Effect of Chromium Supplementation on Glucose Metabolism and Lipids

A systematic review of randomized controlled trials

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OBJECTIVE — A systematic review of the effect of chromium supplementation on glucose metabolism and lipid levels.

RESEARCH DESIGN AND METHODS — A literature search was conducted in MEDLINE and the Commonwealth Agricultural Bureau. Eligible studies were English language randomized controlled trials of chromium supplement intake ≥3 weeks, with ≥10 participants receiving chromium. All trials with glucose metabolism outcomes and trials of individuals with diabetes or glucose intolerance for lipid outcomes were included. Meta-analyses were performed as appropriate.

RESULTS — Forty-one studies met criteria, almost half of which were of poor quality. Among participants with type 2 diabetes, chromium supplementation improved glycosylated hemoglobin levels by −0.6% (95% CI −0.9 to −0.2) and fasting glucose by −1.0 mmol/l (−1.4 to −0.5) but not lipids. There was no benefit in individuals without diabetes. There were some indications of dose effect and differences among chromium formulations. Larger effects were more commonly observed in poor-quality studies. The evidence was limited by poor study quality, heterogeneity in methodology and results, and a lack of consensus on assessment of chromium status.

CONCLUSIONS — No significant effect of chromium on lipid or glucose metabolism was found in people without diabetes. Chromium supplementation significantly improved glycemia among patients with diabetes. However, future studies that address the limitations in the current evidence are needed before definitive claims can be made about the effect of chromium supplementation.

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Chromium is an essential mineral that is thought to be necessary for normal glucose and lipid homeostasis (1–3). Trivalent chromium in a complex known as glucose tolerance factor is considered the biologically active form. It was originally discovered in brewer's yeast (4). Chromium chloride, chromium nicotinate, and chromium picolinate are commonly used formulations of trivalent chromium. Chromium picolinate is a formulation designed to improve absorption (5). Severe chromium deficiency is known to cause reversible insulin resistance and diabetes (6–8). However, the effect of chromium supplementation in individuals who are not severely chromium deficient is unclear. Manufacturers aggressively promote the benefits of chromium in the prevention and treatment of insulin resistance and its associated conditions (type 2 diabetes, dyslipidemia, and cardiovascular disease), and the public has embraced its use. Chromium supplement sales represent ~6% of the U.S. mineral supplement market (9).

To clarify the role of chromium supplementation in the prevention and management of abnormal glucose and lipid homeostasis, we performed a systematic review of randomized controlled trials on the effect of chromium supplement intake on glucose metabolism and lipid profile.

RESEARCH DESIGN AND METHODS

Literature search and eligibility criteria

We conducted a systematic review of the English-language literature on the effects of chromium supplementation on glucose metabolism and lipids in nonpregnant adults in MEDLINE and Commonwealth Agricultural Bureau databases through 8 August 2006 (10). Search terms included chromium, diabetes mellitus, glycemia, glycosylated hemoglobin, metabolic syndrome, insulin resistance, and related terms. Additional publications were identified by domain experts and from review articles and citations included in a petition to the U.S. Food and Drug Administration regarding health claims for chromium picolinate (11).

We evaluated randomized controlled trials of chromium supplements, regardless of formulation. For studies with outcomes related to glucose metabolism, we included studies of individuals with type 1 or type 2 diabetes, glucose intolerance, or normal glucose tolerance. "Glucose intolerance" was defined based on the World Health Organization or American Diabetes Association criteria as either impaired fasting glucose (fasting plasma glucose 5.6–7.0 mmol/l) or impaired glucose tolerance (2-h postload glucose concentration 7.8–11.1 mmol/l); "normal glucose tolerance" was defined as either fasting plasma glucose <5.6 mmol/l or a 2-h postload glucose concentration <7.8 mmol/l (12,13). For studies with lipid

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Abbreviations: AUC-Glu, glucose area under the curve.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

outcomes, we included only studies whose participants had either diabetes or glucose intolerance because chromium's effect on insulin action is the putative mechanism by which chromium may affect lipids (14).

We excluded studies of <3 weeks' duration with <10 participants receiving chromium (but allowed smaller subsets of participants within larger studies), as well as letters, abstracts, and conference proceedings. Two reviewers independently screened abstracts and articles and subsequently extracted data. Discrepancies were resolved by consensus among all co-authors.

Outcomes of interest included glycosylated hemoglobin, fasting glucose, postload gycemia, insulin sensitivity, and lipoprotein (LDL, HDL, and triglyceride) levels.

Quantitative analysis

We evaluated the net difference between the within-treatment (chromium supplementation) effect and the within-placebo effect. For glycosylated hemoglobin, fasting glucose, and the lipoprotein outcomes, we performed random effects model meta-analyses (15). We analyzed HbA_1 and total glycosylated hemoglobin as equivalent to A1C, as they reflect glycemia similarly (16). When necessary, we estimated the SE of the net change from reported variance data, including *P* values. To compare differences across different subanalyses, *t* tests were performed. For other outcomes, we did not perform meta-analysis due to lack of uniformity in measuring these outcomes.

