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Chromium as an Essential Nutrient for Humans

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Chromium is an essential nutrient required for sugar and fat metabolism. Normal dietary intake of Cr for humans is suboptimal. The estimated safe and adequate daily dietary intake for Cr is 50 to 200 μg. However, most diets contain less than 60% of the minimum suggested intake of 50 μg. Insufficient dietary intake of Cr leads to signs and symptoms that are similar to those observed for diabetes and cardiovascular diseases. Supplemental Cr given to people with impaired glucose tolerance or diabetes leads to improved blood glucose, insulin, and lipid variables. Chromium has also been shown to improve lean body mass in humans and swine. Response to Cr is dependent upon form and amount of supplemental Cr. Chromium is a nutrient; therefore, it will only be of benefit to those who are marginally or overtly Cr deficient. Trivalent Cr has a very large safety range and there have been no documented signs of Cr toxicity in any of the nutritional studies at levels up to 1 mg per day.

INTRODUCTION

The role of Cr in animals was reported almost four decades ago (Mertz and Schwarz, 1959) and its essentiality in humans was documented in 1977 (Jeejeebhoy *et al.*, 1977). The signs and symptoms of insufficient dietary Cr are listed in Table 1; all, except the last four, are routinely observed in the general population. Improvements in glucose and insulin variables following Cr supplementation are usually observed in the majority of the population. Anderson *et al.* (1983, 1991a) have reported that the overwhelming majority of subjects with a 90-min blood glucose (following an oral glucose challenge of 1 g/kg body wt) greater than 100 mg/dL improve following Cr supplementation. This is particularly important since the average person over 25 years has a 90-min glucose value greater than 100 mg/dL (Harris, 1990).

The signs and symptoms listed in Table 1 are similar to those reported for non-insulin-dependent diabetes mellitus (NIDDM) and cardiovascular diseases. The connecting link among Cr, NIDDM, and cardiovascular diseases is the role of Cr in insulin function. Improvements in insulin function lead to improvements in essentially all of the signs and symptoms of Cr deficiency listed in Table 1. In the presence of Cr, in a biologically active form, much lower amounts of insulin are required. Biologically active forms of Cr potentiate insulin activity 10-fold or more at low levels of insulin in the *in vitro* epididymal fat cell assay (Anderson *et al.*, 1978). This is important from a human health perspective since many of the complications of diabetes and cardiovascular disease can be traced to elevated levels of circulating insulin. Since Cr potentiates the action of insulin, lower levels are required causing the organism to have lower levels of circulating insulin.

The last four signs and symptoms of Cr deficiency listed in Table 1 have only been observed for patients on total parenteral nutrition. The first report of beneficial effects of Cr on a patient on total parenteral nutrition (TPN) involved a female patient whose diabetic symptoms continued to get worse despite the daily addition of 45 units of exogenous insulin to her TPN fluids (Jeejeebhoy *et al.*, 1977). Since conventional treatments for diabetes were unsuccessful, a new treatment was explored. The addition of Cr to her nutrient solutions led to the reversal of diabetic symptoms. Blood glucose, nerve conduction abnormalities, and problems associated with protein utilization returned to normal within 3 weeks of the onset of Cr supplementation. Forty-five units of exogenous insulin administered to treat her diabetes was no longer required. This work has been confirmed in numerous laboratories (Freund *et al.*, 1979; Brown *et al.*, 1986; Anderson, 1989), and Cr is now routinely added to TPN solutions.

DIETARY CHROMIUM INTAKE

Dietary Cr intake in the United States and most industrialized countries is suboptimal. The estimated safe and adequate daily dietary intake (ESADDI) for Cr is 50–200 μg. However, few diets contain even the minimum ESADDI of 50 μg. The mean daily intake for men consuming normal diets is 33 ± 3 μg and that for women is 25 ± 1 μg (Anderson and Kozlovsky, 1985).

