# Dietary Chromium Supplementation for Targeted Treatment of Diabetes Patients with Comorbid Depression and Binge Eating

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## Abstract

Dietary chromium supplementation for the treatment of diabetes remains controversial. The prevailing view that chromium supplementation for glucose regulation is unjustified has been based upon prior studies showing mixed, modest-sized effects in patients with type 2 diabetes (T2DM). Based on chromium's potential to improve insulin, dopamine, and serotonin function, we hypothesize that chromium has a greater glucoregulatory effect in individuals who have concurrent disturbances in dopamine and serotonin function – that is, complex patients with comorbid diabetes, depression, and binge eating. We propose, as suggested by the collective data to date, the need to go beyond the "one size fits all" approach to chromium supplementation and put forth a series of experiments designed to link physiological and neurobehavioral processes in the chromium response phenotype.

## Diabetes, Depression, and Binge Eating Comorbidity

Worldwide, over 370 million people have diabetes, and diabetes-related healthcare costs are approaching 500 billion U.S. dollars [1]. Lifestyle interventions are effective but difficult to sustain over time [2], and existing drug therapies are limited by side effects and durability. Therefore, significant future progress in treating and preventing diabetes hinges on developing tailored strategies that focus on individuals at greatest risk and that are easily assimilated and sustained.

Diabetes patients that struggle with depression and disordered eating comprise an important high-risk group because they are less compliant with treatment recommendations and suffer

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worse diabetes-related complications and poorer outcomes [3-8]. An estimated 17.6 % [9] to 31 % [10] of diabetic patients have a depressive disorder, and as high as 40 % of T2DM patients [11] and 58 % of type 1 patients [12] have disordered eating, with binge eating being the predominant pathology [13]. Binge eating significantly increases the risk of new-onset T2DM [14] and is associated with higher glycated hemoglobin and body mass index [11] and less weight loss [15] in persons with T2DM. An estimated 1.4 % [16] to 10 % [13] of patients with T2DM meet full diagnostic criteria for binge eating disorder [17].

We hypothesize that the "complex" diabetes patient who suffers with comorbid depression and disordered eating may have a good clinical response to treatment with dietary chromium because of its ability to regulate key neurobiological substrates that are dysregulated in these conditions.

## Neurobiological basis for the hypothesis

T2DM and binge eating are linked through shared cortical and subcortical neural circuitry and signaling pathways involved in food reward, particularly the dopaminergic system, which is highly sensitive to the actions of insulin. The mesolimbic dopamine (DA) pathway has been specifically implicated in the incentive, reinforcing and motivational aspects of food intake [18, 19]. The dopaminergic neurons of the midbrain nucleus, the ventral tegmental area (VTA), play a key role in motivated eating and in processing cues related to the rewarding properties of palatable food [20]. Insulin receptors are expressed on these VTA neurons, and insulin in the VTA can suppress feeding [21]. Importantly, insulin directly inhibits VTA DA neurons [22], which primarily project to the ventral striatum, a key site for regulation of motivated feeding behavior [23]. Insulin-mediated decrease of DA in the VTA is thought to normally suppress the salience of food upon reaching satiety. A plausible consequence of the hyperinsulinemia of T2DM is insulin-resistance of VTA neurons, akin to that seen in other systems of the body. To our knowledge, the possibility of insulin-resistance of VTA DA neurons has not been investigated, but if it occurs, it is proposed that by reducing insulin-induced suppression of VTA DA neuron firing, it would blunt the normally associated waning of food-cue salience with increasing satiety. In addition to the mesolimbic DA projection, VTA DA neurons can project to frontal regions, where DA supports the coupling of attention-related networks [24] that may underlie attentional biases to food cues and reward sensitivity observed in persons who binge eat [25-27].

T2DM, binge eating, and depression are further linked through shared circuits and signaling pathways within the serotonergic system. Like the dopaminergic system, the serotonergic system is highly sensitive to the actions of insulin. In the hypothalamus, insulin administration increases hypothalamic serotonin (5-HT) release [28, 29]. Reciprocally, 5-HT modulates insulin action in the brain [30, 31] having a direct effect on hypothalamic glucose homeostasis [32], which appears impaired in T2DM [33]. 5-HT is also involved in the regulation of bias toward selection of immediate over delayed rewards in dynamic delay discounting tasks [34], control of meal size [35], and sweet preference, as indexed by increased sweet calorie intake following depletion of the serotonin precursor tryptophan [36]. Finally, a large and converging body of evidence from animal and human studies links

5-HT deficiency with depression [37] and demonstrates that lowering 5-HT levels through acute tryptophan depletion precipitates depression symptoms in vulnerable individuals [38, 39].

