

## Review Article

# Chromium, Glucose Intolerance and Diabetes

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Richard A. Anderson, PhD, FACN

*Nutrient Requirements and Functions Laboratory, Beltsville Human Nutrition Research Center, US Department of Agriculture, ARS, Beltsville, Maryland*

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Within the last 5 years chromium (Cr) has been shown to play a role in glucose intolerance, Type 2 diabetes mellitus (Type 2 DM), and gestational diabetes. In addition, diabetes and the neuropathy of a patient on home parenteral nutrition were alleviated when supplemental Cr was added to total parenteral nutrition (TPN) solutions. In a study conducted in China that has been supported by studies in the United States, supplemental Cr as Cr picolinate improved the blood glucose, insulin, cholesterol, and hemoglobin A<sub>1C</sub> in people with Type 2 DM in a dose dependent manner. Follow-up studies of >1 year have confirmed these studies. The requirement for Cr is related to the degree of glucose intolerance: 200 µg/day of supplemental Cr is adequate to improve glucose variables of those who are mildly glucose intolerant. However, people with more overt impairments in glucose tolerance and diabetes usually require more than 200 µg/day. Daily intake of 8 µg of Cr per kg body weight was also more effective than 4 µg/kg in women with gestational diabetes. The mechanism of action of Cr involves increased insulin binding, increased insulin receptor number, and increased insulin receptor phosphorylation. In summary, supplemental Cr has been shown to have beneficial effects without any documented side effects on people with varying degrees of glucose intolerance ranging from mild glucose intolerance to overt Type 2 DM.

### Key teaching points:

- Chromium alleviates glucose intolerance.
- Chromium alleviates Type 2 DM and gestational diabetes.
- Chromium increases insulin receptor phosphorylation.
- Chromium is a safe nutrient supplement.

## INTRODUCTION

Chromium (Cr) is an essential element required for normal carbohydrate and lipid metabolism [1–4]. Signs of Cr deficiency have been documented on numerous occasions, including elevated blood glucose, insulin, cholesterol and triglycerides, and decreased high density lipoproteins (HDL) in humans consuming normal diets (Table 1). More severe signs of Cr deficiency (including nerve and brain disorders) that are reversed by supplemental Cr have been reported for patients on total parenteral nutrition (TPN) [5–7]. Chromium is now routinely added to TPN solutions [8].

While there are numerous, well controlled studies reporting

the beneficial effects of improved Cr nutrition, there are also a few well controlled studies reporting no or minimal beneficial effects of Cr (Table 1). This review will attempt to evaluate the Cr nutrition studies involving humans and try to clarify the field of Cr nutrition.

## CHROMIUM ESSENTIALITY IN HUMANS

The essentiality of Cr in human nutrition was documented in 1977 [5] when a female patient on total parenteral nutrition (TPN) developed severe diabetic-like symptoms that were refractory to insulin. Before Cr supplementation, the patient was

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**Table 1.** Chromium Supplementation Studies of Subjects Without Diabetes