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TABLE 1
Signs and Symptoms of Cr Deficiency in Humans

Impaired glucose tolerance
Fasting hyperglycemia
Glycosuria
Hypoglycemia
Elevated circulating insulin
Decreased insulin receptor number
Decreased insulin binding
Decreased lean body mass
Elevated percent body fat
Increased ocular pressure
Peripheral neuropathy
Encephalopathy
Low respiratory quotient
Abnormal nitrogen metabolism

Note. Source: Adapted from Anderson (1994).

Even well-balanced diets designed by nutritionists do not provide 50 μg of Cr per day (Anderson *et al.*, 1992). Chromium intake per 1000 kilocalories (kcal) usually ranges from 5 to 24 μg with a mean Cr intake per thousand kcal of 15 $\pm$ 1.4 μg (Anderson *et al.*, 1992). Therefore, to meet the minimum estimated safe and adequate intake for Cr would require in excess of 3000 kcal. In one of our exercise studies, the well-balanced diets designed by nutritionists only contained 5 $\pm$ 0.2 μg of Cr per thousand kcal (Anderson *et al.*, 1988). Therefore, 10,000 kcal would need to be consumed to meet the minimum ESADDI and 40,000 kcal to obtain the upper level of the suggested intake.

It has been suggested that the ESADDI for Cr is too high since many diets do not provide the required amounts of Cr. However, the ESADDI is not too high, since people consuming these intakes of Cr respond to supplemental Cr. Chromium is a nutrient and not a therapeutic agent. Therefore, if subjects were consuming adequate amounts of dietary Cr, they would not respond to supplemental Cr. Glucose and insulin variables of subjects with average glucose tolerance declined when they were maintained on diets containing levels of dietary Cr found in the lowest quartile of normal intake (Anderson *et al.*, 1991a).

Foods high in Cr include high bran breakfast cereals, broccoli, green beans, and some brands of beer and wine (Anderson *et al.*, 1992). Both the amount of dietary Cr and the selection of foods are important. Foods high in simple sugars such as fructose (found in soft drinks) and sucrose (table sugar) are not only low in Cr but enhance Cr losses (Kozlovsky *et al.*, 1986). This may partly explain the high incidence of marginal Cr deficiency since many diets are high in simple sugars. Chromium intakes below 50 μg appear to be adequate if diets are high in fruits, vegetables, and grains and low in simple sugars (Offenbacher and Pi-Sunyer, 1980; Anderson *et al.*, 1992).

CHROMIUM, GLUCOSE TOLERANCE, AND DIABETES

The studies involving the Cr effects on glucose and insulin metabolism of patients on TPN supported and encouraged further studies of subjects with varying degrees of glucose intolerance, including diabetics. In addition to the improvements in glucose tolerance discussed above for patients on TPN, improved glucose metabolism in children (Hopkins *et al.*, 1968; Gurson and Saner, 1971), adults with varying degrees of impaired glucose tolerance (Anderson *et al.*, 1983, 1991a; Riales and Albrink, 1981), elderly subjects (Offenbacher and Pi-Sunyer, 1980; Potter *et al.*, 1985; Urberg and Zemmel, 1987), diabetics (Glinsmann and Mertz, 1966; Nath *et al.*, 1979; Anderson *et al.*, 1996a; Mossop, 1983), and hypoglycemics (Anderson *et al.*, 1987; Clausen, 1988) is observed following Cr supplementation.

The relative improvements in blood glucose are proportional to the degree of glucose intolerance. Fasting blood glucose of subjects with 90-min glucose greater than fasting but not in the diabetic range decreased from 90 $\pm$ 3 to 84 $\pm$ 2 mg/dL following 3 months of daily supplementation with 200 μg of Cr as Cr chloride (Anderson *et al.*, 1983). Fasting blood glucose of diabetic subjects with higher fasting glucose decreased from 254 to 119 mg/dL following supplementation with 600 μg of Cr per day as Cr chloride (Mossop, 1983).