Study quality assessment

Methodological quality refers to the design, conduct, and reporting of the clinical study. The quality of each study was assessed by at least two authors using a 3-level classification (17); discrepancies were resolved by consensus of the coauthors. Good-quality studies likely had the least bias; they provided clear descriptions of the populations, settings, interventions, and comparison groups; used appropriate measurement of outcomes; used appropriate analytic methods, including blinding and appropriate controls; had no obvious reporting errors; had <20% drop out and clear reporting of drop outs; reported relevant outcomes quantitatively; and had no obvious bias. Fair-quality studies had some deficiencies but none likely to cause major bias or may be missing information limiting assessment. Poor-quality studies are susceptible to substantial bias, had serious errors in design or analysis, may have had large amounts of missing information or discrepancies in reporting, or had outcomes that were so poorly reported that estimates could not be assessed by the reader.

RESULTS — The literature search yielded 793 citations. We retrieved 96 articles, of which 41 met eligibility criteria (online appendix Fig. 1 [available at http://dx.doi.org/10.2337/dc06-0996]).

Characteristics of all evaluated studies

The studies included 1,198 participants who received four different chromium formulations (all doses throughout are elemental chromium): brewer's yeast (1.28–400 μg/day, 10 studies) (18–27), chromium chloride (50–600 μg/day, 15 studies) (21,22,24,27–38), chromium nicotinate (200–800 μg/day, 5 studies) (39–43), and chromium picolinate (60–1,000 μg/day, 15 studies) (39,44–57). One study did not describe the chromium formulation (400 μg/day) (58). Almost all study participants with diabetes had type 2, although in three studies this was unclear (22,29,31). No study included only patients with type 1 diabetes. Study duration ranged from 3 weeks to 8 months. Nine studies were funded by the food or supplement industry, 18 were funded by nonindustry sources, and 14 did not report funding source. Five studies were graded good quality, 18 fair quality, and 18 poor quality. Several studies attempted to measure participants' baseline chromium status, but a large variety of methods were used, and no study adequately assessed the possible impact of baseline chromium status on outcomes.

Glucose metabolism

Glycosylated hemoglobin. Fourteen studies with 18 intervention arms evaluated the effect of chromium supplementation on glycosylated hemoglobin in 431 participants (receiving chromium) with either type 2 diabetes or glucose intolerance (18–20,28,39,44–51,58) (Fig. 1 and online appendix Table 1). The overall estimate of chromium supplementation in people with diabetes was statistically significant (−0.6% [95% CI −0.9 to −0.2]). However, 11 of 14 interventions found a null or statistically nonsignificant effect. Anderson et al. (44) found a dose effect where high doses of chromium picolinate (1,000 μg/day) were more effective than low doses (200 μg/day, $P < 0.05$), but Kleefstra et al. (45) found no difference between 1,000 and 500 μg/day. No study of participants with glucose intolerance found a statistically significant effect of chromium supplementation on glycosylated hemoglobin (20,39,51).

Fasting glucose

The effect of chromium supplementation in a wide range of doses on fasting glucose was evaluated in 38 studies with 1,140 participants who had either type 2 diabetes, glucose intolerance, or normal glucose tolerance (Fig. 2 and online appendix Table 1).

Participants with type 2 diabetes

Seventeen studies with 23 chromium arms evaluated participants with diabetes (18,19,21–23,28–31,44,46–50,52,58) (Fig. 2*A*). The majority found no effect of chromium supplementation on fasting glucose. Seven of the 17 studies reported a statistically significant reduction in fasting glucose (18,21,23,44,46,48,58), and 2 additional studies stated there were large reductions in fasting glucose but did not report statistical significance (29,52).

The overall estimate for the effect of supplementation with brewer's yeast on fasting glucose was statistically significant (−1.1 mmol/l [95% CI −1.6 to −0.6]) but without a clear dose effect. Consistent with this, the study by Rabinowitz et al. (22) found no significant difference in fasting glucose among participants taking two relatively low doses of brewer's yeast (6 and 18 μg). Chromium picolinate had a significant effect on fasting glucose (−0.8 mmol/l [−1.2 to −0.3]). Across studies, doses of 400 or 1,000 μg/day appear to have had greater effects than lower doses. This was borne out by one study that directly compared doses (44).

Among studies of chromium chloride, there was no significant effect on fasting glucose (−0.3 mmol/l [95% CI −0.9 to +0.2]). The single study with a large effect on fasting glucose used a relatively high dose (600 μg/day), although this study was deficient in numerous ways, including lack of statistical analysis, inadequate randomization, and a range of treatment durations (29).

The two studies that compared brewer's yeast to chromium chloride found no significant difference between the two supplements (21,22).

