

Review Article

Chromium Research from a Distance: From 1959 to 1980

Walter Mertz, MD

Former Director of the Human Nutrition Center, USDA, Beltsville, Maryland (Retired)

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More than 50 years of work have led to the recognition of trivalent chromium as an essential element. Shortly after its identification as an essential element in 1959, its interaction with insulin in vitro and in vivo was established, and the site of action identified as the insulin-sensitive cell membrane. Despite other early clinical successes with chromium supplementation, four major problems have influenced the rate of progress since then: 1) chromium analysis; 2) interaction of chromium with other dietary factors; 3) diagnosis of chromium status; and 4) other controversies, such as the carcinogenic potential of chromium (since disproved) and the lack of an effect on glucose tolerance even in chromium deficient organisms (now explained). These controversies have mostly dissipated as new knowledge integrated seemingly irreconcilable facts and opinions. It is now known that chromium may potentiate the action of insulin either by an effect on insulin dependent functions, or by maintaining these functions with less insulin, or by a combination of both. Despite much progress in the last 30 years, major challenges in chromium research remain, such as the development of practical methods for diagnosing chromium deficiency. Of several approaches for solving this problem, the most feasible might be to standardize the urinary chromium response following an insulinogenic challenge, such as an oral load of glucose or of glucose plus fructose (for maximal stimulation) with urine collection before and during the 2-hour test.

Key teaching points:

- Chromium is recognized as an essential element.
- Chromium potentiates insulin action.
- A major challenge in chromium research is the development of practical methods for diagnosing chromium deficiency.

INTRODUCTION

More than 50 years of work have led to the identification and recognition of trivalent chromium as an essential element, including more than 20 recent years spent outside of the laboratory. Klaus Schwarz accepted me as a student assistant into his laboratory in Mainz, Germany in 1947, and there I became acquainted with his necrogenic diet that induced liver necrosis and, as we later found out, glucose intolerance. Ten years later, he identified selenium as the protective agent against dietary necrotic liver degeneration, and we were able to show that there had to be a second, separate factor required to maintain normal glucose tolerance. We named it "a glucose tolerance factor" [1], and in 1959 we identified it as chromium [2].

The developments of the next 10 years have been reviewed

and referenced in some detail [3]. An account of the state of knowledge at the end of the second decade was presented at the first international chromium symposium in 1979, in Sherbrooke, Canada [4]. Therefore, rather than giving a detailed account of the developments during these 20 years, I will try to summarize the major accomplishments and the major problems. Shortly after the identification of chromium as an essential element, the interaction of the element with insulin in vitro and in vivo had been established, and the site of action identified as the insulin-sensitive cell membrane. Henry Schroeder had published the analytical results of his worldwide autopsy study indicating a continuous decline of chromium concentration in human tissues [5], and he subsequently promulgated his hypothesis of chromium deficiency as one cause of atherosclerosis. He conceived and built the first "trace element controlled

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environment” for small animals on a remote hill near Brattleboro, Vermont, and raised severely chromium deficient rats that became diabetic and died prematurely [6]. Our studies demonstrated that stresses such as blood loss or low protein diets aggravated the consequences of deficiency [7].

Our first results on the beneficial effects of chromium in diabetic patients under metabolic ward conditions with Walter Glinesmann showed significant improvement [8]. Although these results were submitted to the 1964 International Diabetes Congress, they were “to be read by title only.” Meanwhile, Richard Doisy established a productive chromium project with studies in the elderly [9], and Leon Hopkins published his results of chromium supplementation in malnourished children of Jordan and Nigeria [10]. The work of Gürson and Saner in Istanbul not only confirmed the effect on impaired glucose tolerance [11], but also detected a significantly greater rate of weight recovery in the chromium treated children [12]. Four major problems, some of them still unsolved today, have influenced the rate of progress since then.

CHROMIUM ANALYSIS

At the time of the early work on the biological role of chromium, Alan Walsh’s invention of atomic absorption began to be commercialized, and the first instruments promised a much more sensitive and easier method than the previous colorimetric and other procedures. An explosion of analytical data, not always produced by analytical chemists, resulted. The published data on chromium concentrations in blood and urine kept declining then and with every improvement of the instrumentation. Interlaboratory comparisons organized by the International Atomic Energy Agency gave results that were up to 2 orders of magnitude apart and that could not be reconciled [13].