This not only illustrates the relative responses of subjects with varying degrees of glucose intolerance and/or diabetes, but also suggests that non-insulin-dependent diabetic subjects require more Cr than subjects with marginally impaired blood glucose tolerance. Daily supplementation with 200 μg of Cr in the form of Cr chloride, Cr picolinate, Cr nicotinate, or Cr nicotinate–amino acid complex to diabetic subjects was not sufficient to elicit significant improvements in blood glucose (Anderson *et al.*, 1996b). In a follow-up study, supplementation of 100 μg of Cr or 500 μg of Cr as Cr picolinate twice daily to non-insulin-dependent diabetic subjects resulted in improvements in the group receiving 100 μg twice per day and larger consistent improvements in the group receiving 500 μg of Cr two times per day (Anderson *et al.*, 1996b).

Not all studies have reported beneficial effects of supplemental Cr (see review: Anderson, 1989). The lack of effects following Cr supplementation is likely due to the form and amount of supplemental Cr. In the past three decades there have been more than 36 studies reporting beneficial effects of supplemental Cr, less than 10 that have reported no effects, and no controlled studies that have documented any negative effects of supplemental Cr taken orally.

Subjects with diabetes have altered Cr metabolism and require additional Cr due to impaired Cr utilization. Diabetics absorb more Cr than nondiabetics but also have higher urinary losses (Doisy *et al.*, 1976; Anderson *et al.*, 1996b). Diabetics appear to sense a need for addi-

tional Cr which is illustrated by the increased absorption but are unable to utilize the absorbed Cr which is reflected by the increased losses. While Cr concentrations in blood and urinary losses of diabetics are elevated, tissue levels of Cr in diabetic subjects are lower than those of controls. Diabetic mice also have inefficient utilization of Cr and do not respond to supplemental Cr as Cr chloride but do respond to biologically active forms of Cr (Tuman *et al.*, 1978). Biologically active forms of Cr are defined as those that potentiate insulin action in an *in vitro* fat cell assay (Anderson *et al.*, 1978). Examples of insulin-potentiating forms of Cr include Cr–nicotinic acid–glutathione (Anderson *et al.*, 1978), Cr–nicotinic acid–amino acid complexes, and Cr complexes isolated from natural products such as brewer's yeast (Mertz and Schwarz, 1959).

CHROMIUM AND LIPID METABOLISM

Several risk factors of cardiovascular disease, in addition to insulin (discussed above), are improved by improved Cr nutrition. Total cholesterol, LDL- and HDL-cholesterol, total cholesterol/HDL ratio, and triglycerides have all been shown to improve in humans as well as experimental animals following Cr supplementation. Chromium prevents and reverses aortic plaque accumulation in rabbits (Abraham *et al.*, 1982, 1991). Schroeder *et al.* (1970) reported that accident victims had higher aortic Cr concentrations than patients who died of cardiovascular diseases. Newman *et al.* (1978) reported that serum Cr correlated inversely with coronary artery disease (CAD) with a less significant correlation with serum triglycerides. There was no correlation of CAD with serum cholesterol, weight, or blood pressure. Simonoff *et al.* (1984) expanded these observations, stating that "an upper limit for chromium may be established . . . beyond which CAD may be considered extremely unlikely, thus eliminating the need for a certain number of cineangiographic examinations." Tissue and blood Cr levels reported in these early studies are higher than currently accepted values, and these studies need to be repeated.

Chromium supplementation of elderly subjects causes significant decreases in total cholesterol with larger decreases in subjects with the highest levels prior to supplementation (Doisy *et al.*, 1976; Offenbacher and Pi-Sunyer, 1980). Cholesterol in one subject decreased from 339 to 280 mg/dL following 5 months of Cr supplementation at 200 μg/day as Cr chloride plus 100 mg nicotinic acid/day (Urberg *et al.*, 1988). Cholesterol of a second elderly patient decreased from 337 to 260 mg/dL following the same pattern of supplementation. Chromium supplementation (200 μg/day as Cr chloride, 5 days/week for 12 weeks) of 12 men led to significant decreases in serum triglycerides and increases in HDL-cholesterol compared to placebo-treated subjects (Riales and Albrink, 1981). Chromium supplementation (600 μg/day as Cr chloride) of patients being treated for diabetes led to significant improvements in diabetic symptoms and also increases in HDL-cholesterol (Mossop, 1983).