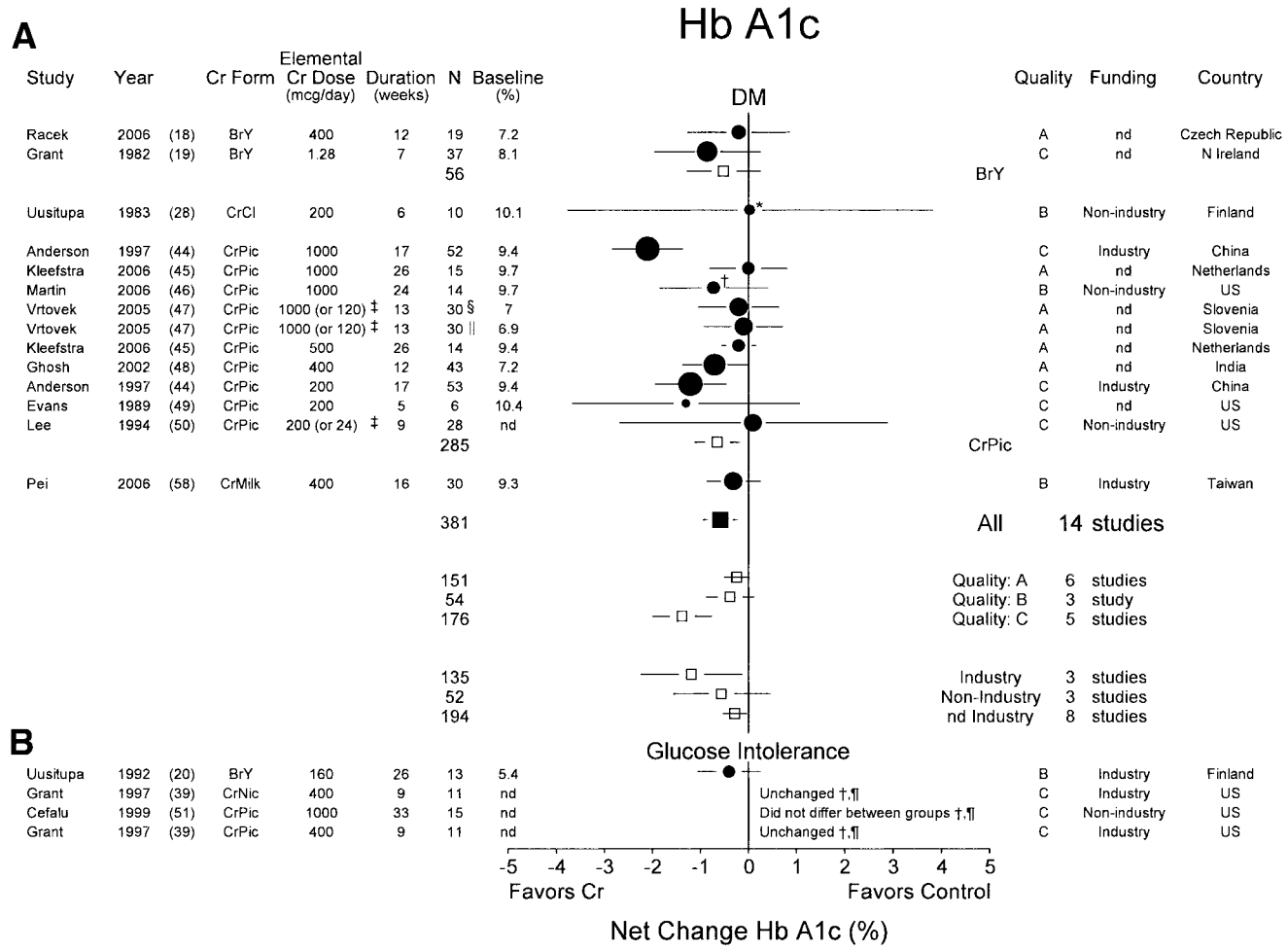

Figure 1—*Meta-analysis of randomized controlled trials of the effect of chromium supplementation on A1C (or other measures of glycosylated hemoglobin) in participants with type 2 diabetes* (A) *and participants with glucose intolerance* (B)*. The point estimates of the net changes (change in chromium arm minus change in control arm) and the corresponding 95% CI for individual studies are indicated by circles and bars. The random effects model summary estimates are indicated by squares and bars. Black squares indicate summary estimate of all studies; white squares indicate subanalyses, as indicated. Studies are arranged by chromium formulation (Cr Form), then dose, and then number of participants consuming Cr* (N)*. Total numbers refer only to studies included in the meta-analyses. "Glucose intolerance" is defined based on the World Health Organization or American Diabetes Association criteria as either impaired fasting glucose (fasting plasma glucose 5.6–7.0 mmol/l) or impaired glucose tolerance (2-h postload glucose 7.8–11.1 mmol/l) (12,13). Quality: A = good; B = fair; C = poor. *Hb A_1, not A1C; †total glycosylated hemoglobin; ‡unclear if dose refers to elemental chromium or total chromium picolinate; §cross-over study (received placebo first, followed by chromium picolinate); ‖cross-over study (received chromium picolinate first, followed by placebo); ¶no numerical data results reported. BrY, brewer's yeast; Cr, chromium; CrCl, chromium chloride; CrMilk, milk powder with chromium (no data on chemical formulation); CrNic, chromium nicotinate; CrPic, chromium picolinate; DM, diabetes; ND, no data.*

Participants with glucose intolerance

Eight studies with 11 arms included participants with glucose intolerance (20,32–34,39,40,53,54) (Fig. 2*B*). None reported a significant effect on fasting glucose. Overall estimates for both chromium chloride and chromium picolinate each found nil effects.

Participants with normal glucose tolerance

Nineteen studies with 23 arms included participants with normal glucose tolerance (Fig. 2*C*), 22 of which found no statistically significant effect of chromium supplementation on fasting glucose (23–27,30–38,41–43,55,56). The studies that evaluated chromium chloride, nicotinate, and picolinate were statistically homogeneous in finding no significant net effect of chromium supplementation. In meta-analysis of brewer's yeast, the studies were statistically heterogeneous and the summary estimate nonsignificant. Across studies, doses of brewer's yeast with >10 μg/day chromium had larger net decreases in fasting glucose than lower doses, which is consistent with the one study that directly compared doses (27).

