Serum chromium does not predict glucose tolerance in late pregnancy[1,2]

Jenny E Gunton, Graham Hams, Rosemary Hitchman, and Aidan McElduff

ABSTRACT

Background: Chromium is an essential element in human nutrition. Serum concentrations of chromium are not well characterized during pregnancy or in gestational diabetes mellitus.

Objective: The objective of this study was to determine whether low plasma chromium concentrations (≤3 nmol/L) are associated with altered glucose, insulin, or lipid concentrations during pregnancy.

Design: The study was conducted prospectively and took place at the medical obstetric clinic of a tertiary referral hospital. Seventy-nine women with abnormal results of a 50-g glucose challenge test in the third trimester of pregnancy were studied. All women had a formal 75-g oral-glucose-tolerance test, and fasting insulin, lipid, and chromium concentrations were determined. Chromium was measured by graphite furnace atomic absorption spectrometry.

Results: The median chromium concentration was 2 nmol/L (95% CI: 0, 12). There were no significant differences in age, plasma glucose, insulin, lipids, calculated insulin resistance, or calculated β cell function between women with normal and those with abnormal (≤3 nmol/L) chromium concentrations.

Conclusions: Plasma chromium during pregnancy does not correlate with glucose intolerance, insulin resistance, or serum lipids. Plasma chromium concentrations may not accurately reflect tissue stores of chromium. Several trials showed a beneficial effect of chromium supplementation on glucose tolerance, insulin, and lipids. A method for assessing body chromium stores is required to allow further study. *Am J Clin Nutr* 2001;73:99–104.

KEY WORDS Chromium, glucose intolerance, gestational diabetes, pregnancy, triacylglycerol, cholesterol

INTRODUCTION

Chromium is considered an essential element for humans. A diet lacking in chromium may result in the development of diabetes mellitus. This phenomenon was first described in patients receiving long-term total parenteral nutrition before the routine addition of chromium (1, 2). Diabetes in these patients was resolved with supplemental chromium therapy (1–3).

Chromium is believed to be an insulin-sensitizing agent and may facilitate insulin attachment to the insulin receptor (4). Chromium may improve insulin sensitivity by activating insulin receptor tyrosine kinase, an effect that has been shown in rats (5), and by inhibiting phosphotyrosine phosphatase (PTP-1), which is a rat homologue of human tyrosine phosphatase (PTP-1B), which inactivates the activated (phosphorylated) insulin receptor. Thus, chromium may promote phosphorylation of, and hence activation of, the insulin receptor, leading to improvement in insulin sensitivity (5).

The dietary requirement for chromium is somewhat controversial. The recommended daily intake in the United States is 0.05–0.2 μg (6). The safe reference dose quoted by the US Environmental Protection Agency is 70 000 μg/d for lifetime exposure (7). It is estimated that 10 million Americans take supplemental chromium, making chromium the second largest-selling mineral supplement after calcium (8).

There are difficulties in the measurement of chromium concentrations. Chromium is a common substance in the general environment and is present in concentrations equal to or greater than those seen in the circulation. This renders contamination a significant problem because the amount of chromium in a sample may increase by much more than the original amount present (6, 9). Contamination is also relevant to studies of hair samples, which are exposed to shampoo, colorants, and the environment. Concentrations of >3 nmol/L in serum and plasma are considered normal (6, 10, 11). Chromium can be measured in urine, but such measurements similarly do not appear to reflect total body chromium status. It is not known whether chromium status in humans can be assessed by measurement of chromium in other bodily fluids or tissues.

We routinely perform oral-glucose-tolerance tests in all women who have abnormal results of 50-g glucose challenge tests during pregnancy (12). Chromium was measured in these women on the morning of the oral-glucose-tolerance test to determine whether serum chromium had any relation to fasting plasma glucose, insulin, cholesterol, or triacylglycerols or to insulin resistance or β cell function derived from the glucose and insulin measurements using the homeostasis assessment model (13). Our hypothesis was that low plasma concentrations of

[1] From the Department of Endocrinology and Pacific Laboratory Medicine Services, Royal North Shore Hospital, St Leonards, Australia.

[2] Address reprint requests to JE Gunton, Department of Endocrinology, Royal North Shore Hospital, St Leonards, NSW 2065, Australia. E-mail: jennyeg@hotmail.com.

