Zinc Supplementation Improves Glucose Disposal in Patients With Cirrhosis

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Zinc deficiency is common in cirrhosis, and was proved to affect nitrogen metabolism. In experimental animals, zinc status may also affect glucose disposal, and acute zinc supplementation improves glucose tolerance in healthy subjects. This study was aimed at measuring the effects of long-term oral zinc supplements on glucose tolerance in cirrhosis. The time courses of glucose, insulin, and C-peptide in response to an intravenous (IV) glucose load were analyzed by the minimal-model technique before and after long-term oral zinc supplements (200 mg three times per day for 60 days) in 10 subjects with advanced cirrhosis and impaired glucose tolerance or diabetes. The test was performed using a simplified procedure, based on 20 blood samples collected within 4 hours from the glucose load. Normal values were obtained in 25 age-matched healthy subjects. Zinc levels were low to normal or reduced before treatment, and were normalized by oral zinc. Glucose disappearance improved by greater than 30% in response to treatment. There were no changes in pancreatic insulin secretion and systemic delivery, or in the hepatic extraction of insulin. Insulin sensitivity (S_I), which was reduced by 80% before treatment, did not change. Glucose effectiveness (S_G) was nearly halved in cirrhosis before treatment (0.013 [SD 0.007] min^{-1} *v.* 0.028 [SD 0.009] in controls; $P < .001$), and increased to 0.017 (SD 0.009) after zinc ($P < .05$ *v.* baseline). The return to normal of plasma zinc levels after long-term zinc treatment in advanced cirrhosis improves glucose tolerance via an increase of the effects of glucose per se on glucose metabolism. Poor zinc status may contribute to the impaired glucose tolerance and diabetes of cirrhosis.

THERE IS A GROWING INTEREST for trace elements in malnutrition in general, and particularly in liver diseases, because of the major role of the liver in transport and storage of trace metals. Zinc, an essential trace metal required for normal function of several metalloenzymes, has been reported to regulate protein metabolism and membrane integrity.[1]

Zinc deficiency was associated with altered nitrogen metabolism, both in experimental models of liver cirrhosis in the rat[2] and in patients with advanced disease.[3] Poor zinc status seems to be common in cirrhosis,[4] and was shown to impair nitrogen metabolism by reducing the activity of urea cycle enzymes.[5] These physiological data form the basis for a potential role of zinc supplementation in hepatic encephalopathy, where controlled clinical studies have so far produced conflicting results.[6-8]

Impaired glucose tolerance and/or diabetes is another feature of cirrhosis,[9,10] commonly related to insulin resistance.[11,12] Recently, a decreased ability of glucose per se to enhance glucose disposal had also been reported.[13] Several studies have investigated the role of zinc status in insulin secretion and metabolism, and in the pathogenesis of diabetes mellitus, in which zinc deficiency and hyperzincuria are frequently observed.[14] Tissue zinc status was found to be lower in genetically diabetic mice, with obesity and insulin resistance with hyperinsulinism (model of insulin-independent diabetes), when compared with streptozotocin-diabetic mice (model of insulin-dependent diabetes)[15]; experimental zinc deficiency in rats decreased glucose tolerance by reducing insulin secretion and sensitivity,[16] but these results were not confirmed by Brown et al.[17] Shisheva and Schechter[18] suggested that zinc may exert an insulin-like effect both in vitro and in vivo.

The involvement of zinc in insulin sensitivity in vivo in humans is poorly documented. In healthy subjects, Brun et al[19] recently showed that acute oral zinc supplementation improves glucose disposal in response to an intravenous (IV) glucose tolerance test. When tested by minimal-model analysis,[20] improved glucose disappearance was not explained by increased insulin sensitivity (S_I), but by enhanced glucose effectiveness (S_G). In diabetes, no correlation was found between serum zinc and glycosylated hemoglobin levels, and pharmacological short-term zinc supplementation did not improve diabetic control.[21]

In the present study, we aimed to measure the effects of long-term oral zinc supplementation on glucose disposal in patients with advanced disease and poor zinc status. The time courses of glucose, insulin, and C-peptide following an IV load were analyzed by the minimal-model technique,[20] to factor out the possible effects on S_I and S_G.