Authors	Subjects	Form ( $\mu\text{g/day}$ )	Duration (week)	Significant Cr effects
Glinsmann & Mertz, 1966 [33]	10 adults	$\text{CrCl}_3$ (150–1000)	3	No effects
Hopkins et al, 1968 [58]	12 malnourished children	$\text{CrCl}_3$ (250)	0.11	Improved glucose tolerance
Levine et al, 1968 [59]	10 elderly	$\text{CrCl}_3$ (150)	12–16	Improved glucose tolerance
Carter et al, 1968 [60]	9 children w/kwashiorkor	$\text{CrCl}_3$ (250)	0.14–0.43	No effects, elevated basal Cr intake
Gurson & Saner, 1971 [61]	15 malnourished children	$\text{CrCl}_3$ (50)	1–6	Improved glucose tolerance
Offenbacher & Pi-Sunyer, 1980 [62]	8 elderly	Yeast Cr (11)	8	Improved glucose tolerance; decreased cholesterol
Riales & Albrink, 1981 [63]	14 men	$\text{CrCl}_3$ (200) 5 days/wk	12	Increased HDL cholesterol
Anderson et al, 1983 [23]	76 adults	$\text{CrCl}_3$ (200)	12	Decrease 90-minute glucose in subjects w/90-minute glucose >5.56 mmol/L; increased 90-minute glucose in subjects w/90-minute glucose <fasting
Offenbacher et al, 1985 [22]	8 elderly	$\text{CrCl}_3$ (200)	10	No effects: subjects were nutrition-oriented & consumed intakes at or above RDA for 8 indicator nutrients
Potter et al, 1985 [49]	5 elderly	$\text{CrCl}_3$ (200)	5	Increased $\beta$ -cell sensitivity using euglycemic clamp
Martinez et al, 1985 [64]	85 elderly women	$\text{CrCl}_3$ (200)	10	Decreased plasma glucose of 80 subjects w/12 minute glucose >5.56 mmol/L not on medication. No effects in women on medication
Bourn et al, 1986 [65]	47 women	$\text{CrCl}_3$ (200)	10	Increased HDL & decreased total cholesterol:HDL ratio in 21 women not on medication. No effects in women on medication
Urber & Zimmel, 1987 [66]	16 elderly	$\text{CrCl}_3$ (200)+100 mg niacin	4	Decreased fasting glucose; improved glucose tolerance
Urberg et al, 1988 [67]	2 men	$\text{CrCl}_3$ (200)+100 mg niacin	52	Decreased total cholesterol
Wang et al, 1989 [68]	10 adults	$\text{CrCl}_3$ (50)	12	Decreased total & LDL-cholesterol
Press et al, 1990 [69]	28 adults	Cr picolinate (200)	6	Decreased total cholesterol, LDL & apoprotein B; increased apoprotein A-1
Lefavi et al, 1993 [70]	34 men	Cr nicotinate (200 and 800)	8	Decreased total cholesterol & total cholesterol:HDL ratio
Anderson et al, 1991 [26]	17 adults	$\text{CrCl}_3$ (200)	5	Improved glucose tolerance & decreased circulating insulin in 9 subjects w/90-minute glucose >5.56 mmol/L
Roebach et al, 1991 [71]	63 adults on beta-blockers	Biologically active Cr (600)	8	Increased HDL cholesterol
Uusitupa et al, 1992 [40]	26 elderly	Yeast Cr (160)	24	No effects
Abraham et al, 1992 [27]	51 adults w/atherosclerotic disease	$\text{CrCl}_3$ (250)	28–64	Increased HDL cholesterol; decreased triglycerides
Wilson & Gondy, 1995 [72]	26 adults	Cr picolinate (220)	14	Decreased insulin in subjects w/initial fasting insulin >35 pmol/L w/o diabetes
Thomas & Gropper, 1996 [73]	14 adults	Cr nicotinate (200)	14	No effects

losing weight, accompanied by glucose intolerance and neuropathy, even when she received 50 units of exogenous insulin per day. When 200  $\mu\text{g}$  of Cr as Cr chloride was added to her TPN solutions for 3 weeks, her diabetic-like symptoms were

alleviated and exogenous insulin was no longer required. This work has been confirmed several times and documented in the scientific literature on two occasions [6,7].

In one of our studies involving Cr supplementation of

trauma patients on TPN [9], one patient had abnormally high blood glucose although the patient was receiving more than 12 µg of Cr daily. When an additional 12 µg of Cr as Cr chloride was added daily to the TPN solutions, the blood glucose dropped from approximately 25 mmol/L to 8.3 mmol/L. Subsequent elimination of the additional Cr from the TPN solutions led to a return of the elevated glucose levels, but these levels were reversed when the additional 12 µg daily of Cr was added back [10].