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TABLE 1
Patient characteristics for the group as a whole and subdivided by serum chromium concentration

	All patients (n = 79)	Patients with chromium ≤3 nmol/L (n = 63)	Patients with chromium >3 nmol/L (n = 16)
Age (y)	32 ± 5[1]	32 ± 4	32 ± 5
Height (cm)	163 ± 6	164 ± 7	162 ± 7
Prepregnancy weight (kg)	58 (44, 98)[2]	60 (34, 130)	56 (45, 79)
Prepregnancy BMI (kg/m^2)	21.9 (16.2, 37.1)	22.0 (14.7, 46.6)	21.5 (18.1, 33.0)
Parity	0.7 (0–3)[3]	0.6 (0–3)	0.8 (0–3)
Pregnancy interval (mo)	14	15	14
Race (white/Asian/Arabic)	50/20/8	41/17/5	10/3/3
Time of gestation (wk)	29 (21, 35)	29 (25, 34)	29 (28, 35)

[1] $\bar{x}$ ± 1 SD.
[2] Median (95% CI).
[3] Median; range in parentheses.

chromium might be associated with insulin resistance and possibly with hyperglycemia or hypertriglyceridemia, or both.

SUBJECTS AND METHODS

Seventy-nine consecutive women with abnormal results of 50-g glucose challenge tests in the third trimester of pregnancy (1-h plasma glucose concentration, ≥7.8 mmol/L) were studied. All women subsequently had a 75-g oral-glucose-tolerance test, interpreted by the guidelines of the Australasian Diabetes In Pregnancy Society (14); a fasting plasma glucose concentration ≥5.5 or a 2-h value ≥8.0 mmol/L is considered abnormal. The mean (±1 SD) age of the women was 32 ± 5 y.

At the time of the oral-glucose-tolerance test, all women had fasting insulin, total cholesterol, triacylglycerol, and chromium concentrations measured. No additional venipuncture was performed in these women and there were no deviations from usual care.

Plasma glucose was measured by the hexokinase method. Insulin was measured by radioimmunoassay (Phadaseph AB, Uppsala, Sweden). Total cholesterol was measured by enzyme colorimetric testing (Boehringer Mannheim Systems, Mannheim, Germany). Triacylglycerols were measured by enzyme colorimetric testing (Boehringer Mannheim Systems).

All chromium samples were collected by one investigator (RH). A butterfly set was used and the adaptor was removed after collection of other fasting blood samples. The blood was then allowed to drip into the specially prepared chromium collection tubes. Chromium was measured by graphite furnace atomic absorption spectrometry with a Varian SpectrAA800 Zeeman effect instrument from Varian Australia P/L, Melbourne.

The sample was diluted 3-fold before analysis with a surfactant solution. A 20-μL aliquot of the diluted sample was atomized from the wall of a graphite furnace in the instrument's workhead by ramped heating to 2700°C. The atomic absorption of ground state chromium atoms was measured at the 357.9-nm line. Nonatomic background absorption at the line was simultaneously measured and subtracted. Solution concentrations were calculated from the maximum atomic signal observed during the atomization pulse relative to a set of matrix-matched calibrators spanning the concentration range (0–96 nmol/L).

Incorporating retained quality-assurance samples in each analysis controlled the determination. The within-run precision at 6 nmol/L was 15% and the between-run precision at 22 nmol/L was 23%. The laboratory performing the determination participates in the quality-assurance program for chromium in serum conducted by Quality Control Technologies (Charlestown, Australia). No alternative techniques for measurement of serum chromium were available.

With use of the homeostasis model (13), insulin resistance was calculated with the formula insulin/(22.5e − $\ln^{\text{glucose}}$). β Cell function was calculated with use of the formula 20 × insulin/(fasting glucose – 3.5).

Means ± 1 SD are presented. Values that were not normally distributed are presented as medians with 95% CIs and were compared by using nonparametric Mann-Whitney rank-sum analysis. Statistics were performed with use of SPSS (version 6; SPSS Inc, Chicago). Our sample size gave a power of ≈95% with an α of 5% to detect a difference of 0.75 SD in fasting glucose, 2-h glucose, insulin, cholesterol, or triacylglycerol (15) between groups with normal compared with abnormal chromium measurements. The procedures were in accord with the Helsinki Declaration of 1975, revised in 1983.

RESULTS

The mean age of the participants was 32 ± 4 y. The median body mass index (in kg/m^2) calculated from prepregnancy weight was 21.9 (95% CI: 16.2, 37.1). The median gestation at testing was 29 wk (95% CI: 25, 31). When women with chromium concentrations ≤3 nmol/L (6, 10, 11) were compared with women with concentrations >3 nmol/L, there were no significant differences in patient characteristics (**Tables 1** and **2**).