At a workshop in the early 1970s most active chromium researchers in the United States met in Columbia, Missouri and agreed on a typical chromium concentration in human urine of about $7 \mu\text{L}$. The proceedings were never published, however, because soon thereafter Barbara Guthrie, a visiting scientist from New Zealand, Wayne Wolf, and Claude Veillon in our Center at the US Department of Agriculture became dissatisfied with the atomic absorption tracing of chromium in urine. Employing the then-available isotope dilution method, they established a new normal value which was another order of magnitude lower [14,15]. Since then, the downward slide of chromium values appears to have ended, not only because of improvements in instrumentation, but also because of the greater availability of standard reference materials for chromium in biological materials.

These developments raised serious doubts about all analytical data published before that time, even those that compared sequential samples with the same method or those with high chromium concentrations (e.g., diets) that were well within the capability of the earlier methods. Recent studies [16] have

confirmed the relative differences detected by Schroeder [5] (decline of concentrations with age), by Hambidge [17] (diagnosis of chromium status in women and children), and by Glinesmann [18] (diagnosis of chromium status in diabetics), but their data were considered insecure, and their approaches were neglected for one or two decades. Another, even more consequential effect of the new analytical values was a drastic change of research priorities. The then-accepted “old” values for chromium in urine demanded the existence of chromium compounds with high bioavailability. For a diet containing $30 \mu\text{g}$ to $100 \mu\text{g}$ of chromium to support a daily loss of $7 \mu\text{g}$, an absorption efficiency of around 10% would be necessary, in contrast to the 1% to 3% known from human and animal studies. This led to the postulate that there had to be “glucose tolerance factors” of substantially higher bioavailability. Although we know of substantial variation in the bioavailabilities of chromium in different foods [19], the new, lower analytical data for chromium excretion have diminished the importance of chromium’s bioavailability for balance. There still remains, however, the important question of whether all absorbed chromium is equally well available for conversion into the biologically active form.

Finally, regardless of analytical accuracy, we have known since the 1960s that the circulating chromium is not in equilibrium with the physiologically important stores, and this fact has deprived us of a practical tool to diagnose chromium status of individuals. This situation is very similar to that of the other essential trace elements, for which special diagnostically meaningful fractions remain to be identified. Thus, one of the major challenges in our field is the development of practical methods of status diagnosis, which will be discussed later.

INTERACTIONS OF CHROMIUM WITH OTHER DIETARY FACTORS

Another problem that has impeded progress is the difficulty of inducing chromium deficiency in experimental animals. The contrast between the consistent impairment of glucose tolerance in our rats raised on a Torula yeast diet or Schroeder’s rats fed a natural diet, on one hand, and the paucity of reports on impressive effects of chromium deficiency in these species during the past 20 years, on the other, strongly suggests some interactions between chromium and another factor that we have hitherto overlooked. The Torula yeast diet, which we used during our early studies and again in the late 1980s, is low in sulfur amino acids, zinc, and selenium, excessive in iron, and contains predominantly saturated fat. Although an interaction between chromium and iron is well known from human studies [20], there is no evidence that any of these trace elements affect the signs of chromium deficiency. A predominance of dietary saturated fatty acids might well affect membrane characteristics and increase the chromium requirement, but the limiting content of sulfur amino acids is a more promising theory. We know

of their requirement for the synthesis of glucose tolerance factor active compounds. The situation reminds us of selenium deficiency in humans and animals, which causes immediate disease only when vitamin E and sulfur amino acids are also limiting. Selenium analyses alone of diets or of tissues do not predict the occurrence of liver necrosis in rats, even though selenium alone prevents the diseases. For chromium also, we know from an evaluation of the literature that the severity of the physiological impairments does not depend alone on the degree of deficiency. A search for interacting, conditioning dietary factors is much needed.

