Chromium (III) Metabolism by the Kidney

DAVID L. DONALDSON, M.D.* and OWEN M. RENNERT, M.D.**

* Department of Pediatrics, ** Department of Pediatrics and Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190

ABSTRACT

The kidney is the principal route of excretion of the essential trace element chromium. Previous studies suggest that five to 40 percent of plasma chromium (III) is ultrafilterable and that 60 to 95 percent of filtered chromium is reabsorbed in the renal tubule. However, less than five percent of a stable Cr(III)-EDTA chelate is reabsorbed; therefore, this complex has been used to measure glomerular filtration. An increased fractional excretion of chromium may result from a glucose challenge or from a volume diuresis. These mechanisms have been postulated to cause an increased urinary excretion of chromium in patients with diabetes mellitus. Investigations of chromium metabolism and excretion must be interpreted with caution because chromium analysis is known to be subject to many sources of error and chromium (III) salts may not be physiologically equivalent to biological chromium complexes. Analytical refinements should permit further delineation of normal chromium homeostatic mechanisms and allow better identification of abnormalities in chromium metabolism.

Introduction

Trivalent chromium has been implicated as an essential nutrient in mammalian systems. The kidney is the principal route of excretion of chromium (III) species. Tracer doses of $^{51}$Cr (III) have been used for the study of the physiological metabolism of orally and parenterally administered metal. Stable $^{51}$Cr (III)-ethylene diamine tetraacetic acid (EDTA) chelates have been used for clinical evaluation of renal function. Experimentally administered hexavalent chromium produces impaired renal tubular function $^{1,2}$; however, under physiological conditions, Cr (VI) is a strong oxidant and is probably rapidly reduced to Cr (III). $^{12,14}$ The metabolism of Cr (III) species is reviewed to facilitate our understanding of the renal metabolism of chromium and its potential aberrations.
Chromium Levels in Serum and Plasma

<table>
<thead>
<tr>
<th>Date</th>
<th>Author</th>
<th>Method</th>
<th>Serum or Plasma</th>
<th>Level ± S.D. (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>Glinsmann</td>
<td>AAS</td>
<td>S</td>
<td>28</td>
</tr>
<tr>
<td>1968</td>
<td>Levine</td>
<td>AAS</td>
<td>S</td>
<td>23.2 ± 4</td>
</tr>
<tr>
<td>1972</td>
<td>Davidson</td>
<td>AAS-GF</td>
<td>P</td>
<td>4.70 ± 0.15</td>
</tr>
<tr>
<td>1974</td>
<td>Pekarak</td>
<td>AAS-GF</td>
<td>S</td>
<td>1.5 ± 0.14</td>
</tr>
<tr>
<td>1974</td>
<td>Hambidge</td>
<td>ES</td>
<td>S</td>
<td>3.1</td>
</tr>
<tr>
<td>1978</td>
<td>Liu</td>
<td>NAA</td>
<td>S</td>
<td>1.67 ± 0.08</td>
</tr>
<tr>
<td>1978</td>
<td>Vermeulen</td>
<td>NAA</td>
<td>S</td>
<td>0.16 ± 0.08</td>
</tr>
<tr>
<td>1978</td>
<td>Kayne</td>
<td>AAS-FF</td>
<td>S</td>
<td>0.14</td>
</tr>
<tr>
<td>1979</td>
<td>Vanderlinde</td>
<td>AAS-GF</td>
<td>S</td>
<td>0.075 ± 0.069</td>
</tr>
<tr>
<td>1980</td>
<td>Rabinowitz</td>
<td>AAS-GF</td>
<td>P</td>
<td>1.1 ± 0.2</td>
</tr>
</tbody>
</table>

AAS = Atomic absorption spectroscopy (flame)
GF = Using a graphite furnace
ES = Emission spectroscopy
NAA = Neutron activation analysis

Chromium Analysis

Difficulties in sample preparation and chromium analytical techniques have accounted for a wide variation in the reported levels of chromium in biological fluids and tissues. For example, the mean human serum chromium concentration, reported to be 23 ng per ml in 1966 has more recently been revised to be in the range of 0.1 ng per ml near the analytical detection limit of present methods (Table I). Improved methods of sample handling, refinements in graphite furnace atomic absorption spectrophotometry and neutron activation analysis have led to delineation of the recently reported concentrations. The special precautions necessary for ultratrace chromium analysis have been reviewed in a recent symposium. The conclusions suggested by past analytical work must be evaluated critically and accepted with caution, if at all, pending more careful studies using ultratrace techniques.

