Biological Trace Element Research
ISSN 0163-4984

Brun J-F, Guintrand-Hugret R, Fons C et al. *Effects of oral zinc gluconate on glucose effectiveness and insulin sensitivity in humans.* **Biol.Trace Elem.Res.** 1995;47:385-92.

0163-4984/94/4701-0000$04.20

Effects of Oral Zinc Gluconate on Glucose Effectiveness and Insulin Sensitivity in Humans

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ABSTRACT

Zinc improves both insulin secretion and insulin sensitivity, and exerts insulin-like effects. We investigated its acute effects on the parameters of glucose assimilation determined with the minimal model technique from frequent sampling intravenous glucose tolerance test (FSIVGTT) in seven healthy volunteers. FSIVGTTs (0.5 g/kg of glucose, followed by 2 U insulin iv injection at 19 min) were performed after the subjects had taken 20 mg zinc gluconate twice (the evening before and 30 min before the beginning of the test) or placebo pills (simple blind randomized protocol). Glucose assimilation was analyzed by calculating Kg (slope of the exponential decrease in glycemia), glucose effectiveness Sg (i.e., ability of glucose itself to increase its own disposal independent of insulin response), and SI (insulin sensitivity, i.e. the effect of increases in insulinemia on glucose disposal). The two latter parameters were calculated by fitting the experimental data with the two equations of Bergman's "minimal model." Zinc increased Kg ($p < 0.05$) and Sg ($p < 0.05$), whereas SI and insulin first-phase secretion did not significantly increase. This study suggests that zinc improves glucose assimilation, as evidenced by the increase in Kg, and that this improvement results mainly from an

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increase in glucose effectiveness (insulin-like effect), rather than an action on insulin response or insulin sensitivity.

Index Entries: Insulin sensitivity; zinc; minimal model.

INTRODUCTION

Experimental zinc (Zn) deficiency in rats decreases carbohydrate tolerance *(1)* by reducing both insulin response *(2)* and insulin sensitivity *(3)*. Zinc (Zn) is involved in insulin physiology at several levels: This metal plays a role in insulin biosynthesis, storage, and release from the B-cells *(4)*. Zn is also a component of enzymes involved in the mechanism of insulin action and in glucose metabolism *(5,6)*. Zn deficiency has been suggested to be a contributing factor to insulin resistance in both IDDM and NIDDM *(1,7)*. Some in vitro studies have demonstrated that Zn ion exerts insulin-like effects *(8)*. However, the involvement of Zn in insulin sensitivity in vivo in humans is poorly documented. Since the minimal model technique offers now a well-recognized and easy to perform measurement of insulin sensitivity and noninsulin-dependent determinants of glucose utilization *(9)*, we investigated the acute effects of Zn on the parameters of glucose assimilation determined with this method.

SUBJECTS AND METHODS

Subjects

Seven voluntary subjects were included in the study. Their mean age was 29.6 yr (23–39 yr). They were three men and four women. Their body mass index was 22.2 ± 3.34 kg/m^2. All subjects were healthy and doing sports only at leisure time. None had a family history of diabetes. Subjects performed two FSIVGTTs in random order. In the Zn session, FSIVGTT was performed after ingestion of 20 mg Zn (Zn gluconate prepared for experimental studies by Aguettant Pharmaceuticals, Lyon, France) the evening before and another 20 mg 30 min after glucose injection. In the placebo session, FSIVGTT was performed after ingestion at the same times of placebo pills.

Intravenous Glucose Tolerance Test (IVGTT) Protocol

No alimentary restriction was imposed; however, subjects were asked to fast for 12 h before commencement of the test at 8:30 AM. A cannula was placed in the cephalic vein at the level of the cubital fossa for

blood sampling at various times, whereas glucose injection was performed in the controlateral cephalic vein. Glucose (0.5 g/kg, solution at 30%) was slowly injected for 3 min. Insulin (O.03 U/kg) was injected intravenously immediately after time 19. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90, and 180 min following the onset of the meal. Times 1 and 3 were used for the determination of insulin early secretory phase *(10)*. Times 10, 20, and 30 were used for calculating Kg *(see below)*. Other times were necessary for minimal model calculations *(9)*.