HDL-cholesterol of 40 patients with atherosclerotic disease increased from 36 to 44 mg/dL following supplementation with 250 μg of Cr as Cr chloride for more than 3 months (Abraham *et al.*, 1992). Triglycerides decreased from 186 to 148 mg/dL. HDL-cholesterol in 72 men taking β-blockers improved following 2 months of Cr supplementation at 600 μg/day (Roeback *et al.*, 1991). People who control their hypertension with β-blockers still have increased risk of CVD due in part to the increase in triglycerides and decrease in HDL associated with taking β-blockers (Lardinois and Neuman, 1988). Chromium counteracts these negative effects of β-blockers.

Chromium may also help control hypertension. Chromium prevents sugar-induced hypertension in spontaneously hypertensive rats (Preuss *et al.*, 1995). Improvements in hypertension occur prior to improvements in glucose and insulin. Studies to elucidate the role of Cr in hypertension in humans are in progress.

Improvements in total cholesterol, like those for glucose and insulin variables, are dependent upon the amount of supplemental Cr. Two hundred micrograms of supplemental Cr as Cr picolinate led to a decrease in total cholesterol with larger decreases when 1000 μg was given per day (Anderson *et al.*, 1996a).

CHROMIUM AND STRESS

Chronic stresses may alter micronutrient requirements. If dietary intake is marginal, the effects of stress could induce signs of deficiency. This is exemplified for the essential nutrient Cr. As discussed above, dietary Cr intake for humans is suboptimal. This is also true for farm animals. Chang and Mowat (1992) demonstrated that average daily gain and feed efficiency increased more than 25% due to supplemental Cr in steer calves following the stress of transit via shipping. Chromium was without effect in the nonstressed periods. Supplemental Cr also decreases serum cortisol and increases immunoglobulin M and total immunoglobulins. Humoral immune response of early lactating cows also improves due to supplemental Cr during times of stress (Burton *et al.*, 1993). Supplemental Cr also counteracts the negative effects of the stress of growth hormone administration to pigs (Evock-Clover *et al.*, 1993).

Stresses that alter Cr metabolism in humans are glucose loading, high simple sugar diets, lactation, infection, acute exercise, chronic exercise, and physical trauma (Anderson, 1994). Urinary losses can be used as a measure of the response to stress, since once Cr is mobilized in response to stress it is not reabsorbed by the kidney but is lost in the urine (Doisy *et al.*, 1976).

TABLE 2
Stress Effects on Urinary Cr Losses of Humans

Stress	Urinary Cr, μg/day	Reference
Basal (nonstress)	0.16 ± 0.02	Anderson *et al.* (1982, 1983)
Acute exercise	0.30 ± 0.07	Anderson *et al.* (1982)
Chronic exercise (training)	0.09 ± 0.01	Anderson *et al.* (1988)
High sugar diet	0.28 ± 0.01	Kozlovsky *et al.* (1986)
Lactation	0.37 ± 0.02	Anderson *et al.* (1993)
Physical trauma	10.8 ± 2.1	Borel *et al.* (1984)

Note. Source: Anderson (1994).

The degree of stress as measured by the stress hormone cortisol is correlated with urinary Cr losses (Anderson *et al.*, 1991b). Mild stresses such as moderate acute exercise elicit increases in Cr losses that are much lower than the effects of severe trauma of sufficient magnitude to elicit treatment in a shock trauma unit (Table 2). When urinary Cr losses are being used to monitor Cr exposure, the dietary, physical, and environmental stresses of the subjects need to be monitored.

Chronic stresses such as eating a high sugar diet may ultimately elicit negative effects on overall health. Not only do high sugar diets increase Cr losses, but they are also usually low in dietary Cr. Therefore, sugar-induced Cr losses, coupled with low Cr intake, may lead to increased signs and symptoms of Cr deficiency. The increases in the chronic diseases such as maturity onset or type II diabetes (NIDDM) and cardiovascular diseases associated with aging may not be normal consequences of aging but rather consequences of suboptimal dietary patterns that are manifest with age.