Twenty-five (31.6%) women had gestational diabetes according to the criteria of the Australasian Diabetes in Pregnancy Society; of these, 7 had elevated fasting concentrations. Fifty-four (68.4%) had normal glucose tolerance; 34.8% of women with low chromium concentrations had gestational diabetes and 27.3% of the women with normal chromium concentrations had gestational diabetes. The median chromium concentrations did not differ significantly between women with normal and those with abnormal glucose tolerance.

There were no significant differences in any test results between the groups with normal and abnormal serum chromium concentrations. There was a trend toward lower triacylglycerol concentrations in women with normal chromium concentrations (2.0 ± 0.6 compared with 2.3 ± 0.8 mmol/L; P = 0.09).

Given that there is some controversy about the normal serum chromium concentration (4, 6, 10, 11), we examined the data to

TABLE 2
Variables in the group as a whole and subdivided by serum chromium concentration

	All patients (n = 79)	Patients with chromium ≤3 nmol/L (n = 63)	Patients with chromium >3 nmol/L (n = 16)
50-g challenge (mmol/L)	8.8 ± 1.0[1]	8.8 ± 1.1	8.6 ± 0.8
Fasting glucose (mmol/L)	4.7 ± 0.6	4.7 ± 0.6	4.8 ± 0.4
2-h glucose (mmol/L)	7.2 ± 1.8	7.4 ± 1.9	6.8 ± 1.2
Insulin (pmol/L)	9.2 (2.9, 30.3)[2]	9.2 (2.9, 34.6)	9.7 (2.0, 16.0)
Total cholesterol (mmol/L)	6.7 ± 1.1	6.7 ± 1.2	6.7 ± 0.9
Triacylglycerol (mmol/L)	2.2 ± 0.7	2.3 ± 0.7	2.0 ± 0.6
Chromium (nmol/L)	2 (0, 10)	1 (0, 3)	5 (4, 11)
Gestational diabetes	25 (31.6)	22 (34.9)	3 (18.8)
Insulin resistance	1.9 (0.5, 7.4)	1.9 (0.6, 7.6)	1.9 (0.4, 6.0)
β Cell function	166 (59, 1068)	166 (74, 3461)	165 (31, 591)

[1] $\bar{x}$ ± 1 SD. There were no significant differences between groups.
[2] Median (95% CI).

determine whether there was any cutoff chromium concentration that appeared to be related to differences in lipids or glucose tolerance. We tested serum chromium concentrations of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, and 6 nmol/L but identified no cutoff value at which any significant differences appeared. There were no significant associations when chromium was tested as a continuous variable (**Table 3**).

Body mass index correlated with fasting blood glucose (P = 0.002), fasting insulin (P < 0.001), calculated β cell function (P = 0.02), and insulin resistance (P < 0.001). The fasting blood glucose correlated with 2-h glucose (P < 0.001), insulin (P < 0.001), and triacylglycerols (P = 0.01). Fasting insulin also correlated with triacylglycerols (P = 0.007). Finally, and importantly, there were no significant correlations between serum chromium concentration and any of the other measures studied.

DISCUSSION

The results of some studies suggested that pregnancy may be associated with chromium depletion (16, 17). These studies used only hair chromium concentrations, and the problems with measurement mentioned in the Introduction of this article may apply to these data. One study examined hair chromium in women with gestational diabetes compared with women with normal glucose tolerance in pregnancy (18) and found lower hair chromium at the end of pregnancy in women with gestational diabetes. The low median serum concentrations in the present study were consistent with other data that showed lower chromium in pregnancy. A literature search did not locate any studies of serum chromium measurement in pregnancy. Studies of chromium supplementation are summarized in **Table 4**.

A randomized study of 24 women with gestational diabetes who received chromium picolinate supplements (4 $\mu g \cdot kg \cdot d^{-1}$) or placebo found significantly lower fasting glucose and insulin concentrations in the women receiving chromium at 8 wk. Peak glucose and insulin concentrations after a 100-g oral-glucose-tolerance test were also significantly lower (53). A case report of a patient with type 1 diabetes who was receiving chromium picolinate supplementation noted a marked improvement in glycemic control (glycated hemoglobin, 11.3–7.9%) over 3 mo (51). One study in which placebo was compared with 200 μg chromium picolinate/d in 48 patients with type 1 diabetes and in114 patients with type 2 diabetes showed that ≈70% of patients receiving chromium reduced their oral hypoglycemic medications or insulin doses (48).