The micronutrient, chromium, has been known to be an essential element in carbohydrate metabolism [40-43]. Given this role in insulin action, chromium may be an ideal alternative therapy for complex T2DM patients with comorbid depression and binge eating because of its "triple-threat" capacity to affect insulin, DA, and 5-HT neurotransmission and thus target the behavioral and psychological correlates of poor glycemic control (see heuristic model in Figure 1). Chromium enhances cellular insulin activity [44-50] which, in turn, promotes increased entry of tryptophan into the brain thereby increasing brain serotonin synthesis [44]. Chromium treatment significantly lowers the cortisol response to 5-hydroxytryptophan suggesting, in particular, enhanced sensitivity of central serotonin$_{2A}$ (5-HT$_{2A}$) receptors [45, 46]. Because of reciprocal interaction of serotonin and DA through direct synaptic connections [51, 52] and through physical 5-HT$_{2A}$–DA$_2$ receptor heterocomplexes [53, 54], the possibility exists for chromium to also influence DA function indirectly via the 5-HT system. That these neural connections occur in the VTA in neurons projecting to the nucleus accumbens provides a plausible neurobiological basis for chromium's capacity to influence eating behavior and mood.

## Supportive evidence for the hypothesis from human studies

Hexavalent chromium (chromium VI) is highly toxic and carcinogenic. However, according to the Council for Responsible Nutrition, dietary supplementation with trivalent chromium (chromium III) is generally considered safe for adults at levels up to 1,000 mcg/day [55]; side-effects are typically mild and include unexplained bruising, nosebleed, rash, decreased urination, lethargy, loss of appetite, nausea or vomiting, sleep disturbances, headache, and dizziness. Except at supra-physiologic doses over extended treatment periods, trivalent chromium has essentially no known genotoxic or carcinogenic risk [56]; and, since 2005, the FDA has recognized trivalent chromium in the form of chromium picolinate as a safe nutritional supplement that may reduce the risk of insulin resistance and possibly T2DM. The combination of chromium picolinate combined with biotin, which is thought to synergize the effects of chromium [57, 58], is also well tolerated and associated with minimal adverse effects [59, 60]. In addition to chromium picolinate, other trivalent chromium complexes include chromium niacin, chromium D-phenylalanine, and chromium salicylate. Like chromium picolinate, these complexes, as well as the novel chromium chelate, chromium histidinate, exert glucoregulatory and immunoregulatory effects in diabetes [61, 62].

In placebo-controlled trials, dietary supplementation with chromium with and without the addition of biotin has been reported to improve glucose regulation, depression, and binge eating in patient populations [59, 63, 64]. Studies in diabetes have nearly exclusively focused on patients with T2DM but there are case report data suggesting benefit in type 1 diabetes, as well [65]. Recent meta-analyses indicated that chromium supplementation lowers blood glucose in T2DM patients [66-68] but not all patients derive this benefit [60, 69-71] or show improvements in glycated hemoglobin [72]; pre-treatment insulin sensitivity

explains ∼40 % of the clinical response to chromium [71, 73], with individuals who are more insulin resistant trending toward greater improvements in glucose regulation post-treatment. In contrast, most, but not all, studies focused on dietary chromium supplementation in samples of non-diabetic overweight or obese individuals have failed to find a significant impact of chromium picolinate on glucose regulation [74]; the reasons for this lack of an effect in obesity, per se, are not precisely known. However, given that hyperglycemia, by definition, is present in diabetic compared to the non-diabetic state, this metabolic parameter could be postulated as a major contributing reason to explain this observation. Chromium supplementation has also been shown to reduce depression symptoms and carbohydrate cravings in antidepressant-refractory patients with dysthymic disorder [75-77] and to reduce food intake and hunger levels in non-depressed overweight women with carbohydrate cravings [78]. In addition, our group recently reported reduced binge eating in overweight individuals with binge eating disorder following a 6-month chromium supplementation trial [79], possibly due to improvements in cognitive processes (i.e., inhibitory control) that underlie healthy eating behavior.

In adults with mild cognitive impairment, chromium supplementation increased cerebral activation and enhanced performance during various learning, recall, and recognition memory tasks, independent of any changes in peripheral glucose or insulin concentration [80]. Cognitive deficits that contribute to the development and maintenance of obesity and eating disorders are especially pronounced among obese persons with co-morbid binge eating disorder [81, 82]. Binge eating, like other binge-type substance use, is linked to excess allocation of attention to binge-associated stimuli [83, 84]. This attentional bias may reflect profound Pavlovian learning, as demonstrated in models of alcohol abuse and smoking [85-87]. Through such control of attention, food cues may thus facilitate compulsive food intake. The neural basis of attentional bias is not well understood, but may involve dysfunction in executive control signals from the prefrontal cortex regulating mesolimbic DA projections.