Beneficial effects of Cr are not limited to patients on TPN. Children, the elderly, people with Type 1 and 2 diabetes mellitus (DM), as well as those with low blood sugar, have all been shown to display positive effects in response to supplemental Cr (Table 1). In addition to humans, beneficial effects of supplemental Cr have been observed in rats, mice, squirrel monkeys, guinea pigs, rabbits, fish, pigs, cattle, and horses [2–4].

### SUGGESTED AND/OR ESTIMATED SAFE AND ADEQUATE DAILY DIETARY INTAKES FOR CHROMIUM

In 1979, an American Medical Association Panel [11] recommended the daily administration of 10 to 15 µg of Cr for adult TPN patients and 0.14 µg/kg to 0.20 µg/kg for pediatric patients. Fleming et al [12] recommended 10 µg to 20 µg daily for adults, and Green et al [13] proposed 0.2 µg/kg/day for infants and children. However, the Cr content of adult TPN solutions may not be adequate for severely stressed patients. For example, neurological symptoms of a patient on TPN, who was also receiving metronidazole returned to normal within 3 weeks after further addition of Cr (250 µg/day for 2 weeks) to the TPN fluids [14]. By contrast, TPN solutions may be too high for infants and children [15], leading to negative effects that include reduced growth [16]. The basal Cr content of TPN solutions varies widely and should be monitored [8].

The estimated safe and adequate daily dietary intake (ES-ADDI) for Cr is shown in Table 2 [1]. Similar values were proposed in 1980. The ESADDI for infants of 10 µg to 40 µg is based upon breast milk Cr concentrations obtained before 1980 that were often 10-fold higher than presently accepted values [17]. Recent values for breast milk Cr are in the region of 0.18 µg/L [17 and cited references]. The American Academy of Pediatrics [18] recommends that breast milk be the sole

source of nutrients for children from 4 to 6 months of age. Based on the present ESADDI of 10 µg to 40 µg for children, children would need to consume more than 55.6 liters of breast milk daily to obtain the minimum suggested daily intake of 10 µg [17]. Although breast milk is likely to have a higher Cr bioavailability than other sources, this has not been documented.

The normal dietary Cr intake for adults is also below the minimum ESADDI of 50 µg. Anderson and Kozlovsky [19] measured the daily Cr intake of 22 female and 10 male subjects for 7 consecutive days. Not a single subject had a mean daily Cr intake of 50 µg or more. Mean SEM daily intake was 25±1 µg for the women and 33±3 µg for the men. Similar or slightly higher values have been reported in other countries [20]. The Cr content of 22 daily diets designed by nutritionists to be well balanced ranged from 8.4 µg to 23.7 µg per 4.18 MJ (1000 kcal) with a mean±SEM Cr concentration of 13.4±1 µg per 4.18 MJ [21]. Mean Cr intake for freely chosen diets was 15±1 µg per 4.18 MJ, which is nearly identical to the value observed previously [19]. Assuming a mean Cr concentration of 15 µg per 4.18 MJ, more than 12 MJ would have to be consumed to obtain the minimum ESADDI and more than 50 MJ (12,000 kcal) for the upper limit of 200 µg of the ESADDI.

Since it is difficult to obtain the minimum suggested Cr intake of 50 µg, does this mean that the ESADDI is too high? On the contrary. There is no evidence that the ESADDI for adults is too high, and numerous studies have documented that normal dietary Cr intake is suboptimal (Table 1). Over the past three decades there have been more than 23 published Cr supplementation studies involving subjects who do not have clinical diabetes (Table 1). All but five of these reported at least one significant positive effect of supplemental Cr. The most readily observed benefit reported in the majority of the studies was improved blood sugar and/or insulin (Table 1). Not only is the amount of Cr consumed daily important, but specific foods may negatively affect Cr status as well. For example, foods high in simple sugars are not only usually low in Cr but enhance Cr losses. Chromium intakes of 30 µg to 40 µg per day would likely be adequate if well balanced diets low in simple sugars and high in fresh fruits and vegetables were consumed. This inference would be similar to the well balanced diets in the study by Offenbacher et al [22], in which subjects consuming diets containing 37 µg/day of Cr and adequate in eight other indicator nutrients did not respond to supplemental Cr.