Nonfasting (post–glucose load) measures of glycemia

Various glycemia measurements were reported after a variety of oral glucose tolerance tests in 25 studies in 822 participants receiving chromium (online appendix Tables 1–3). There was little consistency in glucose load, timing of measurements, or outcome metrics used. Thus, meta-analysis was not performed.

Participants with type 2 diabetes

Among the seven studies of participants with diabetes (19,21–23,28,31,44), only one found a statistically significant im-

provement in 2-h postload glycemia with either 200 or 1,000 μg/day chromium picolinate; the net decrease was greater with the higher dose supplement (−1.9 vs. −1.4 mmol/l, respectively) (44). The remaining studies of brewer's yeast or chromium chloride reported net changes in 2-h postload glucose of −1.2 to +0.3 mmol/l or a net change in the glucose area under the curve (AUC-Glu) of −24 to +24%, none of which was statistically significant.

Participants with glucose intolerance

Among the nine studies of participants with glucose intolerance (20,32–34,39,46,53,54,58), only Anderson et al. (32,33), in two separate studies of 200 μg/day chromium chloride, reported statistically significant improvements in postload glucose levels with chromium supplementation: in one, an 8% reduction in 4-h AUC-Glu (but not in 3-h AUC-Glu) and in the other a 1.1 mmol/l reduction in 90-min postload glucose. Other studies of all four chromium formulations reported nonsignificant changes in AUC-Glu of −21 to +3% and in various timed postload glucose levels of −1.5 to +0.4 mmol/l.

Participants with normal glucose tolerance

No consistent effect of chromium on postload glycemia was reported among the 14 studies of participants with normal glucose tolerance (23,25–27,31–34,36,37,41,43,55,56). In contrast to their other findings, Anderson et al. (32) found that in participants with normal glucose tolerance, the 90-min postload glucose level significantly increased in participants on 200 μg/day chromium. Across other studies of all four chromium formulations, no effect was evident, with AUC-Glu changing between −17 and +2% and various timed postload glucose levels changing between −2.3 and +1.8 mmol/l but without statistical significance.

Insulin sensitivity

Nine studies, with 138 participants receiving chromium, reported data on insulin sensitivity in participants with either normal glucose tolerance or glucose intolerance (24,27,37,46,51,54,56–58) (online appendix Table 4). Each study used a different surrogate of insulin sensitivity based on fasting or postload values of glucose and insulin (insulin-to-glucose ratio, homeostasis model assessment of insulin resistance, and "relative insulin") or after an intravenous glucose tolerance test (S_i). Only one study used the euglycemic-hyperinsulinemic clamp (46). All but two studies reported no significant change in insulin sensitivity. Cefalu et al. (51), in a study of 1,000 μg/day chromium picolinate in obese participants with a first-degree relative with diabetes, found a 70% net improvement in S_i estimated by the minimal model after an intravenous glucose tolerance test. However, there was a 25% (nonstatistically significant) difference in baseline S_i between the chromium and the control groups. In a later study by an overlapping group of researchers, Martin et al. (46) found that patients with moderately controlled type 2 diabetes (fasting glucose between 6.9 and 9.4 μmol/l at baseline) taking 1,000 μg/day chromium picolinate had a statistically significant increase in glucose disposal during a euglycemic-hyperinsulinemic clamp, whereas those on placebo had a nonsignificant decrease. However, no analysis was reported that directly compared chromium with placebo, and our estimate of the net change, using reported data, was nonsignificant (+13 mg/min per fat-free mass [95% CI −29 to +55]).

Lipid profiles

Eighteen studies, with 655 participants receiving chromium, reported lipid data in participants with either type 2 diabetes or glucose intolerance (18–23,28,29,44–46,48–50,52–54,56,58) (Fig. 3 and online appendix Table 5).

LDL cholesterol

None of the nine studies with LDL cholesterol data reported a statistically significant effect, regardless of chromium formulation or dose (18,20,28,45,48–50,53,58). The overall estimate of effect for chromium supplementation in all participants was nonsignificant (−0.31 mmol/l [95% CI −0.73 to +0.11]).

HDL cholesterol

Twelve studies evaluated HDL cholesterol (18–21,28,29,44,45,48,50,53,58). Two studies of lower-dose brewer's yeast (1 and 23 μg) in participants with type 2 diabetes found similar large, statistically significant net increases in HDL cholesterol (19,21), but chromium enriched, high-dose brewer's yeast (400 μg) did not affect HDL cholesterol in a third study (18). The single study of brewer's yeast in participants with glucose intolerance found no net effect (20). The three studies of chromium chloride supplementation in participants with diabetes were heterogeneous, finding a range of effects (0.0–0.6 mmol/l) (21,28,29). All six studies of chromium picolinate in participants with either diabetes or glucose intolerance found no effect on HDL cholesterol (44,45,48,50,53,58).

Individual studies found no difference in effect between brewer's yeast and chromium chloride or between different chromium picolinate doses (21,44,45).

Triglycerides

Seventeen studies reported on triglyceride effect (18–23,28,44–46,48–50,52–54,56,58), 15 of which found no statistically significant effect. Overall estimates for the tested chromium supplements (brewer's yeast, chromium chloride, and chromium picolinate) were each nonsignificant in participants with either type 2 diabetes or glucose intolerance (44,49,52), as was meta-analysis across the studies.

Study heterogeneity

We analyzed a number of factors to explain the statistically heterogeneity of most of the meta-analyses.