Such interacting dietary factors might play a role in human chromium nutrition as well as offer an answer to this puzzling question: Why is it that the strongest, most convincing manifestations of chromium deficiency are reported from developing areas with less than optimal nutritional status (Northern and Eastern rim of the Mediterranean, Nigeria, South Africa, India, and China) [21] and not in the industrialized countries with a high consumption of refined carbohydrates? We know that the latter should cause and aggravate chromium deficiency. Is it possible that marginal intakes of secondary, interacting factors in the populations of developing countries raise their chromium requirement? This would remind us again of the selenium situation and of the difference in the incidence of the Keshan disease in the populations of China and New Zealand, despite near identical selenium intakes.

DIAGNOSIS OF CHROMIUM STATUS

Today's only method to diagnose chromium deficiency in individuals is retrospective: demonstrated reduction of insulin resistance after chromium supplementation of individuals and reappearance of resistance after the supplement is withdrawn. Although concentrations in blood, hair, and sweat are known to decline with age, suggesting some physiological significance, their diagnostic usefulness in individuals is uncertain, except perhaps in cases of severe deficiency. At least four approaches to a diagnosis could be considered for their physiological basis and feasibility:

- 1) There is evidence for at least some homeostatic regulation of chromium metabolism, in that excesses are excreted in the urine and absorption efficiency increases with decreasing intakes [22]. Such regulation suggests that a chromium deficient individual might retain a larger fraction of an oral chromium load than one in adequate status, i.e., excrete correspondingly less.
- 2) More promising might be investigation of the hypothesis that the total chromium in blood (and urine) consists of several chemical species of which one or more correlate with the physiologically important pool. Chemical speciation efforts could begin on the basis of the known composition of active chromium compounds.

- 3) The "relative chromium response", which is the rise or decline of serum chromium following a glucose load, has been shown by two investigators independently to correlate with the chromium nutritional status of small groups of individuals [23,24]. The concept, however, is not universally accepted, since several studies have failed to detect any concentration increases in response to glucose. A well designed human study of the effect of supplementation on the relative chromium response in older people could resolve the existing controversy.
- 4) The most promising and feasible approach might be the standardization of the urinary chromium response following an insulinogenic challenge, such as an oral load of glucose or of glucose plus fructose (for maximal stimulation) with urine collection before and during the 2-hour test. We know that young, supposedly chromium adequate persons increase their chromium excretion following an oral load with simple carbohydrates and that the magnitude of that response is related to the insulinogenic property of the sugar [25]. It is reasonable to expect that an individual who does not have adequate stores of biologically active chromium to interact with insulin and its receptors would excrete less of the element than a person with normal stores.

Each of these approaches to establish a valid diagnostic procedure would require a substantial effort. If successful, it would substantially improve the scientific basis not only for chromium supplementation of individuals but also for public health measures.

CONTROVERSIES, PAST AND PRESENT

Chromium research, like most new fields, had to content with many serious controversies that arose especially during the early years. Looking at these from the distance of 50 years, I am impressed by how they disappeared when new knowledge integrated seemingly irreconcilable facts and opinions. The first obstacle against accepting an essential role for chromium, the fact that the element was universally recognized as a carcinogen, disappeared with the recognition that the biologically essential trivalent form cannot be oxidized in the living organism to the carcinogenic hexavalent state. Another controversy arose when the intestinal absorption of some trivalent compounds was close to "zero" by then-available analytical methods. The opinion "zero absorption is not compatible with essentiality" resolved itself as analytic methods improved. The failure of some early studies to confirm effects of supplementation on glucose tolerance produced much skepticism, until the basic law of nutrition was accepted that every nutrient improves only functions that are impaired because of the nutrient's deficiency. The lack of an effect on glucose tolerance even in chromium deficient organisms in some studies, leading

to controversies, is now explained by the fact that chromium may potentiate the action of insulin either by an effect on insulin dependent functions, or by maintaining these functions with less insulin, or by a combination of both.

One unresolved controversy remains. It relates to the nature of the biologically active form of chromium, glucose tolerance factor, for which differences of chemical composition and structure have been proposed by different authors. In most of these examples, the solution was not an "either/or" choice, but the integration of apparently contradictory data and interpretations by new knowledge. That this tradition may continue into the future is my sincere wish to all my friends and colleagues in the field.

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