CHROMIUM TOXICITY

The reference dose for trivalent Cr is 1000 μg/kg/day and the upper limit of the ESADDI is only 3 μg/kg/day (Dourson, 1994). 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 appreciable risk of deleterious effects over a lifetime." Therefore, toxic effects of supplemental Cr are highly unlikely. There have been no documented signs of Cr toxicity in any of the nutritional Cr supplementation studies conducted over the past three decades utilizing supplemental trivalent Cr at levels up to 1 mg/day. Addition of Cr chloride or Cr picolinate to the diet of rats at levels more than a thousand-fold comparable to intake for humans also did not elicit any signs of toxicity of trivalent Cr (Anderson *et al.*, 1997).

SUMMARY

In summary, dietary Cr intake of humans is suboptimal. Suboptimal Cr intake is associated with signs and symptoms of Cr deficiency that are similar to those for diabetes and/or cardiovascular diseases. Normal daily stresses as well as those associated with aging increase Cr requirements. While signs and symptoms of Cr toxicity are usually limited to occupational exposure and involve a small portion of the population, the signs and symptoms of Cr deficiency are widespread.

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QUESTIONS AND ANSWERS

A, MR. RICHARD FAGLIANO; DR. RICHARD ANDERSON (SPEAKERS)
Q, QUESTIONER (AUDIENCE)

Q: A point of clarification for Mr. Fagliano. The first question is, do you have any exclusion criteria for people who might have occupational exposure to chromium from your study—people who might be working as platers for example? Secondly, hearing what Dr. Anderson has said, did you have some feel for the proportion of people in your study population who might be taking vitamin supplements plus added minerals, and did you exclude those from your analysis? The third point is about diagnostic criteria. Did you have any preestablished diagnostic criteria to decide whether or not some abnormality in spirometry, for example, is related to a defect from chromium exposure? Thank you.

A: Let me start with the first point about whether we gathered information on occupational questions. First, of the people we screened from workplaces, we had information on what they did at that workplace. There was one workplace, a leather-tanning operation, which we did exclude. We included only those workers who were not directly involved with that process. The second part of your question which was the. . . .

Q: Mineral supplements.

A: Supplements, okay. We asked people for information on what supplement they normally took, by brand name. And by doing supermarket surveys we gathered the chromium content of each of those brands. We were dealing with a population again in 1992 and 1993 which may have been before the boom in chromium supplementation because very few people in either our baseline or our screened population reported taking any supplements. There were a few that had relatively high levels of chromium. Many people took the Centrum kind of supplements which have small quantities of chromium, 30 μg or so.

Q: Centrum Silver.

A: Yes, the regular Centrum I believe had 30 (μg) at the time. And we didn't see any kind of increase due to that kind of level of supplementation. I would like to mention that we also asked people whether they were seeing a physician for diabetes. In the questionnaire, and at least in the adult group, the people who self-reported as having diabetes did have, on average, higher chromium levels, and that was taken into account in the adjustment model. The third point was about the protocols for the physicians, the screening physicians as well as the follow-up physicians. We had detailed written protocols which are in our report, and I'd be happy to give you a copy of it. They did have detailed criteria on how to evaluate each of the aspects that they were looking at.

Q: Sorry, I don't want to hog the microphone, but they may have detailed guidelines for the protocol on how to do the spirometry. My question is, did you give them any kind of criteria on whether some abnormality that they find on spirometry is due to chromate exposure or due to endogenous factors or something else.

A: Right. Not quite that specifically—there was actually a considerable amount of clinical judgment that had to be involved, given all other tests and exposure histories of the individuals. So there was no magic number based on the spirometry results at which they would be considered chrome affected or not. Data would have to be taken into a context of all the other tests and occupational and medical histories of that particular individual. So there was clinical judgment involved in that last step. Again, I'd be happy to show you the protocols that were being followed.

Q: Point of clarification for either Dr. Anderson or Mr. Fagliano. Mr. Fagliano showed urinary concentrations for children under 6 years old. I wondered, and perhaps I missed it, were those concentrations within the normal range for children?