Laboratory Measurements

All samples were analyzed for insulin by a radioimmunoassay (kit SB-INSI-5 from the international CIS) and glucose with a Beckman glucose analyzer. The within-assay coefficient of variation (CV) for insulin was determined by repetitive measurements of the same sample and was between 8.6 (low values) and 9.7% (high values). The between-assay CV for insulin was between 12.5 (low values) and 14.4% (high values). The sensitivity (lowest detectable value) was 2 μU/mL.

Measurement of Insulin Sensitivity

The least-square slope of the log of the absolute glucose concentration between 10 and 30 min after the glucose bolus was used as an index of glucose tolerance Kg, according to Conard et al. *(11)*. This Kg value describes glucose assimilation by tissues and depends on three factors: insulin release, insulin sensitivity, and glucose effectiveness independent of insulin. Minimal model analysis of IVGTT according to Bergman et al. *(9)* with the homemade software TISPAG, which uses a nonlinear least-square estimation, gave the values of insulin sensitivity (SI) and glucose effectiveness (Sg). SI and Sg are calculated from the following equations:

$$dG(t)/dt = -[p1 + X(t)]\, G(t) + p1\, Gb \quad (1)$$

$$G(0) = Go \quad (2)$$

$$dX(t)/dt = -p2\, X(t) + p3\, [I(t) - Ib] \quad (3)$$

$$X(0) = 0 \quad (4)$$

where $G(t)$ and $I(t)$ are plasma glucose and insulin concentrations, $X(t)$ is the insulin in a compartment remote from plasma ("insulin action"), and p1–p3 are model parameters. Go is the glucose concentration that one would obtain immediately after injection, if there were instantaneous mixing in the extracellular fluid compartment. Gb and Ib are basal values of glucose and insulin. Parameter $p1$ represents Sg, i.e., the fractional disappearance rate of glucose, independent of any insulin response, and $p3$

and $p2$ determine the kinetics of insulin transport, respectively, into and out of the remote insulin compartment where insulin action is expressed. Insulin sensitivity, SI, is an index of the influence of plasma insulin to change glucose's own effect on glucose concentration. Thus, SI is equal to $-p3/p2$.

Statistics

Results are presented as mean ± the SE of the mean. Variables were compared using the two-tailed nonparametric test of Wilcoxon for paired data. Significance was defined as $p < 0.05$.

RESULTS

Zn significantly increased Kg (3.04 ± 0.32 vs 2.19 + 0.43 $min^{-1} \times 10^2$ $p < 0.05$) (Fig. 1). Sg, as shown in Fig. 2, was also increased by Zn (3.89 ± 0.35 vs 2.82 ± 0.52 $min^{-1} \times 10^2$ $p < 0.05$) By contrast, SI (5.31 ± 2.43 vs 2.49 ± 0.7 $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1} \times 10^4$) and insulin first-phase secretion (I_{1+3}: 49.67 ± 8.44 vs 74.83 ± 13.2 μU/mL) did not significantly increase.

Fig.1

Fig. 2

DISCUSSION

The insulin sensitivity index, SI, determined from the FSIVGTT by resolving the two differential equations of the minimal model, is a useful measure of insulin sensitivity capable of differentiating sensitivities among a normal population *(12)* and of detecting insulin resistance in obese or diabetic subjects *(13–14)*. A limitation of the technique is the cases where no insulin response occurs during FSIVGTT. In this case, the assumptions of the model are no longer valid, and alternative protocols using insulin or tolbutamide injection at the 20th min are required (13–15). In this article, we used the insulin protocol as described by the team of Bergman *(15)*. Increasing the insulin levels above baseline has been shown to improve the reliability of the test *(16)*. Comparison with the glucose clamp, which is the most widely used and recognized measurement of insulin sensitivity, has shown that the modified minimal model technique gives the same results and is equivalent *(16)*.

The results presented above indicate that Zn gluconate improves the coefficient Kg of glucose assimilation. This does not seem to be related to modifications of insulin release, which is a major determinant of Kg *(11)*, since I_{1+3} remains unchanged. Actually, insulin first-phase secretion exhibits rather a tendency to decrease. The other determinants of Kg are insulin sensitivity and glucose assimilation independent of insulin, which can both be calculated with the minimal model analysis. Noninsulin-dependent glucose assimilation Sg is increased ($p < 0.05$). By contrast, insulin sensitivity (SI) is not significantly modified, and neither are

parameters p2 and p3, which are used for calculating it. These data suggest that the acute effects of Zn on glucose assimilation in sedentary healthy subjects are explained by a noninsulin-dependent increase in glucose consumption by tissues rather than by modifications of insulin sensitivity.