Chromium formulation

Some heterogeneity could be explained by differences in effect between the various chromium formulations. Among participants with type 2 diabetes, the effects of brewer's yeast, chromium chloride, and chromium picolinate on fasting glucose were each significantly different from each other ($P < 0.02$), such that studies of brewer's yeast had the greatest net effect (−1.1 mmol/l), followed by chromium picolinate (−0.8 mmol/l) and chromium chloride (−0.3 mmol/l). Similarly, among studies of participants with normal glucose tolerance, brewer's yeast was significantly more likely to reduce fasting glucose than chromium chloride (−0.2 vs. +0.1 mmol/l, $P = 0.01$) and to raise HDL cholesterol than chromium picolinate (+0.21 vs. −0.02, $P = 0.002$). In the few studies that directly compared different chromium formulations, none found differences (21,22,24,27,39).

Dose effect

The association between chromium dose and effect was difficult to interpret, in part

A

Study	Year		Cr Form	Elemental Cr Dose (mcg/day)	Duration (weeks)	N	Baseline (mmol/L)	Quality	Funding	Country
Racek	2006	(18)	BrY	400	12	19	8.2	A	nd	Czech Republic
Bahijri	2000A	(21)	BrY	23.2	8	74	10.7	B	Non-industry	Saudi Arabia
Rabinowitz	1983	(22)	BrY	18	17	28	11.3	C	Non-industry	US
Offenbacher	1980	(23)	BrY	10.8	8	4	5.7	B	Industry	US
Rabinowitz	1983	(22)	BrY	6	17	30	11.3	C	Non-industry	US
Grant	1982	(19)	BrY	1.28	7	37	9.2	C	nd	N Ireland
						192				BrY
Mossop	1983	(29)	CrCl	600	9-17 *	13	14.3	C	nd	Zimbabwe
Abraham	1992	(30)	CrCl	250	13	13	9.7	B	nd	Israel
Bahijri	2000A	(21)	CrCl	200	8	67	10.7	B	Non-industry	Saudi Arabia
Uusitupa	1983	(28)	CrCl	200	6	10	10.3	B	Non-industry	Finland
Rabinowitz	1983	(22)	CrCl	150	17	28	11.3	C	Non-industry	US
Sherman	1968	(31)	CrCl	150	16	7 ‡	nd	C	Non-industry	US
Sherman	1968	(31)	CrCl	150	16	3 §	nd	C	Non-industry	US
						128				CrCl
Anderson	1997	(44)	CrPic	1000	17	52	9.8	C	Industry	China
Martin	2006	(46)	CrPic	1000	24	14	9.4	B	Non-industry	US
Vrtovek	2005	(47)	CrPic	1000 (or 120) ‖	13	30 ¶	9.1	A	nd	Slovenia
Vrtovek	2005	(47)	CrPic	1000 (or 120) ‖	13	30 #	8.9	A	nd	Slovenia
Ghosh	2002	(48)	CrPic	400	12	43	6.9	A	nd	India
Rabinovitz	2004	(52)	CrPic	400	3	39	10.5	C	nd	Israel
Anderson	1997	(44)	CrPic	200	17	53	10.2	C	Industry	China
Evans	1989	(49)	CrPic	200	5	6	10.3	C	nd	US
Lee	1994	(50)	CrPic	200 (or 24) ‖	8	28	nd	C	Non-industry	US
						256				CrPic
Pei	2006	(58)	CrMilk	400	16	30	10.9	B	Industry	Taiwan
						606				All 21 studies
						122				Quality: A 4 studies
						212				Quality: B 7 studies
						272				Quality: C 10 studies
						139				Industry 4 studies
						289				Non-Industry 10 studies
						178				nd Industry 7 studies

nd on SE †

-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4

Favors Cr — Favors Control

Net Change Glucose (mmol/L)

B

Study	Year		Cr Form	Elemental Cr Dose (mcg/day)	Duration (weeks)	N	Baseline (mmol/L)	Quality	Funding	Country
Uusitupa	1992	(20)	BrY	160	26	13	5.2	B	Industry	Finland
Anderson	1983	(32)	CrCl	200	13	21 **	nd	C	nd	US
Anderson	1983	(32)	CrCl	200	13	20 ††	nd	C	nd	US
Anderson	1991	(33)	CrCl	200	4	17	5.1	B	nd	US
Martinez	1985	(34)	CrCl	200	10	11 ‡‡	6.2	B	Non-industry	Canada
Martinez	1985	(34)	CrCl	200	10	8 §§	5.4	B	Non-industry	Canada
						77				CrCl
Crawford	1999	(40)	CrNic	600	9	18	5.7	C	Industry	US
Grant	1997	(39)	CrNic	400	9	11	5.3	C	Industry	US
Volpe	2001	(53)	CrPic	400	12	20	5.1	B	Industry	US
Grant	1997	(39)	CrPic	400	9	11	4.9	C	Industry	US
Gunton	2005	(54)	CrPic	100	13	20	5.5	A	nd	Australia
						40				CrPic
						148				All 9 studies
						20				Quality: A 1 study
						69				Quality: B 5 studies
						59				Quality: C 3 studies
						51				Industry 3 studies
						19				Non-Industry 2 studies
						78				nd Industry 4 studies

nd on SE †

-2 -1.5 -1 -0.5 0 0.5 1 1.5 2

Favors Cr — Favors Control

Net Change Glucose (mmol/L)