MATERIALS AND METHODS

Patients

We studied 10 subjects (nine men and one woman) with cirrhosis, aged 39 to 67 years (median, 53) with a wide range of hepatocellular dysfunction (Table 1). Their mean body mass index was 25.6 (SD 3.6) kg/m^2 (range, 21.5 to 31.5). Patients were selected on the basis of a fasting blood glucose less than 8 mmol/L, but impaired glucose tolerance (n = 6) or diabetes (n = 4) after an oral glucose tolerance test (World Health Organization criteria) and high-normal or elevated basal insulin and C-peptide levels. They were in fairly stable condition and did not require changes in diuretics treatment during the study period (spironolactone 100 to 200 mg/d in five patients, associated with furosemide 25 mg/d in two cases). No other medication potentially affecting glucose metabolism was administered. Three had cirrhosis of alcoholic origin, but had been abstaining from alcohol for ≥6 months. Two patients had no esophageal varices at endoscopy, three patients had small-sized varices, four had medium-sized varices, and one had large varices, which had been treated by endoscopic sclerotherapy after bleeding. All had normal potassium levels, and consumed a weight-maintaining diet containing 30 to 35 kcal/kg body weight and 250 g carbohydrates and 1 g/kg protein during the 3 days preceding the IV

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Table 1. Clinical and Laboratory Data of Patients With Cirrhosis Before Zinc Supplementation

Patient No.	Sex	Etiology of Cirrhosis	Glucose Tolerance	Age (yr)	BMI (kg/m²)	Albumin (g/L)	Bilirubin (mg/dL)	Prothrombin Activity (%)	Galactose Elimination (mg/kg/min)	Child-Pugh Score
1	M	HCV	IGT	43	21.7	42.5	1.58	69	3.43	6
2	M	HCV	IGT	61	21.5	36.7	1.19	73	3.23	5
3	M	HCV	DM	50	22.7	22.1	5.18	35	3.02	13
4	F	PBC	IGT	48	21.8	41.0	2.16	58	3.34	8
5	M	Alcohol	DM	39	27.0	42.5	0.70	68	4.25	6
6	M	Alcohol	IGT	60	27.6	38.1	0.50	75	5.81	5
7	M	HCV	IGT	59	21.9	24.9	0.95	60	2.97	10
8	M	HCV	DM	67	31.6	31.8	1.05	74	3.72	6
9	M	HCV	DM	65	27.5	36.4	1.16	81	4.47	5
10	M	Alcohol	IGT	43	27.4	34.6	5.72	51	3.28	9
Mean				52	25.1	35.1	2.02	64	3.57	
SD				9	3.6	7.0	1.87	14	0.88	
Normal values						>42	<0.4	>80	>6.0	—

Abbreviations: BMI, body mass index; M, male; F, female; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; IGT, impaired glucose tolerance; DM, diabetes mellitus.

glucose tolerance test. The average zinc content of the diet was 15.5 mg/d.

After basal assessment, all patients received an oral supplementation of zinc sulfate (200 mg three times per day) for 60 days. Such supplementation corresponds to approximately 136 mg zinc per day. In two cases (patients no. 1 and 10), the supplementation period was limited to 35 and 42 days, respectively, because of problems unrelated to zinc supplementation. During this period, no changes in the diet and/or drug treatment were allowed.

Control values for model-derived parameters were obtained in an unselected population of 25 non-obese, healthy subjects, with an age range of 24 to 70 years (median, 48), tested by the frequently sampled IV glucose tolerance test (FSIGT). All had normal routine liver function tests and no history of previous liver disease. Their mean body mass index was 24.0 (SD 3.4) kg/m^2 (range, 18.2 to 30.6).

All subjects gave informed consent to take part in the study. Since no ethical committee is operating in our department, the protocol was submitted to the Senior Staff Committee, which approved it.