A randomized placebo-controlled study of 180 individuals with type 2 diabetes compared placebo, supplementation with 200 μg Cr/d, and supplementation with 1000 μg Cr/d (50). Glycated hemoglobin values improved significantly in both groups receiving supplemental chromium at 4 mo (by 1.0% and 1.9%, respectively). Total cholesterol also decreased significantly at 4 mo in the high-dose group. Other studies showed improvement in lipids with chromium therapy, particularly triacylglycerols (47, 54).

TABLE 3
Correlation coefficients (r) of the variables for 79 patients

	BMI	Fasting blood glucose	2-h blood glucose	Insulin	β Cell function	Insulin resistance	Total cholesterol	Triacylglycerols
Chromium	–0.051	–0.005	–0.082	–0.176	–0.107	–0.159	–0.007	–0.152
BMI		0.361[1]	0.140	0.463[2]	0.285[3]	0.514[2]	–0.012	0.230
Fasting blood glucose			0.449[2]	0.456[2]	–0.304[1]	0.639[2]	–0.266[3]	0.305[1]
2-h blood glucose				0.091	–0.141	0.202	–0.17	0.194
Insulin					0.1	0.970[1]	–0.202	0.305[1]
β Cell function						0.021	0.05	–0.017
Insulin resistance							–0.277[3]	0.298[1]
Total cholesterol								0.232[3]

[1] P < 0.01.
[2] P < 0.001.
[3] P < 0.05.

TABLE 4
Summary of studies of chromium supplementation[1]

Diabetes mellitus status	Reference	No. of subjects	Form of supplementation and dosage	Duration	Significant effects
			μg/d		
No	Hopkins et al (19)	12	$CrCl_3$, 250	1 d	↑ GT
No	Levine et al (20)	10	$CrCl_3$, 150	12–16 wk	↑ GT
No	Carter et al (21)	9	$CrCl_3$, 250	1–4 d	None
No	Gurson et al (22)	15	$CrCl_3$, 50	1–6 wk	↑ GT
No	Riales and Albrink (23)	14	$CrCl_3$, 200	12 wk	↑ HDL chol
No	Anderson et al (10)	76	$CrCl_3$, 200	12 wk	Variable
No	Offenbacher and Pi-Sunyer (6)	8	$CrCl_3$, 300	10 wk	None
No	Potter et al (24)	5	$CrCl_3$, 200	5 wk	↑ BCF
No	Martinez et al (25)	85	$CrCl_3$, 200	10 wk	↑ GT
No	Bourn et al (26)	47	$CrCl_3$, 200	10 wk	↑ HDL
No	Urberg and Zemmel (27)	16	$CrCl_3$, 200, niacin	4 wk	↑ GT
No	Urberg et al (28)	2	$CrCl_3$, 200, niacin	52 wk	↓ chol
No	Wang et al (29)	10	$CrCl_3$, 50	12 wk	↓ chol, ↓ LDL
No	Press et al (30)	28	Cr pic, 200	6 wk	↓ chol, ↓ LDL
No	Lefavi et al (31)	34	Cr nic 2–800	8 wk	↓ chol
No	Anderson et al (32)	17	$CrCl_3$, 200	8 wk	↑ GT
No	Roeback et al (33)	63	BA Cr, 600	8 wk	↑ HDL
Yes	Roeback et al (33)	63	BA Cr, 600	8 wk	↑ HDL
Yes	Glinsman and Mertz (34)	6	$CrCl_3$, 180–1000	<20 wk	↑ GT in 3 of 6
No	Glinsman and Mertz (34)	10	$CrCl_3$, 180–1000	1–50 wk	None
No	Offenbacher and Pi-Sunyer (35)	8	Yeast Cr, 11	8 wk	↑ GT, ↓ chol
Yes	Offenbacher and Pi-Sunyer (35)	8	Yeast Cr, 11	8 wk	↑ GT, ↓ ins
No	Abraham et al (36)	51	$CrCl_3$, 250	28–64 wk	↑ HDL, ↓ TG
Yes	Abraham et al (36)	25	$CrCl_3$, 250	28–64 wk	↑ HDL, ↓ TG
No	Uusitupa et al (37)	26	Yeast Cr, 160	24 wk	None
Yes	Uusitupa et al (38)	10	$CrCl_3$, 200	6 wk	↓ ins (60 min)
No	Wilson and Gondy (39)	26	Cr pic, 220	14 wk	↓ ins
No	Thomas and Gropper (40)	14	Cr nic, 200	14 wk	None
Yes	Sherman et al (41)	7	$CrCl_3$, 50	16 wk	None
Yes	Nath et al (42)	12	Reduced Cr, 500	8 wk	↑ GT, ↓ ins, ↓ chol
Yes	Rabinowitz et al (43)	43	$CrCl_3$, 150	16 wk	None
Yes	Mossop (44)	26	$CrCl_3$, 600	16–32 wk	↓ fasting glucose
Yes	Elias et al (45)	6	Yeast Cr, 21	2 wk	↓ fasting glucose
Yes	Evans (46)	11	Cr pic, 200	6 wk	↓ Hb A_{1c}, ↓ LDL
Yes	Lee and Reasner (47)	28	Cr pic, 200	8 wk	↓ TG
Yes	Ravina (48)	162	Cr pic, 200	10 d	↓ glucose, ↓ ins
Yes	Thomas and Gropper (49)	5	Cr nic, 200	8 wk	None
Yes	Anderson et al (50)	185	Cr pic, 200–1000	16 wk	↓ Hb A_{1c}, ↓ chol
Yes	Fox and Sabovic (51)	1	Cr pic, 600	1 wk	↓ Hb A_{1c}
Yes	Jeejeebhoy et al (1)	1	$CrCl_3$, 200	1 wk	Reversal of diabetes
Yes	Freund et al (2)	1	$CrCl_3$, 100	1 wk	Reversal of diabetes
Yes	Brown et al (3)	1	$CrCl_3$, 200	1 wk	Reversal of diabetes
Gestational	Jovanovic-Peterson et al (52)	8	Cr pic, 1–600	3–10 wk	↓ glucose