A: Well, to our knowledge, when we began the screening project there were no published data on what was normal in children. So we collected information in our baseline survey of children in preschool settings outside of Hudson County throughout the state of New Jersey. We tried to basically establish what those ranges were. The amounts of chromium in the baseline childrens' urines were pretty much considered similar to what was seen in the adults in terms of concentration. So there were no great differences in the preschool population in our baseline. Where we saw the differences was in our screened groups—not in our baseline groups.

Q: And Dr. Anderson, you're not aware of normal ranges of chromium in children?

A: In the work that we have done, when we look at different populations, we don't really see a big difference. Now there is some work where they've actually looked at age, where they've looked at anywhere from a couple years old on up to 60. There is a little bit of an effect that as you get older and older, your chromium concentrations do go down.

Q: I raised that question because as a child grows it might need more of that nutrient and therefore you would expect higher levels. I'm not saying that's the case, of course. I'm just asking a point of clarification.

A: Except if you look at the flip side of that, as you get older your absorption of chromium goes down, and we think that's part of the reason why the incidence of diabetes and cardiovascular disease actually goes up, because this high sugar diet and low intake and low absorption over decades gradually catch up to you and you do see that your blood glucose continues to go up, and of course your insulin continues to go up, and then the incidences of diabetes and cardiovascular disease also tend to go up.

Q: Thank you.

Q: Some questions for Mr. Fagliano. Could you comment on the fact that the study suggested that possibly a third of Americans, when examined in a random sample in 1974, had a diagnosable skin disease, and similarly Swannbeck and Metting in 1985 in a self-administered questionnaire that was later validated by clinical examinations found that, on an average, over all age groups, 10% of the population were found to have eczematous dermatitis on their hands. Would you not think that the prevalence of 2% of your population is low?

A: Two percent—in the initial screening examination?

Q: Yes.

A: Well, the criterion that was applied was not simply the presence of a dermatological condition. It was one that was not explainable by anything else that the person may have reported, and it had to be temporally related, so that if someone had had it all their lives, but didn't move into the county until, or for that work—in that particular workplace, they were not considered eligible for the follow-up evaluation, so I don't think those numbers are directly comparable.

Q: I see. Could you tell me about the qualifications of the people who made that assessment?

A: The initial evaluation?

Q: Yes.

A: These were physicians from the two different sources. One group was from the Jersey City Medical

Center. These were emergency room physicians by and large trained in emergency medicine. The second group consisted of physicians from the Robert Wood Johnson Medical School who were also doing some of the screening evaluations. These were trainees in environmental/occupational medicine.

Q: I see. Am I correct in assuming then that there were no dermatologists who participated in those assessments?

A: In the initial assessments?

Q: Yes.

A: That's correct. In the follow-up examinations, board-certified occupational environmental physicians did the evaluations. If they so chose, board-certified dermatologists would also do an examination.

Q: You mentioned that you had six subjects who might have had chromium-related disease. Could you tell me how that was confirmed? Were any epicutaneous tests carried out to establish the presence of chrome allergy, or what criteria were applied to determine they had irritant contact dermatitis, related to chromium exposure?

A: These were not my judgments of course; these were judgments of the physicians.

Q: No, this is a protocol question.

A: Right. Well, in the protocol, we left it up to the dermatologists to decide whether or not to do patch testing.

Q: But was it done?

A: It was done only on one individual.

Q: So on the other four you did not confirm it?

A: That's correct. The reason being that the individuals declined further testing. So we don't really know the prevalence of chrome sensitivity in that group of people.

Q: We don't know that they were chrome sensitive either, do we?

A: No, we do not.

Q: You said that all but one of those identified could be explained as an occupational association and this is kind of supplemental to the spirometry question. If that's so, and if there was relevance to their occupational association, that means you only have one individual where this was a question as to whether it was an environmentally caused, primary irritant or allergic contact dermatitis; is that correct?

A: The word, the judgments that were made for these individuals, was whether or not chromium could be a possible cause or contributing cause to the condition that these individuals were experiencing. That's the judgment that the physicians were asked to make on these individuals.

Q: Could you tell me that in that one instance—was that confirmed by patch testing?

A: I've explained that I believe. There was one individual patch tested. That person was not positive for chrome sensitivity.