FSIGT

The experimental protocol started between 8 and 8:30 AM, after an overnight fast. A butterfly needle was inserted into an antecubital vein for blood sampling, with patency being maintained by slow-saline drip. Basal blood samples were collected at time −8 minutes and −3 minutes, after which glucose (300 mg/kg body weight) was infused within 1 minute, starting at time 0. Additional samples were collected via a three-way stopcock at time 3, 4, 5, 6, 8, 10, 15, 25, 30, 35, 40, 50, 75, 110, 150, 180, 210, and 240 minutes. This sampling schedule differs from the classical 30-sample protocol,[13] being characterized by a reduced number of samples (n = 20). It was derived by the following statistical procedure. From a cohort of 17 cirrhotic patients tested by the same investigators with the full 30-sample protocol,[13] an optimal 12-sample schedule[22] was designed for each patient using individual parameter estimates of the minimal model of glucose disappearance, and of the insulin and C-peptide secretion and kinetics model.[13] By pooling all optimal samples determined in each patient of the whole cohort, a distribution of 204 samples was obtained, which was then approximated with a reduced sampling schedule by distributing evenly the number of original samples falling between two new samples. The final number of samples, 20, was chosen to allow an acceptable precision of parameter estimates.

Sampling tubes contained 10 U powdered heparin and 1 mg NaF; samples were kept on ice until centrifugation. Glucose was immediately measured, whereas insulin and C-peptide were later determined after storage at −20°C.

Assays

Glucose was measured in duplicate by the glucose oxidase technique on an automated analyzer. The coefficient of variation of any single determination was ±1.5%. Insulin was measured by an immunoenzymometric assay (AIA-PACK IRI, AIA-1200 system; Tosoh, Tokyo, Japan) with intraassay and interassay coefficients of variation for the quality control ≤7%. C-peptide was measured by radioimmunoassay (Lisophase; Tecnogenetics, Milan, Italy), with coefficients of variation ≤13%.

FSIGT Data Analysis

The time courses of glucose, insulin, and C-peptide were analyzed by the minimal-model technique.[20] A detailed description of the method, its usefulness, use, and widespread applications in different pathophysiological conditions can be found in recent review articles.[20,23] Briefly, the minimal model of glucose disappearance[20] provides two indexes, one of which is the insulin sensitivity index, S_I. It quantifies the ability of insulin to make tissues to dispose of glucose and liver to inhibit glucose production. The other index is glucose effectiveness, S_G, defined as the ability of glucose per se to enhance its own disappearance without any dynamic change in insulin concentration. S_G includes the contribution of basal insulin on glucose disposal in insulin-dependent tissues, and the effects of hyperglycemia per se on both insulin-dependent and non–insulin-dependent tissues. The former component is also called the basal insulin effect (BIE), and is expressed as the product of S_I times basal insulin concentration. The second component, which is remarkably larger, is termed "glucose effectiveness at zero insulin" (GEZI), and is calculated as the difference between total S_G and BIE.[24]

The minimal model of insulin secretion and kinetics, by analyzing insulin and C-peptide peripheral concentrations, allows the reconstruction of basal and dynamic rates of prehepatic insulin secretion and posthepatic insulin appearance into systemic circulation.[25]

Calculations

Parameter K_G (glucose disappearance rate, % per minute), used as an index of glucose tolerance, was calculated as the slope of the regression of ln(glucose) on time, in the interval between 10 and 40 minutes following a glucose load. Total insulin secretion and total systemic delivery were calculated as the integral from 0 to 240 minutes of the

C-peptide secretion rate and the insulin posthepatic appearance rate, respectively. Hepatic insulin extraction was computed as the percent difference between the prehepatic delivery rate and the posthepatic rate of appearance.

Statistical Analysis

On the basis of previous studies, both S_I and S_G were expected to be considerably reduced in cirrhosis. Because of uncertainty in parameter estimation by the model and variability on repeated measurements, only a 30% change in mean S_I or S_G was considered clinically relevant. On this basis, the sample size necessary, given an α error of 0.05 and a β of 0.20, estimated on the first five patients where an improvement in S_G became apparent, gave a total number of 10 cases. Differences between control and cirrhotic patients were tested for significance using Student's *t* test for unpaired data. Differences between values measured at baseline and following zinc supplementation were tested by *t* test for paired data, or by rank-sum test when appropriate. Correlation coefficients between various parameters were also calculated, using parametric and nonparametric tests. *P* values less than .05 were considered statistically significant. Data are expressed as the mean (SD) unless otherwise designated.

RESULTS

Zinc levels were low to normal or frankly reduced in cirrhosis before treatment (Table 2). After oral zinc, they increased on average by nearly 70% and were above the lower limit measured in healthy subjects in our laboratory in all cases, including the two patients who received zinc sulfate supplementation for a shorter period.