## The Hypothesis

Identifying other explanatory factors is the key to unlocking chromium's full potential as a complementary approach to T2DM. As illustrated in Figure 1, we hypothesize that patients with T2DM along with comorbid depression and binge eating will have a greater response to chromium than patients without these comorbidities. Treatment trials that examine the effects of chromium on neurocircuitry underlying the cognitive, emotional, and behavioral processes that contribute to poor glucose control are needed. Studies that systematically examine food-cue attentional bias and fronto-mesolimbic connectivity during DA and 5-HT precursor depletion studies in patients with T2DM would be especially instrumental in advancing our understanding of the chromium response phenotype. From such studies we would anticipate showing that (1) chromium supplementation improves DA and 5-HT functioning, as evidenced by post-treatment reductions in sensitivity to depletion of DA and 5-HT precursors and improved functional connectivity between the prefrontal cortex and ventral tegmental area, and that (2) these effects are more pronounced in patients with versus without comorbid symptoms of depression and binge eating. By demonstrating how chromium treatment alters neural circuits underlying depressed mood and conditioned

responses to food cues, these studies may reveal novel therapeutic targets and increase understanding of how to optimize chromium use in diabetes treatment.

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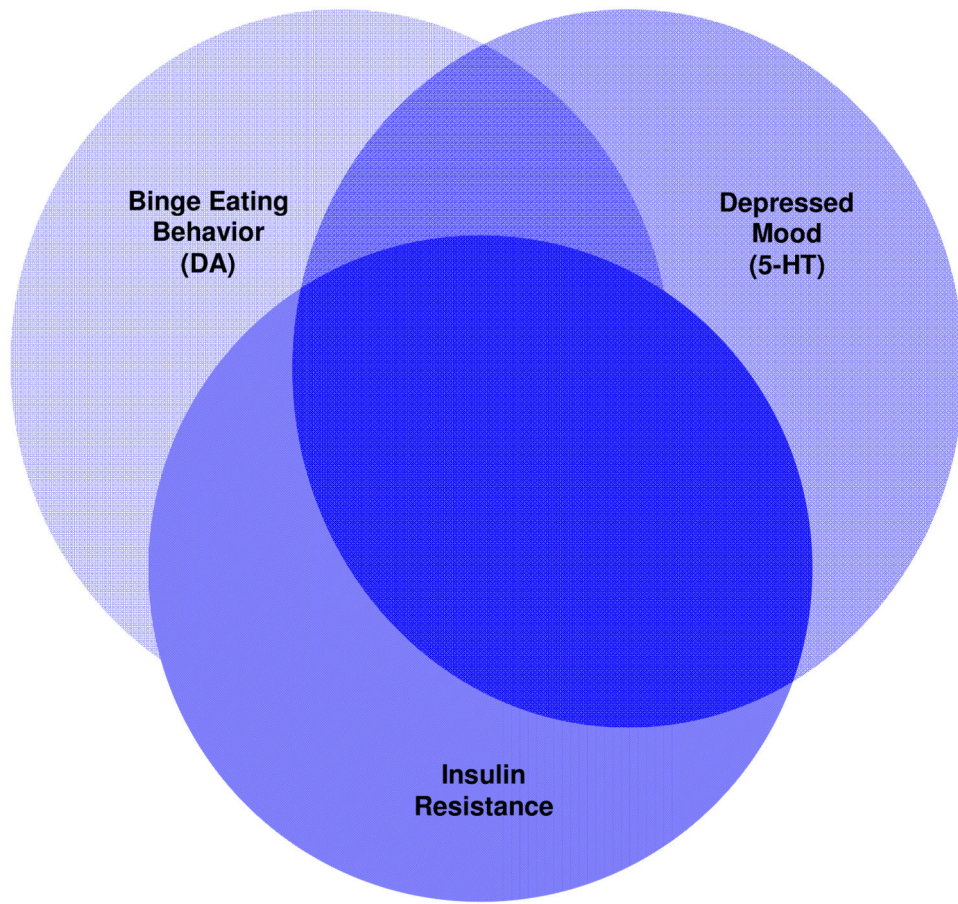87. Robinson TE, Berridge KC. Addiction. Ann Rev Psychol. 2003; 54:25–53. [PubMed: 12185211]

**Figure 1. Heuristic Model of the High Chromium Response Phenotype**