**Table 2.** Suggested and/or Estimated Safe and Adequate Daily Dietary Intakes for Chromium

Age group	Recommended Cr dose
Children 7 years to adult	50–200 µg
Ages 4 to 6 years	30–120 µg
Children 1 to 3 years	20–80 µg
Infants 0.5 months to 1 year	20–60 µg
Infants aged ≤6 months	10–40 µg

### CHROMIUM SUPPLEMENTATION IN PEOPLE WITH GLUCOSE INTOLERANCE AND DIABETES

The response to Cr is related to the degree of glucose intolerance. We [23] conducted a study involving Cr supplementation of normal free-living subjects free of diabetes. Subjects with 90-minute glucose greater than 5.56 mmol/L (oral

glucose challenge of 1 g/kg body wt) responded to supplemental Cr with a decrease in 90-minute blood glucose. Blood glucose of subjects with good glucose tolerance (defined as 90-minute glucose less than 5.56 mmol/L but greater than fasting) was unchanged by supplemental Cr. These subjects had good glucose tolerance and showed no signs of Cr deficiency; therefore they did not respond to additional Cr. The blood glucose of subjects who tended to have low blood sugar (90-minute glucose less than fasting) increased after Cr supplementation. A follow-up study confirmed that subjects with low blood sugar respond to supplemental Cr [24]. In the follow-up study, a decrease in the area of the glucose tolerance curve below fasting (increased blood glucose in response to a glucose challenge) was associated with increased insulin binding, increased insulin receptor number, and alleviation of hypoglycemic symptoms, including blurred vision, sweating, trembling, sleepiness, etc. This work has been confirmed [25]. The mechanism whereby supplemental Cr leads to a decrease in blood glucose of subjects with elevated blood glucose and an increase in people with hypoglycemia is that Cr functions by regulating or potentiating insulin action. Improved insulin efficiency in people with elevated blood glucose leads to a more efficient removal of glucose from the blood. In people with hypoglycemia, supplemental Cr also leads to a normalization of insulin function that leads to increased insulin efficiency and a return to normal concentrations more quickly in response to a glucose challenge [24].

Further documentation that the Cr requirement is related to the degree of glucose intolerance was reported by Anderson et al [26] in a study in which subjects consumed low Cr diets. Consumption of diets comprised of normal foods containing less than 20  $\mu\text{g}$  of Cr daily resulted in no significant changes in the glucose and insulin variables of subjects with good glucose tolerance (as defined above), but consumption of these same diets by people with 90-minute glucose values greater than 5.56 mmol/L resulted in increased blood glucose and insulin levels that were reversed by supplemental Cr (200  $\mu\text{g}/\text{d}$  as Cr chloride).

## CHROMIUM AND BLOOD LIPIDS

In addition to improvements in blood glucose and insulin due to supplemental Cr, there have been at least 8 studies involving Cr supplementation of subjects without diabetes whose blood lipids improved following Cr supplementation. Such improvements are usually greatest in subjects with the highest blood lipids, but significant changes may take several months to appear [3]. In the study of Abraham et al [27], with 250  $\mu\text{g}$  Cr as Cr chloride, increased HDL cholesterol and decreased triglycerides did not appear until 6 to 16 months. Although we have not observed significant effects of 200  $\mu\text{g}/\text{day}$  of Cr as  $\text{CrCl}_3$  on blood lipids in our studies, Cr supplementation periods only lasted 3 months or less. Even so, several studies (Table 1) have reported beneficial effects of Cr

on blood lipids in 3 months or less. The variable response to Cr in blood lipids is likely similar to responses in blood glucose and will be discussed later (see the section on Why Aren't All the Studies Positive?)