Fasting glucose concentrations were less than 8 mmol/L in all patients at baseline (Table 2), and not different after zinc supplementation. Fasting insulin levels were above the upper limit of our control population in 50% of cases, whereas fasting C-peptide levels were elevated in all patients but one. They did not change significantly after treatment (Table 2).

The time courses of glucose, insulin, and C-peptide after IV glucose are shown in Fig 1. There was a systematic trend towards lower glucose levels in the central part of the curve, and

Table 2. Plasma Zinc Levels and Fasting Concentrations of Glucose, Insulin, and C-Peptide in Individual Patients Before and After Zinc Supplementation

Patient No.	Plasma Zinc (mg/dL)		Fasting Glucose (mmol/L)		Fasting Insulin (pmol/L)		Fasting C-Peptide (pmol/L)	
	Before	After	Before	After	Before	After	Before	After
1	80	117	5.9	5.4	68	84	849	760
2	88	143	5.6	5.2	31	40	621	601
3	53	96	4.6	5.1	61	72	885	816
4	65	97	4.8	5.2	74	117	912	1037
5	83	132	6.0	5.7	38	81	847	809
6	94	150	5.4	5.3	137	111	958	539
7	84	165	4.8	5.3	120	110	697	792
8	79	103	7.3	6.3	193	194	1290	1078
9	74	150	7.2	7.0	130	118	1851	1671
10	63	135	5.4	5.2	200	139	777	601
Mean	77	128*	5.7	5.6	105	107	971	870
SD	11	24	0.9	0.6	61	30	332	331
Normal values	>95		<6.5		<100		<650	

*Significantly different from pretreatment levels ($P < .0001$, paired *t* test).

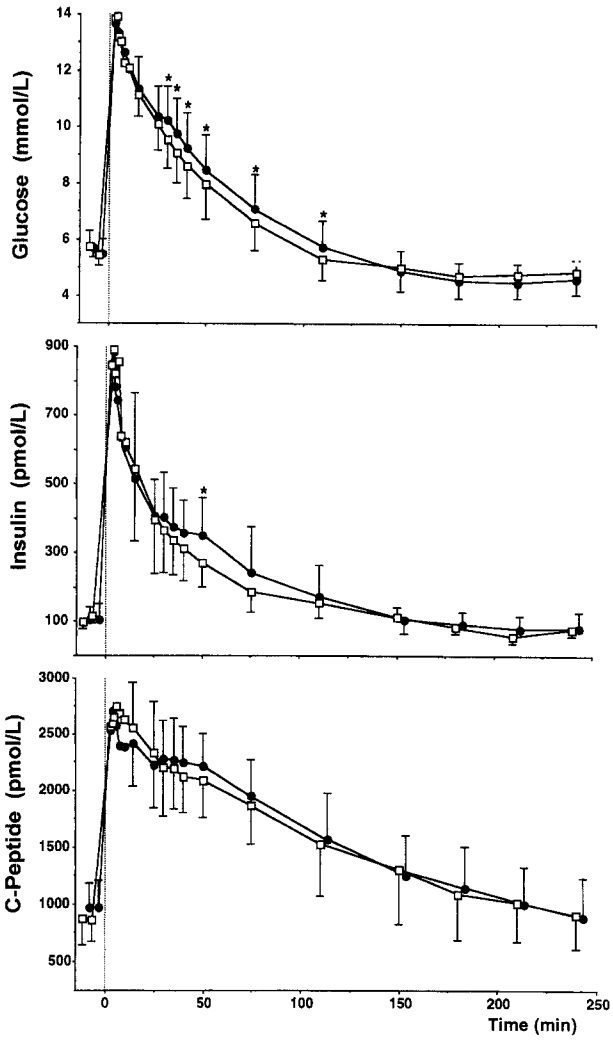

Fig 1. Time course of plasma concentration of glucose, insulin, and C-peptide during the FSIGT before (●) and after (○) zinc supplementation (mean ± 2 SE). Note that the 95% confidence intervals of the means were not reported in the first part of the curve. *Statistically significant difference in response to zinc treatment ($P < .05$, paired *t* test).