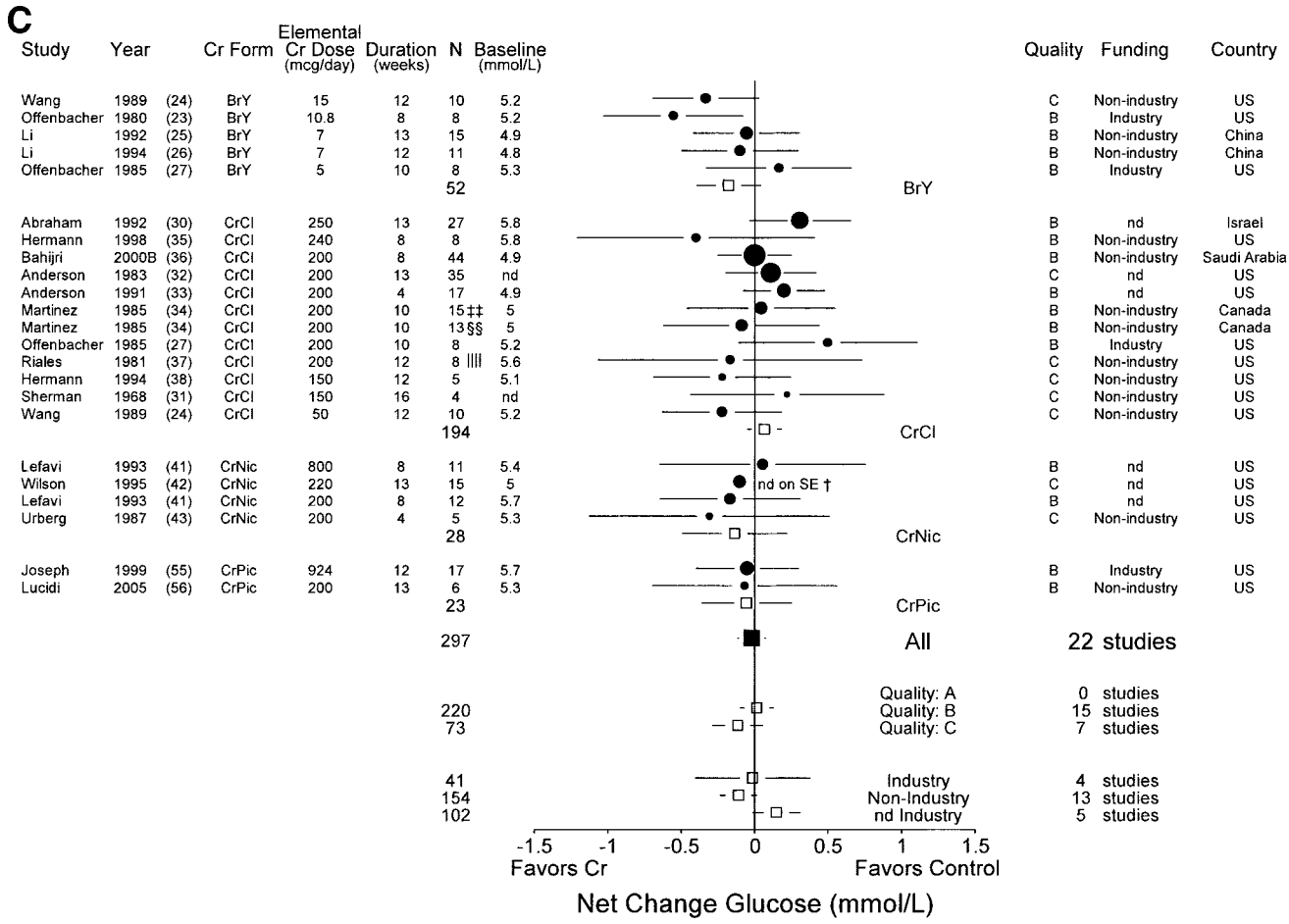

Figure 2—*Meta-analyses of randomized controlled trials of the effect of chromium supplementation on fasting glucose in participants with type 2 diabetes (A), participants with glucose intolerance (B), and participants with normal glucose tolerance (C). See Fig. 1. "Normal glucose tolerance" is defined as either fasting plasma glucose <5.6 mmol/l or 2-h postload glucose concentration <7.8 mmol/l (12,13). *Range of times when final FBS was drawn; †only point estimate reported (not included in meta-analyses); ‡participants with non–insulin-dependent type 2 diabetes; §participants with insulin-dependent type 2 diabetes; ‖unclear if dose refers to elemental chromium or total chromium picolinate; ¶cross-over study (received placebo first, followed by chromium picolinate); #cross-over study (received chromium picolinate first, followed by placebo); **glucose level 90 min after glucose tolerance test <100 mg/dl but greater than fasting glucose level; ††glucose level 90 min after glucose tolerance test >100 mg/dl; ‡‡study participants taking a "medication with hyperglycemic potential;" §§study participants not taking a "medication with hyperglycemic potential;" |||one participant had type 2 diabetes, and the remaining participants had normal glucose tolerance.*

because the exact dose was unclear in a number of chromium picolinate studies and the number of studies using different doses were small for several outcomes. In patients with diabetes, the effect of chromium picolinate on glycosylated hemoglobin and fasting glucose may have been greater in those studies that definitely used chromium doses of at least 200 μg/day or of 1,000 μg/day, respectively (Figs. 1*A* and 2*A*). However, both of these possible effects were largely driven by the single study that directly compared 200 μg and 1,000 μg chromium picolinate, which found greater effects with the higher dose (44). In participants with normal glucose tolerance, doses of brewer's yeast of at least 10 μg/day chromium may also have lowered fasting glucose more than lower doses, a finding confirmed by one study (27) (Fig. 2*C*). Most studies that compared doses did not find differences for several outcomes (21,22,27,41,44,45).

