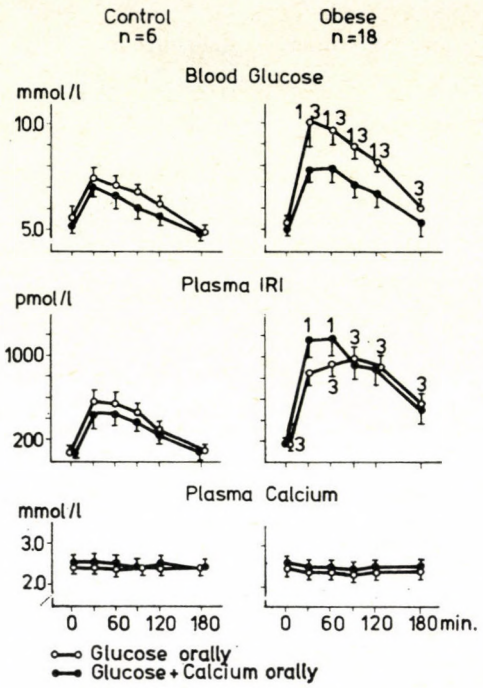

FIG. 3. Effect of oral glucose and oral glucose + calcium on blood glucose, plasma IRI and calcium levels (mean ±SE). 1 $p < 0.05$ Glucose vs Glucose + calcium; 3 $p < 0.05$ Control vs Obese

oral calcium load (Fig 3). None of these values showed significant changes after oral calcium load in 6 controls. No changes were detected in plasma calcium concentrations following oral calcium and glucose intake in either group (Fig 3).

The above demonstrated influences of oral calcium on plasma IRI and blood glucose levels during oral glucose tolerance test were, however, variable in the overweight children. The stimulation of glucose-induced IRI secretion and decreased blood glucose levels after oral calcium load were marked and occurred only in obese children with IGT (Fig 4), whereas in the group with NGT it had no effect whatsoever.

The early phase of glucose-induced IRI response was defective in the IGT group, demonstrating lower plasma IRI concentrations at 30 min (543.0 ± 76.8 pmol/l) than in the NGT group (1072.0 ± 154.5 pmol/l) ($p < 0.01$). Plasma IRI after oral glucose + calcium load was similar in the NGT and IGT obese subgroups (Fig 4).

Age (NGT: 12.3 ± 0.46 yr, IGT: 10.3 ± 1.8 yr), body fat (NGT: 36.9 ± 0.74%, IGT: 37.2 ± 0.78%) and duration of obesity (NGT: 6.4 ± 0.7 yr, IGT: 4.7 ± 0.78 yr) were not different in the two obese subgroups.

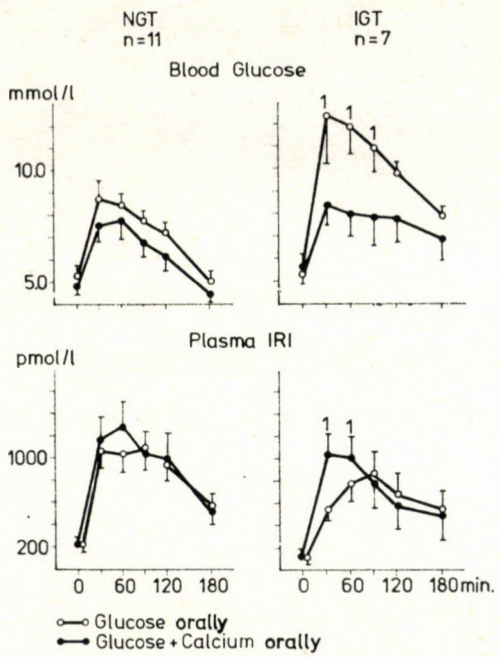

FIG. 4. Effect of oral glucose and oral glucose + calcium on blood glucose and plasma IRI levels (mean ±SE) in obese children with normal (NGT) and impaired (IGT) glucose tolerance. 1 $p < 0.05$ Glucose vs Glucose + calcium

DISCUSSION

In the present study IV or oral calcium by itself, or IV calcium in combination with glucose load had no effect on blood glucose and plasma IRI levels in obese and control children. Increased glucose-induced insulin secretion and a secondary fall in blood glucose concentration was observed in obese children with IGT, but not in children with NGT and controls after oral calcium load.

The role of extracellular calcium in the secretion of insulin is well documented. High and low extracellular calcium levels have been shown to enhance and suppress, respectively, glucose-induced IRI secretion in vitro [5, 11, 13] and in vivo [14, 23, see 22 for review]. In patients with islet cell tumour, IV calcium infusion caused a release of insulin and proinsulin, but no such effect was obtained in normal subjects [10]. Calcium apparently acts on β cell membrane or enters the cell before insulin release [16]. Such a direct effect of calcium on pancreatic β cells, however, was unlikely in the present investigation since an increase in plasma calcium concentration following IV calcium administration did not influence glucose-induced insulin response. An insulin secretogogue gastrointestinal factor stimulated by oral calcium might explain why IV calcium had no effect on insulin secretion whilst

oral calcium had such an effect. To date, gastric inhibitory polypeptide (GIP) best fulfils the criteria for such a factor [3]. GIP is released at the ingestion of glucose and fat [1, 2] and potentiates glucose-induced IRI release [1, 7, 19]. Exaggerated GIP response of obese subjects and animals [4, 8, 21] to glucose or standard test meal has been reported. The higher the GIP response to glucose, the more pronounced insulin response is observed [4]. The IV administration of purified GIP increased IRI secretion in the early phase of glucose tolerance test [7], resembling the effect of oral calcium in obese children with IGT observed in the present study.

On the basis of the present results and earlier data it can be hypothesized that oral calcium increases glucose-induced IRI secretion by stimulating GIP secretion in the obese subgroup with IGT and a low insulin response, whereas in the hyperinsulinaemic obese children with NGT the presumably high GIP level cannot be stimulated further by oral calcium. It is likely that the enteroinsular axis can be stimulated by oral calcium in obese children with IGT as it was observed in diabetics by Fujita et al [9]. The pathological significance of the present observation, however, is not known and needs further investigation.

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D Molnár MD
József Attila u 7
H-6723 Pécs, Hungary