a reduced undershooting in the final part. Point-by-point analysis showed a statistically significant reduction in plasma glucose in the period from 30 to 110 minutes after the glucose load. Glucose disappearance (K_G) was less than 1.50%/min, considered the lower limit for normal subjects, in all cases but one at the basal, pretreatment assessment (0.87 [0.30] %/min). It increased to 1.15 (0.43) at the end of the experimental period ($P < .01$). It remained on average lower than in controls ($P < .05$), but in three patients, K_G was now in the normal range. Interestingly, K_G minimally improved in patients with cirrhosis and diabetes at an oral glucose tolerance test (from 0.72 [0.35] %/min to 0.89 [0.49]), whereas in patients with impaired glucose tolerance, K_G increased from 0.97 (0.24) to 1.33 (0.31) ($P < .05$).

Fasting and total insulin secretion during the course of the test (measured on C-peptide time course) and systemic insulin delivery (measured on insulin time course) were variable, and

remarkably increased in most patients in comparison to the control population. They did not change systematically after zinc treatment (Table 3), although there was a trend towards lower insulin concentrations in the central part of the curve. Hepatic insulin extraction, which ranged from 61% to 96% before treatment, did not change in response to oral zinc.

S_I was markedly reduced (by 80%) before treatment (1.53 [0.66] 10^{-4} min^{-1}/ [μU/mL]) when compared with control values (7.97 [3.26]). Following zinc supplementation, S_I increased nonsystematically by only 18% (1.82 [1.00]; P = not significant; Fig 2). Also, S_G was reduced by greater than 50% before treatment (0.013 [0.007] min^{-1} *v.* 0.028 [0.009] in controls; $P < .001$), but increased systematically to 0.017 (0.009) at the end of the treatment period ($P < .05$ *v.* baseline; Fig 3). However, in only four cases, it reached the lower limit of our control population (0.017 min^{-1}). In the two patients who received zinc sulfate for a shorter period, S_G increased from 0.012 min^{-1} to 0.016 and from 0.005 to 0.009, respectively.

The increase in S_G was mostly confined to patients with impaired glucose tolerance (from 0.015 [0.009] to 0.021 [0.009]; $P < .025$). In patients with diabetes mellitus, S_G increased minimally from 0.011 (0.005) to 0.013 (0.004) (not significant). In the whole population, improved S_G was due to an increase in both BIE (increasing from 0.0013 [0.0007] min^{-1} to 0.0018 [0.0011]) and, more remarkably, in GEZI (increasing from 0.010 [0.010] min^{-1} to 0.016 [0.009]; $P < .05$).

In cirrhotic patients and on repeated testing (n = 20), S_G was strictly associated with K_G ($r = -.777$; $P < .001$), accounting for greater than 60% of K_G variance. Plasma zinc levels were not correlated with glucose disappearance ($r = .389$), S_I ($r = .182$), or S_G ($r = .441$; $P = .051$) when the 20 experiments were considered. However, the change in zinc levels was significantly correlated with the change in glucose disappearance ($r_s = .675$; $P = .043$) and in S_G ($r_s = .689$; $P = .039$) (Fig 4).

DISCUSSION

This study shows that chronic zinc supplementation, restoring normal plasma zinc levels in zinc-deficient patients with cirrhosis, produces a small but significant improvement in glucose disposal after an IV glucose load. The rationale for a potential usefulness of zinc supplementation on glucose tolerance in cirrhosis is based on the following: (1) the effects of zinc on glucose metabolism; (2) severe hypozincemia in cirrhosis and effectiveness of zinc supplements in restoring normal zinc levels; and (3) impaired glucose tolerance associated with advanced liver disease.

Table 3. Model-Derived Parameters of Pancreatic Insulin Secretion and Systemic Insulin Delivery Before and After Zinc Supplementation (mean [SD])

	Pretreatment	After Zinc	Control Values*
B-cell secretion			
Basal (pmol/L/min)	62.1 [26.1]†	65.2 [36.8]†	34.0 [14.7]
Total (nmol/L in 240 minutes)	27.9 [8.5]†	28.0 [12.0]†	15.5 [8.1]
Systemic delivery			
Basal (pmol/L/min)	6.7 [5.2]	10.1 [10.1]	6.7 [4.4]
Total (nmol/L in 240 minutes)	5.2 [3.5]†	5.9 [3.7]†	2.6 [1.2]
Hepatic insulin extraction (%)	79 [12]	78 [12]	80 [9]

*Control values were obtained in a population of 25 normal subjects.