## CHROMIUM AND DIABETES

In Table 3, it is clear that 200  $\mu\text{g}$  of Cr as Cr chloride is not sufficient to elicit a positive response in those with Type 2 DM. The studies of Sherman et al [28] and Rabinowitz et al [29] with 150  $\mu\text{g}$  of Cr as  $\text{CrCl}_3$  showed no effects of supplemental Cr. The positive effect of 200  $\mu\text{g}$  as  $\text{CrCl}_3$  in the study of Uusitupa et al [30] on 60-minute insulin is questionable; moreover, the remaining variables measured were not altered by supplemental Cr. The studies that report positive effects of supplemental Cr on people with diabetes usually involve 400  $\mu\text{g}$  or more of Cr. Mossop [31] reported a decrease in fasting glucose from 14.4 mmol/L to 6.6 mmol/L following 16 to 32 weeks of daily supplementation with 600  $\mu\text{g}$  of Cr as Cr chloride. Nath et al [32] reported positive effects with 500  $\mu\text{g}/\text{day}$ , and Glinsmann and Mertz [33] used up to 1000  $\mu\text{g}/\text{day}$  of Cr as Cr chloride. Abraham et al [27] reported positive effects on blood lipids with 250  $\mu\text{g}/\text{day}$ , but it took 28 to 64 weeks for effects to be significant. The reasons for the slow response may be due to the form and amount of Cr.

Other forms of Cr, especially Cr picolinate, are more effective than Cr chloride in human and animal studies [34]. Two hundred micrograms of Cr daily as Cr picolinate leads to improved glucose and lipid variables in people with Type 2 DM [35,36] with a better response at 1000  $\mu\text{g}/\text{day}$  [37]. Women with gestational diabetes also respond better to 8  $\mu\text{g}$  per kg body weight of Cr as Cr picolinate than to 4  $\mu\text{g}/\text{kg}$  [38].

## WHY AREN'T ALL THE STUDIES POSITIVE?

If Cr has an effect on those with impaired glucose tolerance and Type 2 DM, why aren't all the studies involving these subjects positive? There are a number of reasons. First of all, human studies include subjects of diverse genetic and nutritional backgrounds living in environments of varying degrees of stress, all of which may affect Cr metabolism [39]. Varying results of supplemental Cr may also be due to the diet, selection of subjects, the duration of the study, and the amount and type of supplemental Cr. In Table 3 it is obvious that studies involving subjects with diabetes receiving 200  $\mu\text{g}/\text{day}$  of supplemental Cr as Cr chloride did not report beneficial Cr effects [28–30], whereas similar studies employing 400  $\mu\text{g}$  or more of Cr as Cr chloride reported positive effects of supplemental Cr [31–33]. Essentially all the studies employing the more bioavailable Cr picolinate have reported positive effects (Table 3), with greater effects reported at 1000  $\mu\text{g}/\text{day}$  than at 200  $\mu\text{g}/\text{day}$  [37].