Chromium as an Essential Trace Element

Experimentally produced chromium deficiency has been reported to result in impaired glucose tolerance in rats and squirrel monkeys. Oral or parenteral supplementation with Cr (III), especially in a form extracted from Brewers yeast called “glucose tolerance factor” (GTF), results in normalization of glucose tolerance. Prolonged chromium deficiency in the rat has also been reported to cause elevated serum cholesterol levels and an increased incidence of aortic plaques. A significant decrease in serum cholesterol occurs when Cr (III) supplementation is given to rats on a hypercholesterolemic diet.

Impaired glucose uptake and CO₂ production in response to physiological levels of insulin are seen in adipocytes from chromium deficient animals. In vitro or in vivo supplementation with Cr (III) salts or GTF-chromium corrects these responses. The molecular mechanism for this synergy of Cr (III) with insulin has not been clarified, although an interaction of insulin and Cr (III) with membrane disulfides has been suggested.

Chromium is widely distributed throughout the human body. Stillborn and infant tissues have relatively higher levels of chromium which decline rapidly in the first two decades of life. An exaggerated age-related decrease in tissue chromium concentrations has been reported in individuals from more developed countries. This observation and knowledge of the effects of chromium deficiency in experimental animals have led investigators to speculate that chromium deficiency may be a contributing factor to the increased incidence of noninsulin dependent diabetes mellitus and atherosclerosis seen in these countries.

Chromium supplementation in diabetics and in elderly subjects with impaired glucose tolerance has resulted in normalization of glucose tolerance in some cases but not as consistently as in experimental models. Supplementation with GTF-chromium has been shown to normalize impaired glucose tolerance, to
lower fasting and post-prandial serum cholesterol levels, and to produce a significant reduction in serum insulin levels in some hyperglycemic adult subjects.11,29,30

Iatrogenic chromium deficiency resulting in insulin-requiring diabetes mellitus has been reported in two patients who were treated for extended periods with intravenous hyperalimentation.15,26 Following chromium supplementation, withdrawal of insulin therapy was rapidly accomplished. These experimental, epidemiological, and clinical findings have lent support to the tenet that chromium is an essential trace element in man (table II).

Metabolism of Chromium (III) Species

Less than one percent of orally administered chromium (III) salts is absorbed owing to a tendency of the metal ions to crosslink through water or hydroxide ions in neutral or basic solutions.12,61 Once absorbed, $\text{Cr}^{3+}$ (III) is transported principally by the iron transport protein, transferrin.23 Intravenously administered $\text{Cr}^{3+}$ (III) chloride disappears rapidly from the blood and is concentrated 10 to 100 times in tissues throughout the body.24 Whole body disappearance of very small amounts of intravenously administered $\text{Cr}^{3+}$ has been described by compartmental analysis as reflecting three regression rates with $t_{1/2}$'s of 0.5, 5.9 and 83.4 days. These rates probably reflect the combined result of excretion of excess isotope, physiological incorporation of the trace element and slow mobilization of a portion of the intravenously administered metal ion which becomes tightly bound to certain body tissues, especially collagen.38

GTF-chromium, which has been tentatively identified as a low molecular weight, dialyzable complex of Cr (III) with nicotinic acid, glycine, cysteine, and glutamic acid,57 has a significantly greater gastrointestinal absorption (10 to 25 percent),36 enhanced placental transport34 and a greater efficacy in restoring impaired glucose tolerance in vivo and in vitro compared to Cr (III) salts.35 Whether there is endogenous conversion of orally and parenterally administered Cr (III) to GTF-chromium or whether there is more than one physiological pool of chromium in the body has not been established.

Renal Excretion of Chromium (III)

Both orally12 and parenterally5,24 administered $\text{Cr}^{3+}$ (III) are excreted primarily by the kidney. In the dog, Collins et al observed eighty percent of intravenously administered $\text{Cr}^{3+}$ (III) to be excreted in the urine.5 Only small amounts were found in the feces. The renal clearance of intravenously administered $\text{Cr}^{3+}$Cl$_3$ decreases exponentially with time. A similar exponential decrease was observed in the dialyzable plasma chromium which declined from 9 to 12 percent initially to two to five percent after eight hours. Assuming glomerular filtration of the dialyzable $\text{Cr}^{3+}$ (III), it was calculated that 63 percent of this fraction is reabsorbed in the renal tubules.