†Significantly different from control values.

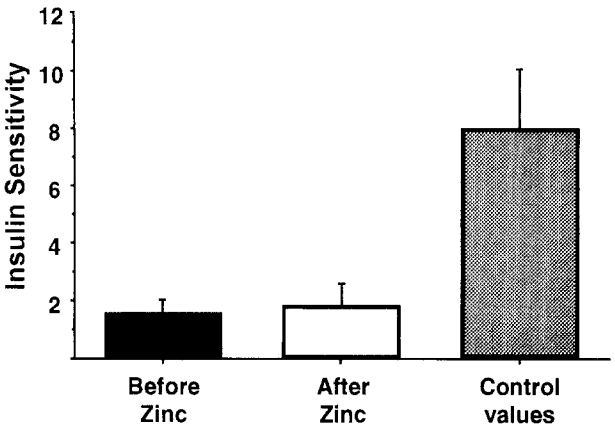

Fig 2. Insulin sensitivity (in $10^{-4}min^{-1}$ [μU/mL]) in cirrhotic patients, before (■) and after zinc supplementation (□), and in control subjects (▨) tested by the FSIGT. Data are presented as the mean ± 2SE.

The link between zinc status and glucose metabolism has long been investigated since the demonstration that zinc constitutes an integral part of the insulin molecule. There is a large body of experimental evidence supporting a role of zinc on insulin secretion,[15,16] consistent with the importance of zinc in insulin storage inside pancreatic β cells. More recently, a number of studies have related zinc status to insulin activity. In experimental animals, zinc pretreatment increases insulin binding to liver plasma membranes and attenuates insulin degradation,[26] and increases lipogenesis[18] by a mechanism complementary to insulin. Trace elements, including zinc, have insulinomimetic properties,[27] possibly mediated by an action at the level of insulin receptor tyrosine kinase.[28] In zinc-deficient animals, S_I measured by the clamp technique was shown to be reduced because of a postreceptor defect.[29]

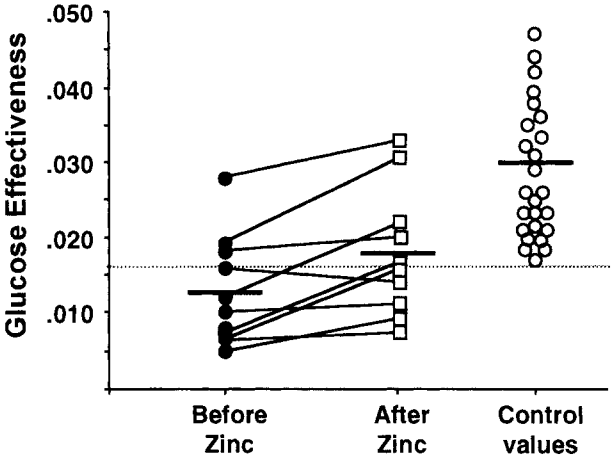

Fig 3. S_G (in min^{-1}) in cirrhotic patients, before (●) and after zinc supplementation (□), and in control subjects (○) tested by the FSIGT. Data in individual patients with cirrhosis are connected with a line. Mean values are indicated by horizontal bars. The pointed horizontal line identifies the lower limit of the control population.