[1] GT, glucose tolerance; chol, cholesterol; BCF, β cell function; pic, picolinate; nic, nicotinate; BA, biologically active; ins, insulin; Hb A_{1c}, glycated hemoglobin; TG, triacylglycerol.

A 1985 review (55) identified 23 studies of chromium supplementation in subjects without diabetes. Of these, 18 studies showed improvement in lipid, glucose, or insulin concentrations (n = 504). These studies are summarized in Table 4. Five studies showed no effect of chromium in subjects without diabetes. These studies were small, with a total of 67 patients in all the studies combined. None of the negative studies used chromium picolinate. Picinolate is a stereoisomer of nicotinic acid.

The review also identified 16 studies of chromium supplementation in patients with type 2 diabetes, which are also shown in Table 4. Of these studies, 13 showed a significant improvement in glucose, insulin, or lipid concentrations. These studies included a total of 502 patients. There were 3 studies, with a total of 55 subjects, in which no effect was found.

The form of chromium supplementation, as well as its dose, may be important. The studies with negative results (5 in subjects without diabetes and 3 in subjects with diabetes) used $CrCl_3$ (5 studies), chromium nicotinate (2 studies), or yeast chromium (1 study). These studies did not use chromium picolinate. The generally small size of these studies in both diabetic and nondiabetic subjects implies a lower power to detect a true difference. In only one of the supplementation studies was serum chromium

measured; modern techniques were used and care was taken to avoid contamination before and after therapy. That study did not find a correlation between change in serum chromium and improvement in glucose tolerance.

Picolinate is an isomeric form of nicotinic acid. Tissue concentrations of chromium have been studied in rats (56). Chromium absorption was studied for chromium chloride, chromium potassium sulfate, chromium picolinate, and other forms of chromium. Hepatic chromium incorporation was most pronounced with chromium picolinate. None of the studies with any of the forms of chromium showed harmful effects of chromium supplementation.

Few data are available regarding tissue concentrations of chromium, and adequate concentrations of tissue chromium are not known. The results of a study using intravenously administered $^{51}Cr^{3+}$ suggest that there is a plasma pool of chromium in relatively rapid equilibrium with tissue compartments (34). The plasma pool was very small (≈0.13 μg) and the turnover time was 5–12 min. Chromium accumulation in muscle, adipose tissue, and liver were shown, with much slower turnover, and larger pools, of up to 190 times the plasma pool (25 μg). Thus, chromium in serum may not accurately reflect total body stores, and body stores may be relevant to the effects on insulin action.

This study confirmed, with careful collection and sample preparation, that plasma chromium concentrations are lower than those reported in many previous studies but similar to those of other investigators who used careful collection methods and technique. The measurement of chromium in serum did not correlate with measurements of insulin resistance, glucose tolerance, or lipids in pregnant women, even though the study was appropriately powered. This study did not indicate whether tissue concentrations of chromium are related to these measures.

Further studies are needed, including *1*) investigation of tissue concentrations of chromium and *2*) further studies of chromium supplementation, which should incorporate measurements of serum chromium to ascertain whether baseline chromium or changes in serum chromium are predictive of a therapeutic effect.

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