Investigators have reported changes in serum or plasma chromium concentrations (table III) and in urinary

### TABLE II

<table>
<thead>
<tr>
<th>Chromium Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Glucose tolerance</td>
</tr>
<tr>
<td>+ Immunoreactive insulin levels</td>
</tr>
<tr>
<td>+ Serum cholesterol</td>
</tr>
<tr>
<td>+ Incidence of aortic plaques</td>
</tr>
</tbody>
</table>

### TABLE III

<table>
<thead>
<tr>
<th>Renal Handling of Chromium (III) Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-40 percent ultrafilterable in plasma</td>
</tr>
<tr>
<td>Calculated 70-95 percent reabsorbed</td>
</tr>
<tr>
<td>Volume diuresis increases excretion</td>
</tr>
<tr>
<td>&gt; 95 percent of stable Cr (III)-EDTA chelate is excreted</td>
</tr>
</tbody>
</table>

* Average half-lives.
TABLE IV
Suggested Indices for Assessment of Chromium Metabolic Status

<table>
<thead>
<tr>
<th>Response to chromium or GTF-chromium supplementation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue chromium levels.</td>
</tr>
<tr>
<td>Chromium-51 turnover studies.</td>
</tr>
<tr>
<td>Plasma and urinary chromium following a glucose load.</td>
</tr>
<tr>
<td>Twenty-four hour urinary chromium excretion.</td>
</tr>
</tbody>
</table>

GTF = Glucose tolerance factor

chromium excretion (table IV) in response to a glucose challenge. Glinsmann et al\textsuperscript{5} and Levine et al\textsuperscript{28} have reported a rise in serum chromium in response to a glucose challenge, but the levels were many fold higher than presently accepted values. Rabinowitz et al\textsuperscript{41} have also recently reported that in most normal subjects, plasma chromium levels increased following a glucose challenge. Davidson and Burt\textsuperscript{8} reported a fall in plasma chromium concentration in normal non-pregnant women in response to either an oral or intravenous glucose load. Pekarek et al\textsuperscript{40} have also shown serum chromium concentration to fall following an intravenous glucose load. Liu and Morris\textsuperscript{30} performed three hour glucose tolerance tests (GTT) in non-pregnant women and measured fasting and one hour serum chromium levels. They found a decrease in serum chromium at one hour in their normal subjects prior to GTF-chromium supplementation but an increase after supplementation. Using the most current ultratrace techniques, Vanderlinde et al\textsuperscript{58} have found both fasting and two hour post-prandial serum chromium concentration in normal controls to be so near their limits of detection\textsuperscript{28} that it was not possible to detect a significant change.

Schroeder\textsuperscript{47} first reported a rise in the chromium concentration in the urine in response to a glucose tolerance test. Gursen and Saner\textsuperscript{18} have reported a significant increase in urinary chromium excretion rate and chromium to creatinine ratio (fractional excretion of chromium or $FE_{Cr}$) in normal subjects during the three hours following an oral glucose challenge. Rabinowitz et al\textsuperscript{41} have also found an increase in $FE_{Cr}$ when fasting and two hour post-prandial urine collections were compared. When $FE_{Cr}$ was correlated with a number of other variables, the only positive correlation was with urinary volume and no correlation was seen with blood sugar, with $FE$ of sodium potassium, calcium or magnesium, or with urinary glucose or osmolality. Rabinowitz and coworkers found $16 \pm 3$ percent (range 6 to 28 percent) of plasma chromium to be ultrafilterable (MW < 10,000 daltons) while $91 \pm 4$ percent of urinary chromium was ultrafilterable. Using the mean $FE_{Cr}$ for the entire study and assuming 15 percent of the plasma chromium to be ultrafilterable, it was calculated that 80 percent of filtered chromium was reabsorbed. Vanderlinde et al\textsuperscript{58} report no significant post-prandial change in $FE_{Cr}$.

Davidson et al\textsuperscript{9} have studied the renal excretion of endogenous chromium in response to both glucose and water loading. Although they found considerable variation in baseline levels in normal adult subjects, they observed a decrease in urinary chromium concentration and $FE_{Cr}$ during the four hours following a glucose load. However, a diuresis produced by oral water loading caused a 110 percent increase in $FE_{Cr}$. In dogs, the $FE_{Cr}$ was 150 percent greater with normal saline diuresis than with a vasopressin induced anti-diuresis. Neither the plasma chromium concentration nor the ultrafilterable fraction (40 percent) changed significantly during these experiments. Those results suggest that chromium excretion can be increased by increasing urine volume. Reabsorption of greater than 96 percent of the filterable chromium load was calculated.
The preceding studies suggest the following points regarding the renal handling of physiological Cr (III) (table III): (1) 5 to 40 percent of plasma chromium is ultrafilterable; (2) 70 to 95 percent of filtered chromium is reabsorbed; and (3) diuresis may contribute to increased excretion. In 1978, Guthrie et al.20 pointed out background correction and related problems in the determination of chromium in urine by graphite furnace atomic absorption spectrophotometry may partially explain the divergence of published values for chromium in urine. The reported relationship of increased urinary excretion of chromium with increased urinary volume may be accounted for by the higher chromium levels found in previous analyses. Therefore, this and other conclusions made on the basis of older analytical data need to be examined and confirmed using present ultratrace techniques.