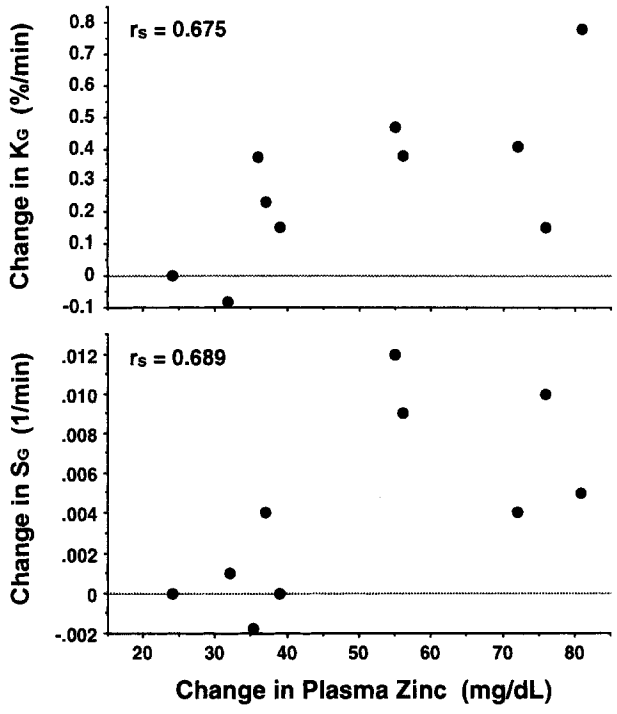

Fig 4. Correlation between changes in plasma zinc levels and changes in glucose disappearance (K_G) and glucose effectiveness (S_G) in patients with cirrhosis and altered glucose metabolism in response to oral zinc supplementation.

In humans, conflicting data are available on the relationship between zinc, insulin secretion and activity, and glucose control.[30] Zinc supplementation does not improve metabolic control in type II diabetes,[21] and deleterious effects were reported in type I diabetes.[31] In healthy subjects, Brun et al[19] found that acute zinc treatment improves the rate of disappearance of glucose after an IV load via an increase in non–insulin-dependent glucose uptake, without any change in insulin secretion and sensitivity.

As for the relationship between zinc status and cirrhosis, the present study confirms that plasma zinc levels are reduced in cirrhosis, in association with hyperzincuria.[32,33] Zinc treatment, either with zinc sulfate[3,7,8] or zinc acetate,[6] improves or normalizes zinc status, as was the case in the present study. Apparently, zinc treatment produces a remarkable improvement in clinical and biochemical data, although conflicting results were reported on hepatic encephalopathy.[6-8] The metabolic effects were mainly related to a specific activity of zinc on hepatic metabolism,[2,3] but also a more general, nutritional effect was considered.[2]

A similar mechanism might also be operative on the altered glucose metabolism of cirrhosis. Although insulin resistance was reported to be the main determinant of impaired glucose tolerance in cirrhosis,[12] more recent data have suggested that the effects of glucose per se are reduced as well, mainly in patients with frank diabetes[34,35] and in relation to poor nutritional status.[13] There is evidence that in the presence of insulin resistance, as shown in cirrhosis, the contribution of S_G to total glucose disposal becomes critical, and small changes in S_G are likely to produce relevant effects.[36]

The methodology used in the present study allows a dissection of the metabolic effects of insulin on glucose metabolism from the effects of glucose per se, and a general analysis of factors responsible for glucose disposal after an IV glucose load.[20] The results obtained in patients with cirrhosis are in fairly good agreement with data previously reported in a different series with similar degree of hepatocellular failure and glucose intolerance,[13] supporting the use of the simplified procedure developed in the present study. They also fit with values reported in the literature regarding S_I and S_G, repeatedly measured by different methods in cirrhosis.[34,35,37] The high value of hepatic insulin extraction produced by the model, largely exceeding values obtained by direct measurements,[38] is not surprising. The minimal-model approach does not consider only first-pass extraction, which usually refers to direct measurements performed by invasive arterial-hepatic vein difference techniques, but provides a figure of the total amount of hormone degraded in the liver. In keeping with the quantitative model-derived analysis of hepatic extraction is also a qualitative, model-independent rough calculation of the molar ratio of the areas under the concentration-time curves of insulin and C-peptide in the two groups. This averaged 0.85 (0.09) in controls, and 0.86 (0.07) and 0.87 (0.05) in cirrhosis before and after treatment, respectively.

Improved glucose disposal after zinc supplementation was entirely due to increased non–insulin-mediated glucose uptake, without any systematic effect on insulin secretion and sensitivity. The relevance of S_G in total glucose disappearance has been already outlined in previous studies in dogs, where the contribution of insulin-independent glucose disappearance during an IV glucose tolerance test was estimated to be 57%.[39,40] By using the same formula,[39] we calculated that S_G accounted for a net glucose disappearance of 10.8 (4.9) g in cirrhosis before zinc supplementation, corresponding to 51% of injected glucose. This value increased to 13.7 (3.5) g (63.5%) after zinc treatment. These values depend on the estimation of the glucose space, assumed to be equal to 0.65 times 27% of body weight.[41] These assumptions are not necessarily true in cirrhosis, where the glucose space may be larger due to increased extracellular water.[42] This would increase the contribution of S_G to glucose disappearance even further.