Study quality and funding source

For glycosylated hemoglobin in participants with type 2 diabetes (Fig. 1*A*) and for fasting glucose in participants with diabetes or normal glucose tolerance (Fig. 2*C*), poor-quality studies (B or C) had significantly greater favorable net effects than high-quality studies (A) ($P < 0.03$).

There was a trend among studies of fasting glucose in participants with diabetes (Fig. 2*A*) in that studies funded by industry had greater net improvements than other studies ($P = 0.06$). For other outcomes and subpopulations, there was no evidence of bias based on study quality or funding source.

CONCLUSIONS — Three-quarters of the 36 studies reviewed found no statistically significant effect on measured outcomes. However, most of the studies were inadequately powered; thus, lack of a statistically significant result may not indicate a lack of effect. Almost one-half of the studies were of poor quality, and there was substantial heterogeneity across studies in chromium formulations and doses used, in settings (and thus possibly underlying states of chromium nutrature), and in results. Though meta-analysis resulted in statistically significant improvements in glycemic control among patients

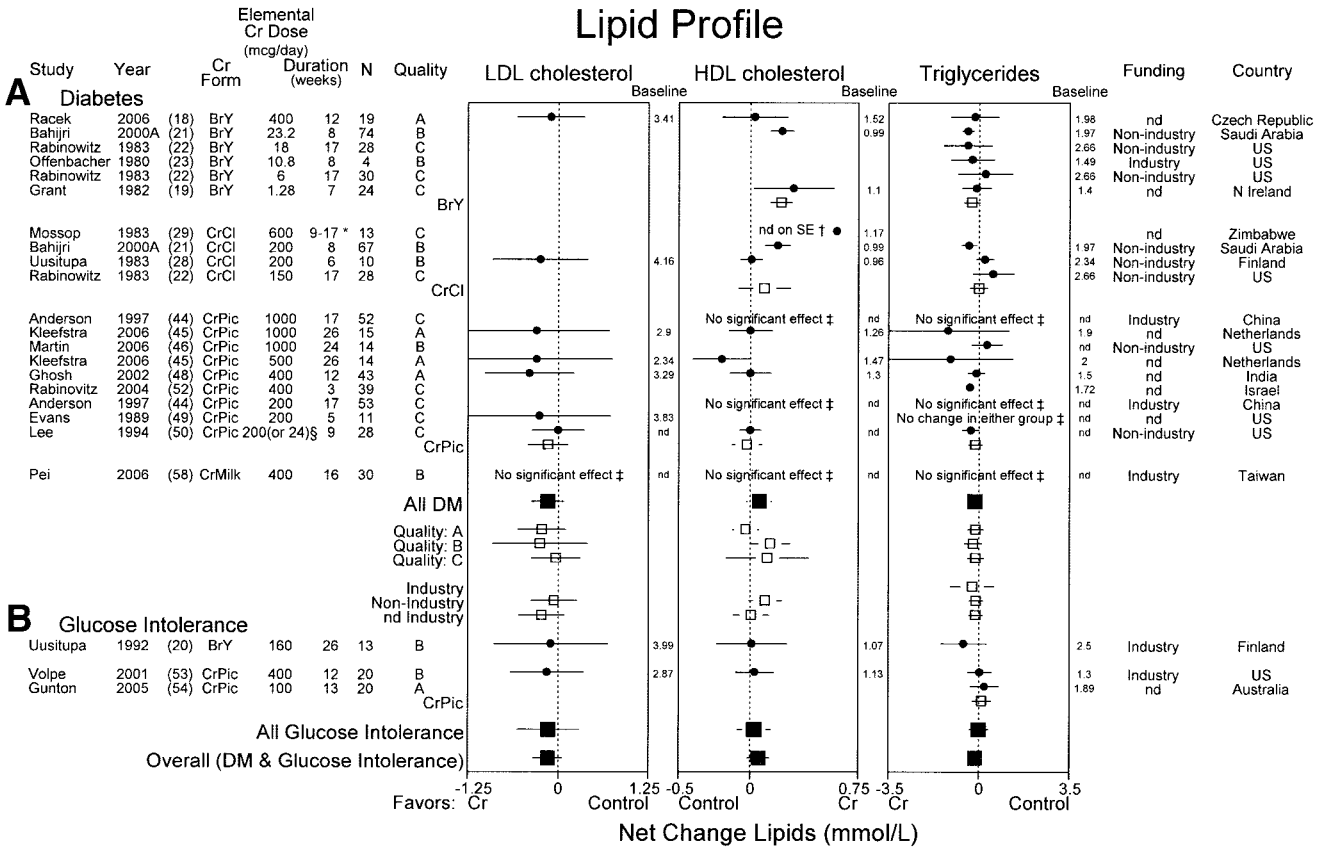

Figure 3—*Meta-analyses of randomized controlled trials of the effect of chromium supplementation on lipids, including LDL, HDL, and triglycerides, in participants with type 2 diabetes* (A) *and participants with glucose intolerance* (B)*. See Fig. 1. Gray squares indicate summary estimates of combination of all studies, regardless of glucose status. *Range of times when final HDL level was drawn; †variance data not reported and not included in meta-analysis; ‡no results data reported; §unclear if dose refers to elemental chromium or total chromium picolinate.*

with type 2 diabetes, given the poor quality and heterogeneity of much of the data, future studies that address the limitations in the current evidence are needed before definitive claims can be made about the effect of chromium supplementation.