**THE USE OF $^{51}$Cr (III)-EDTA TO MEASURE GLOMERULAR FILTRATION RATE**

Because $^{51}$Cr (III)-EDTA forms a stable low molecular weight chelate, its clearance has been used to measure glomerular filtration.53 The mean clearance ratio of this complex to the clearance of inulin has been reported to be 0.95 ± 0.03. This difference in clearance is probably due to binding of the metal or the chelate by plasma protein; this hypothesis is supported by the finding of 1.5 to 2.0 percent of the $^{51}$Cr (III)-EDTA in serum samples that are non-dialyzable. Svendsen et al.55 have suggested that the $^{51}$Cr (III)-EDTA clearance can be easily corrected to give a better approximation of glomerular filtration than the creatinine clearance for GFR’s in the range of 5 to 20 ml per min per m². However, adequate corrections cannot be made for $^{51}$Cr (III)-EDTA clearances below 4 to 5 ml per min per m².

**Chromium Metabolism and Excretion in Diabetes Mellitus**

Alterations in chromium metabolism which may result from abnormal body chromium pools and/or abnormal renal handling of chromium have been suggested to exist in diabetes mellitus. Besides the response to chromium supplementation, indices which have been used for the evaluation of chromium metabolism in diabetes include (table IV): (1) tissue chromium levels; (2) chromium turnover studies; (3) plasma and urinary chromium levels in response to a glucose or insulin challenge (tables V and VI); (4) 24 hour urinary chromium excretion; and (5) fraction of urinary chromium present in a volatile form.

Analyses of tissues of diabetic subjects have given equivocal results as to a depletion of body stores of chromium. Hepatic chromium content has been reported to be significantly lower in diabetic than in non-diabetic subjects.37 Hair chromium levels have been reported to be lower in the diabetic children21 and in some diabetic adults.42 However, in another study, no consistent differences in chromium concentration were seen in the liver and

**TABLE V**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author</th>
<th>Subjects</th>
<th>Chromium Concentration Following Glucose Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973</td>
<td>Davidson8</td>
<td>Normal</td>
<td>Serum 4.70 ± 0.15, Plasma 3.12 ± 0.21</td>
</tr>
<tr>
<td>1974</td>
<td>Pekarek1</td>
<td>Normal</td>
<td>Fasting 1.50 ± 0.14, Post-glucose 0.85 ± 0.19</td>
</tr>
<tr>
<td>1978</td>
<td>Liu30</td>
<td>Normal</td>
<td>Hyperglycemic Serum 1.89 ± 0.36, Plasma 1.03 ± 0.22</td>
</tr>
<tr>
<td>1979</td>
<td>Vanderlinde58</td>
<td>Normal</td>
<td>Glucose Challenge 0.075 ± 0.069, Nondetectable</td>
</tr>
<tr>
<td>1980</td>
<td>Rabinowitz41</td>
<td>IDDM</td>
<td>0.24 ± 0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NIDDM</td>
<td>1.1 ± 0.2</td>
</tr>
</tbody>
</table>

IDDM = Insulin dependent diabetes mellitus
NIDDM = Non-insulin dependent diabetes mellitus
TABLE VI
Urinary Chromium Excretion in Response to a Glucose Challenge

<table>
<thead>
<tr>
<th>Date-Author</th>
<th>Subjects</th>
<th>Fasting</th>
<th>Following Glucose Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973-Davidsen</td>
<td>Normal</td>
<td>1.65 ± 0.18</td>
<td>1.15 ± 0.18</td>
</tr>
<tr>
<td>1978-Gurson18</td>
<td>Normal</td>
<td>7.17 ± 0.89</td>
<td>10.70 ± 1.55</td>
</tr>
<tr>
<td>1979-Vanderlinde58</td>
<td>Normal</td>
<td>0.21 ± 0.14</td>
<td>0.20 ± 0.12</td>
</tr>
<tr>
<td>1980-Rabinowitz41</td>
<td>Normal</td>
<td>0.60 ± 0.52</td>
<td>0.52 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>13.69 ± 1.45</td>
<td>13.05 ± 1.78</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>0.21 ± 0.14</td>
<td>0.20 ± 0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.60 ± 0.52</td>
<td>0.52 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>2.9 ± 0.7</td>
<td>4.81 ± 1.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 ± 1.2</td>
<td>4.5 ± 1.56</td>
<td></td>
</tr>
</tbody>
</table>