Any comment regarding the mechanism for improved S_G remains merely speculative. Enzymes involved in glucose disposal do not belong to the group of metalloenzymes, and a specific activity of zinc at this level cannot be supported. In response to zinc, improved nutritional status and liver function were already observed.[3] In the present study, the Child-Pugh score improved by 1 to 3 points in six patients, remained stable in three, and deteriorated (by 1 point) in only one patient; prothrombin activity increased by 5% ($P < .05$ *v.* baseline). Improved nutritional status and liver function were not observed during a 3-month follow-up evaluation of a control series of untreated cirrhotic patients with a similar degree of hepatocellular failure,[3] in keeping with a specific effect of zinc supplementation. If the results are nutritionally related, the action of zinc is more likely to involve glucose transporters on

cell membranes of both hepatocytes and peripheral tissues, as also suggested in other experiments,[35] and/or a modification of the glucose transporter structure (receptorial mechanism). Also, a postreceptor mechanism has been involved.[43] Increased S_G might reflect not only an enhanced activity of the insulin-independent glucose transporters GLUT1 and GLUT2 (namely in the liver),[44] but also an accelerated glucose-induced recruitment of the insulin-dependent GLUT4 transporters in muscle, and their activation through a mechanism distinct from insulin.[45]

Finally, zinc stimulation of glucose metabolism might occur via insulin-like growth factor I (IGF-I). Zinc supplementation increases plasma levels of IGF-I in humans,[46] stimulating growth and anabolism.[47] IGF-I stimulates glucose uptake independent of insulin in experimental animals,[48] and in humans during physiological and pathological conditions.[49] Shmueli et al[50] showed that IGF-I levels are reduced in cirrhosis, in the presence of elevated insulin-like growth factor-binding protein I, and the defect correlated with the reduced total glucose uptake during a hyperinsulinemic euglycemic clamp. The minimal model includes in the parameter S_G any non–insulin-mediated glucose disappearance, including IGF-I–stimulated glucose uptake. Measurements of IGF-I in response to zinc treatment in cirrhosis are needed to clarify this topic.

The minimal model does not explicitly account for the loss of glucose in the urine. In general, during a FSIGT, glucose is elevated above the renal threshold for a brief period, ie, during the so-called mixing period often neglected in the analysis.[51] The effect of urinary loss on model-derived parameters has never been directly evaluated. In a simulation study in type II diabetes, reduced glomerular filtration rate with renal failure responsible for a reduced urinary loss of glucose was shown to decrease S_G.[52] Theoretically, supplementation-induced hyperzincuria might favor the urinary loss of glucose, thus increasing S_G. Data from the literature do not support this hypothesis. In diabetes, no correlation was ever reported between urinary zinc loss, urinary glucose excretion, fasting plasma glucose, and glycosylated hemoglobin.[53] On the contrary, hyperglycemia or glucose infusion increased urinary zinc,[14] but the problem has not been fully investigated. Based on the calculations regarding the effects of S_G on net glucose disappearance,[39] supplementation-induced hyperzincuria can hardly account for an increased urinary loss of glucose equal to the increased net glucose disappearance of 2.9 g estimated by S_G. Such a concept is also supported by the finding that blood glucose levels are increased slightly above the renal threshold of 10 mmol/L for a short period (20 to 30 minutes), without differences in the first part of the glucose curve in relation to zinc supplementation.

Patients enrolled in the present study represent a selected group of subjects with glucose intolerance or diabetes at an oral glucose tolerance test, associated with hyperinsulinemia and insulin resistance, and a variable degree of hepatocellular failure. Glucose tolerance was not tested by an oral glucose tolerance test at the end of the treatment period, but it is conceivable that accelerated glucose disposal after an IV load may reflect improved glucose tolerance after an oral challenge. In only three cases K_G returned to normal values, but the improvement observed in nearly all patients, and specifically in patients with impaired glucose tolerance, makes zinc supplementation a relevant therapy in patients with cirrhosis with abnormal glucose tolerance.

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