In people with type 2 diabetes, our results show that, on average, chromium picolinate supplementation lowered A1C by 0.6% and that brewer's yeast and chromium picolinate lowered fasting glucose by 1.1 and 0.8 mmol/l, respectively. Overall, chromium supplementation did not affect lipid levels in people with type 2 diabetes or glucose intolerance, although brewer's yeast supplementation did statistically significantly raise HDL cholesterol by 0.21 mmol/l, which was a significantly greater effect than chromium picolinate.

Dose effects would provide confirmation of a beneficial effect of chromium supplementation. However, the dose effects were found across studies primarily for chromium picolinate and were driven largely by a single study (44). Likewise, a single study drove a possible difference between higher and lower dose brewer's yeast on fasting glucose in participants with normal glucose tolerance (27). Four other studies found no differences among different doses (21,22,41,45). Assessment of dose effects was hampered by the small number and size of studies comparing different doses.

In people with either normal glucose tolerance or glucose intolerance, chromium supplementation did not appear to have an effect on measures of glycemia, nor did chromium improve lipid profiles among people with glucose intolerance.

Chromium is thought to be a cofactor necessary for optimal insulin action (1–3). Therefore, chromium supplementation may exert its potential benefits by improvement in insulin sensitivity. Nearly all studies that examined the effect of chromium on insulin sensitivity found no significant effect. The exception, Cefalu et al. (51), found a statistically significant improvement in insulin sensitivity in relatives of patients with diabetes in a small study with considerable differences in baseline insulin sensitivity. Although the authors properly controlled for pre-randomization levels in their analyses, the large difference raises the concern that either the groups were not adequately randomized or that the distribution of insulin sensitivity values may have been skewed for some unknown reason. Even with adjustment, interpretation of the results is difficult, and future studies would need to confirm the finding. On the basis of this study, the U.S. Food and Drug Administration recently gave chromium picolinate the food-related health claim that it "may reduce the risk of insulin resistance, and therefore possibly may reduce the risk of type 2 diabetes . . . however, the existence of such a relationship between chromium picolinate and either insulin resistance or type 2 diabetes is highly uncertain" (59). Assessing the effect of chromium on insulin sensitivity is further hampered by the lack of studies with robust measures of insulin sensitivity, such as the euglycemic-hyperinsulinemic clamp.

Differences in effect between the four different chromium formulations were difficult to assess. Subgroup meta-analyses did show some statistically sig-

nificant and some qualitative differences in effects between formulations, such that brewer's yeast and chromium picolinate significantly lowered fasting glucose in people with type 2 diabetes, while the effect of chromium chloride was nonsignificant; brewer's yeast raised HDL cholesterol levels more than chromium chloride and chromium picolinate. However, these and other indirect comparisons across studies are hypothesis-generating only. With few studies directly comparing different factors such as dose and formulation, it is difficult to be conclusive about differences in effect. Only five studies directly compared different chromium formulations, and none found any differences among them. However, it is notable that brewer's yeast had similar effects as other chromium formulations despite substantially lower doses of chromium, possibly suggesting that another component in brewer's yeast has an effect on insulin sensitivity. We were unable to evaluate differences in formulation and dose together; however, the differences in effect of low–chromium dose brewer's yeast compared with high-dose chromium in other formulations suggest that the effect of chromium doses may not be comparable in different formulations.

Overall, the quality of the studies on chromium supplementation was poor and thus subject to bias. We observed major deficiencies such as lack of blinding or allocation concealment, inadequate randomization, high dropout rates, nonstandard outcome measurements, and inadequate reporting regarding the chromium product being investigated, the study methodology, the eligibility criteria, the statistical analyses, the baseline characteristics, and the outcomes. Our finding that for glucose outcomes, poor-quality studies were significantly more likely to yield favorable net effects than good- or fair-quality studies suggests that much of the apparent effects found may be largely due to biases related to poor methodology and reporting.

Similarly, there was a trend in at least one set of studies—those evaluating fasting glucose in participants with diabetes—that industry-sponsored studies may have been more likely to find a net benefit of chromium supplementation. In addition, the possibility of either conscious or unconscious biases, including publication bias where "negative" studies were withheld, must be considered. However, conclusions regarding funding source bias may be spurious, given the relatively few studies available for analysis. Due to lack of an adequate measure of chromium nutrature and few such analyses, we were unable to address whether relatively chromium-depleted people would be more likely to benefit from supplementation.

Our meta-analysis is limited by the overall poor quality and heterogeneity of available studies. While we were able to explain some of the heterogeneity as being related to chromium dose, study quality, or funding source, there remained large differences in results across studies, even after accounting for different chromium formulations.

In conclusion, we found that chromium supplementation in patients with type 2 diabetes may have a modest beneficial effect on glycemia and dyslipidemia. In contrast, there was no beneficial effect of chromium supplementation on glycemia or lipids in those without diabetes. The large heterogeneity across these studies and the overall poor quality limit the strength of our conclusions. By elucidating the body of evidence on chromium supplementation, our meta-analysis highlights the questions that remain and the issues that need to be addressed in future randomized trials of chromium on glucose and lipid metabolism.

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