In addition, response to Cr is related to the degree of glucose

**Table 3.** Chromium Supplementation Studies of Subjects With Type 2 Diabetes Mellitus

Authors	Subjects	Form ( $\mu\text{g}/\text{days}$ )	Duration (weeks)	Significant Cr effects
Glinsmann & Mertz, 1966 [33]	6 adults	$\text{CrCl}_3$ (180–1000)	Up to 20	Improved glucose tolerance
Sherman, 1968 [28]	7 men	$\text{CrCl}_3$ (150)	16	No effects
Nath et al, 1979 [32]	12 adults	Reduced Cr (500)	8	Decreased glucose, insulin & cholesterol
Offenbacher & Pi-Sunyer, 1980 [62]	8 adults	Yeast (10.9)	8	Improved glucose tolerance; decreased circulating insulin
Rabinowitz et al, 1983 [29]	43 men	$\text{CrCl}_3$ (150)	16	No effects
Mossop, 1983 [31]	26 adults	$\text{CrCl}_3$ (600)	16–32	Improved fasting glucose
Uusitupa et al, 1983 [30]	10 adults	$\text{CrCl}_3$ (200)	6	Decreased 60-minute insulin
Elias et al, 1984 [74]	6 adults	Yeast Cr (21)	2	Decreased fasting glucose; increased insulin sensitivity
Evans, 1989 [35]	11 adults	Cr picolinate (200)	6	Decreased blood glucose, hemoglobin $A_{1c}$ , cholesterol & LDL cholesterol
Roebach et al, 1991 [71]	63 adults	Biologically active Cr (600)	8	Increased HDL cholesterol (involved subjects w & w/o diabetes on beta-blockers)
Abraham et al, 1992 [27]	25 diabetics w/ atherosclerotic disease	$\text{CrCl}_3$ (250)	28–64	Increased HDL cholesterol; decreased triglycerides
Lea & Reasner, 1994 [75]	28 adults	Cr picolinate (200)	8	Decreased triglycerides
Ravina et al, 1995 [36]	114 Type 2; 48 Type 1	Cr picolinate (200)	1.4	Decreased glucose; decreased insulin, sulfonyl urea or metformin requirements
Jovanovic-Peterson et al, 1995 [38]	8 women w/gestational diabetes	Cr picolinate (2,4, or 8 $\mu\text{g}/\text{kg}$ bwt)	—	Improved blood glucose
Thomas & Gropper, 1996 [73]	5 adults	Cr nicotinate (200)	8	No effects
Anderson et al, 1997 [37]	185 adults	Cr picolinate (200 or 1000)	16	Increased glucose tolerance; decreased circulating insulin, fasting glucose, cholesterol, hemoglobin $A_{1c}$

intolerance. Subjects with good glucose tolerance who do not need additional Cr do not respond to supplemental Cr [2,3]. Subjects consuming adequate Cr and well balanced diets also do not respond to additional Cr [22]. This correlation is consistent with the study of Uusitupa et al [40] in which subjects with glucose intolerance that did not improve when subjects were put on a good diet also did not improve when they were given supplemental Cr. Chromium is a nutrient and not a drug, and it will therefore benefit only those who are deficient or marginally deficient in Cr. In addition, glucose intolerance and Type 2 DM are due to a number of causes, only one of which is Cr deficiency.

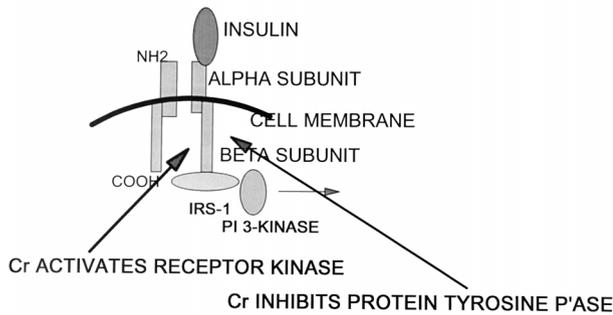
## CHROMIUM: MODE OF ACTION

A proposed mode of action of Cr in the regulation of insulin is shown in Fig. 1. Chromium increases insulin binding to cells due to increased insulin receptor numbers [24]. The insulin

receptor is present in essentially all cells, but its concentration varies from approximately 40 receptors per cell for erythrocytes to more than 200,000 receptors for adipocytes and hepatocytes [41]. The insulin receptor is composed of two extracellular alpha subunits with a molecular weight of 135,000 that contain the insulin binding site, and two transmembrane beta-subunits with a molecular weight of 95,000 [42].