IDDM = Insulin dependent diabetes mellitus

several other autopsy tissues from diabetic Pima Indians compared to normals. Doisy has shown that insulin dependent diabetics concentrate two to four times more $^{51}$Cr (III) into the plasma pool than do normal subjects after oral administration of the isotope. The plasma radioactivity disappeared much more rapidly in diabetic subjects and is reflected by a two fold increase in $^{51}$Cr (III) output in the urine. Increased urinary excretion of intravenously administered $^{51}$Cr (III) was also reported.

Liu and Morris have shown a more pronounced decrease in serum chromium concentrations in subjects that had a hyperglycemic GTT response than in controls. Following four months supplementation with a chromium-rich Brewer's yeast extract, both normal and hyperglycemic groups had lower fasting chromium levels. The controls had elevated one hour plasma chromium levels, but little change was observed in the hyperglycemic group even though they had slightly improved glucose tolerances. Both groups show significantly lower total immunoreactive insulin levels during a GTT following supplementation. Gurson and Saner found a significant increase in chromium excretion rate and $FE_{Cr}$ in diabetic patients compared to normals. However, the diabetics did not show the same post-prandial increases that were seen in normals.

Rabinowitz et al have examined the various suggested parameters of chromium status in both obese and non-obese patients with NIDDM as well as in patients with IDDM. They found no significant difference in hair chromium concentrations in these groups. The insulin dependent diabetics had elevated fasting plasma chromium concentration. Non-obese patients with NIDDM had slightly lower plasma chromium levels and a smaller rise in plasma chromium following a meal than any of the other group. Vanderlinde et al have reported significantly increased fasting serum and urine levels of chromium in insulin dependent diabetics. They found a statistically significant fall in the post prandial serum chromium levels but not in urine levels in these subjects.

Norms for 24 hour urinary chromium excretion have been published, as well as comparative levels for patients with diabetes mellitus (table VII). Hambridge and Rabinowitz have reported that insulin dependent diabetic children and adults have significantly lower chromium excretion levels than controls.

* Non-insulin dependent diabetes mellitus.
† Insulin dependent diabetes mellitus.
adults have significantly increased 24 hour urinary chromium excretion. Recently Routh reported a much lower urinary excretion in normal adults of 1.1 μg per 24 hours (range 0.45 to 2.35 and concentration 0.79 μg per L). His findings are in agreement with Vanderlinde et al using an improved analytical system and independently verified by Veillon et al by stable isotope dilution.

Although there is not a detectable volatile chromium fraction in plasma, a decreased prevalence and concentration of a volatile fraction of chromium has been reported in the urine of diabetics. The significance of this finding is still controversial. Thus, although the aberrations in chromium metabolism are suggested to be present in diabetes mellitus, the variability in the analytical measurements makes it difficult to demonstrate conclusively those abnormalities.

**Discussion**

Quantitative and isotopic studies demonstrate that the kidney is the principal excretory organ for the trace element chromium. Previous studies suggest there may be more than one body pool of chromium, and that GTF-chromium, a low molecular weight, dialyzable Cr (III) complex, may be the biologically active form of the element. Urinary chromium appears to be derived chiefly from a dialyzable fraction of the plasma chromium. It is not clear whether excretable chromium increases or decreases in response to a glucose load. There is evidence that there is renal tubular reabsorption of a major portion of the low molecular weight chromium that is filtered through the glomerulus. However, diuresis may result in increased chromium excretion.

It has been postulated that patients with diabetes mellitus have increased chromium excretion owing to increased mobilization of their chromium stores secondary to elevated blood glucose levels and increased urinary volume. The presently proposed renal handling of chromium would suggest that altered chromium excretion may occur in disorders of the kidney characterized by high urinary output and renal tubular dysfunction. The examination of this possibility awaits the application of careful analytical techniques, a better characterization of the ultrafilterable chromium fraction, and a clearer understanding of the normal physiological metabolism of chromium (III) by the kidney.

**References**