These data are in agreement with several studies that have demonstrated that Zn mimics insulin in vitro and in vivo *(5,6,8)*. This divalent metal stimulates glucose transport *(17,18)* and D-[$^{3\text{-}3}$H] glucose incorporation into lipids *(19)*. It increases glucose oxidation by the pentose phosphate pathway in rat adipocytes *(17)*. Shisheva et al. *(8)* have demonstrated that the insulin-like effects of Zn in rat adipocytes are the result of the Zn ion itself, and occur by a mechanism unrelated and complementary to the action of insulin or vanadate. Zn administration was shown to be effective in lowering blood glucose levels in experimentally diabetic rats *(8)*. However, the latter study used very high supraphysiological doses of Zn. In our study, interestingly, a significant effect of Zn was found at physiological doses (20 mg Zn taken 12 h and 30 min before the test).

Although SI does not increase after acute Zn intake, our study does not rule out the possibility of a beneficial effect of Zn on SI, either after longer administration of this metal, at higher doses, or in individuals with insulin resistance, in whom this parameter is low. However, in our sample of healthy, young volunteers, Kg and Sg always increase after Zn intake, whereas SI and I_{1+3} exhibit more erratic variations.

In conclusion, this experiment shows that acute oral Zn load, at physiological doses, improves glucose-induced glucose disposal, and thus improves intravenous glucose tolerance. This effect could be related to the insulin-like effects of this metal, which have been reported at higher, supraphysiological doses in animals.

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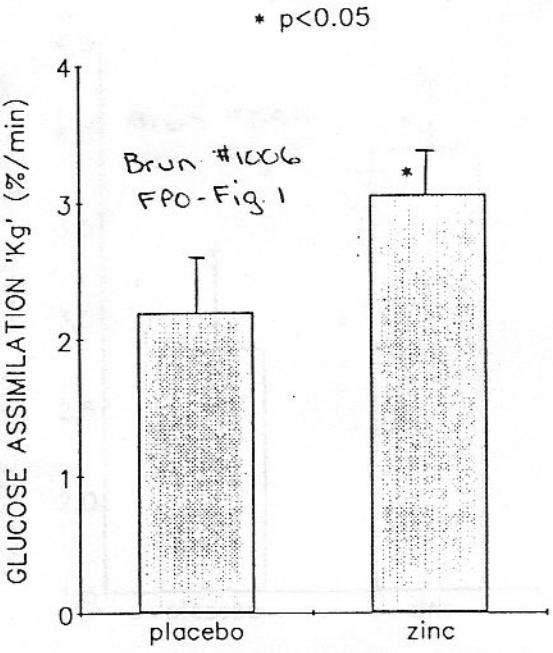

Fig. 1. Influence of Zn gluconate (20 mg 12 h before and 30 min before) on glucose assimilation Kg vs placebo. Zn increases Kg ($p < 0.05$).

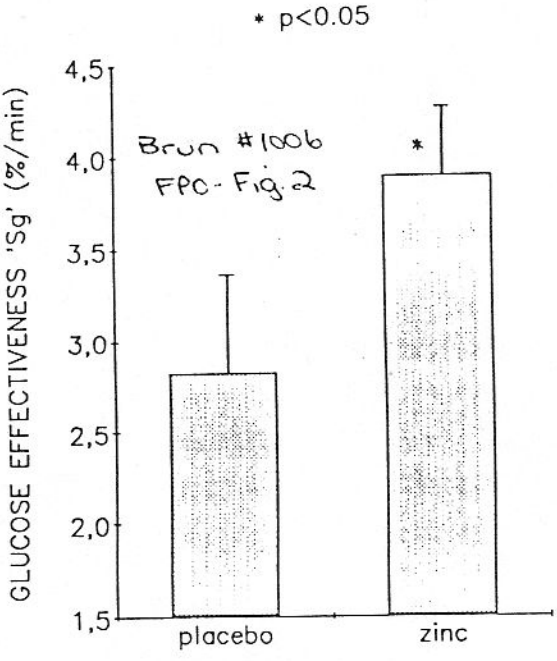

Fig. 2. Influence of Zn gluconate vs placebo on glucose effectiveness Sg calculated with the minimal model. Zn increases Sg ($p < 0.05$).