Wortmanin is an antifungal agent that inhibits phosphatidylinositol 3'-kinase, which in turn also inhibits many effects of insulin stimulation in insulin-dependent cells [43,44]. Wortmanin also inhibits Cr potentiation of insulin activity [45, unpublished observations]. This suggests that Cr, like insulin, affects protein phosphorylation-dephosphorylation reactions. Once insulin binds to the alpha subunit of the insulin receptor, a specific phosphorylation of the beta subunit occurs through a cascade of intermolecular phosphorylation reactions [41,42,46]. The enzyme partly responsible for the phosphorylation, which leads to increased insulin sensitivity, is insulin

## Cr & INSULIN ACTION



**Fig. 1.** Mode of action of Cr in potentiation of insulin. Cr increases insulin binding to cells by increasing insulin receptor number. Cr also increases insulin sensitivity by increasing insulin receptor phosphorylation. Cr potentiation of insulin is inhibited by wortmanin, which inhibits the enzyme, PI 3-kinase (phosphatidylinositol 3'-kinase).

receptor tyrosine kinase, which is activated by Cr [47]. A low molecular weight Cr binding compound does not affect the protein kinase activity of rat adipocytes in the absence of insulin but stimulates kinase activity 8-fold in the presence of insulin. Removal of Cr from the low molecular weight Cr binding compound results in the loss of kinase potentiating activity [47]. Chromium also inhibits phosphotyrosine phosphatase (PTP-1), a rat homolog of a tyrosine phosphatase (PTP-1B) that inactivates the insulin receptor [45, unpublished observation]. The specific inhibition of insulin receptor phosphotyrosine phosphatase activity needs to be studied more closely since a low molecular weight Cr binding substance has also been shown to activate a membrane phosphotyrosine phosphatase [48]. The activation by Cr of insulin receptor kinase activity and the inhibition of insulin receptor tyrosine phosphatase would lead to increased phosphorylation of the insulin receptor, which is associated with increased insulin sensitivity [41,42,46]. Increased glucose utilization and beta-cell sensitivity have also been demonstrated using the hyperglycemic clamp technique [49].

## SAFETY OF SUPPLEMENTAL CHROMIUM

Trivalent Cr, the form of Cr found in foods and nutrient supplements, is considered one of the least toxic nutrients. The reference dose established by the US Environmental Protection Agency for Cr is 350 times the upper limit of the ESADDI of 200  $\mu\text{g}/\text{day}$ . The reference dose is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects over a lifetime" [50]. This conservative estimate of safe intake has a much larger safety factor for trivalent Cr than for almost any other nutrient. The ratio of the

reference dose to the RDA is 350 for Cr, compared to less than 2 for zinc, roughly 2 for manganese, and 5 to 7 for selenium [50]. We [51] demonstrated a lack of toxicity of Cr chloride and Cr picolinate in rats at levels several thousand times the upper limit of the ESADDI for humans (based on body weight). There was no evidence of toxicity, nor have there been any documented toxic effects in any of the human studies involving supplemental Cr.

## SUMMARY

The response to Cr supplementation for glucose, insulin, lipids, and related variables is related to the amount and form of supplemental Cr, the degree of glucose intolerance, and the duration of the study. Subjects with glucose intolerance but not diabetes usually respond to 200  $\mu\text{g}$  of Cr daily as Cr chloride or other more bioavailable forms of Cr. People with good glucose tolerance (90 minute glucose less than 5.56 mmol/L but greater than fasting following an oral glucose challenge) do not respond to supplemental Cr regardless of form. Patients with Type 2 DM require more than 200  $\mu\text{g}$  daily of supplemental Cr. Diabetics usually have a higher requirement for Cr and have impaired mechanisms to convert Cr to a usable form [52,53]. Response time to Cr varies from less than 10 days to sometimes more than 3 months. Response to Cr is also related to stress, and beneficial effects are greater under physical or dietary stresses [39,54–56]. Also, response to supplemental Cr is related not only to dietary Cr intake but also to the types of diets consumed, since some dietary components such as simple sugars increase Cr losses [57]. Glucose intolerance and diabetes are also due to a number of causes unrelated to dietary Cr intake.

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