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Concerns on the Use of Chromium in Type 2 Diabetes Mellitus; Needs to Conduct Major Meta-analysis

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Diabetes Mellitus (DM) is a serious and costly metabolic disorder of the new world (Azimi-Nezhad *et al*., 2008) which is expected to rise to 552 million people by 2030. The incidence of DM in Iran is estimated between 1.3-14.5% (Azimi-Nezhad *et al*., 2008). In Iran, almost 2.43 million people suffer from type 2 DM (Javanbakht *et al*., 2011) that seems growing, regarding environmental pollution that has been newly considered as a cause of diabetes in whole world (Mostafalou and Abdollahi, 2012). In a cost analysis study in Iran, Javanbakht *et al*. (2011) estimated that total annual costs of type 2 DM is about 3.78 (2.04 direct and 1.73 indirect) billion USA dollars. They calculated that 842 USD direct and 864 USD indirect costs per capita including complications (49%) and drugs (24%) as the main parts of direct costs. The best strategies to control diabetes are pharmacotherapy, proper diets, supplement adjuvants and lifestyle modifying (Psaltopoulou *et al*., 2010). Considering the growing trend of DM and cost of current therapies and also the mechanisms of DM (Rahimi *et al*., 2005), use of antioxidant supplementary to pharmacological regimens could help reduce cost and increase efficacy (Hosseini and Abdoallahi, 2012). Among supplements for diabetes therapy, chromium is known to increase insulin sensitivity (Ali *et al*., 2011). Chromium may increase insulin receptors, stimulate the liver enzyme glucokinase and increase pancreatic B islets (Fuhr *et al*., 2005). The oligopeptide apochromoduline (also known as apo-low-molecular-weight chromium-binding substance) is important for the activation of the insulin receptor. The degree of activation of the insulin receptor depends on the number of chromium ions bound to this peptide (with a minimum of 0 and a maximum of 4 ions) and this may lead to an 8-fold difference in insulin receptor activation (Davis and Vincent, 1997). Chromium III is the most stable, safe and proper form for lipid and carbohydrate metabolism in people with DM (Sharma *et al*., 2011). Many studies indicated the benefit of chromium picolinate in DM (Wang *et al*., 2010). Increased chromium intake seems effective in diabetes by increasing insulin sensitivity (Martin *et al*., 2006), enhancing muscle strength (Hao *et al*., 2011), losing weight and fat (Martin *et al*., 2006), delaying ageing (Janson, 2006) and powering body antioxidant capacity (Cheng *et al*., 2004), these all are good for diabetic patients (Sharma *et al*., 2011). In addition, chromium could modify serum lipid profile (Janson, 2006) by reducing triglyceride and total cholesterol and increasing HDL-cholesterol. Clinical trials in DM have demonstrated that adding chromium to diet could result in reduction of blood sugar, insulin sensitivity and glucose tolerance (Sharma *et al*., 2011). In a double-blind, placebo controlled, randomized clinical trial, Cefalu *et al*. (2010) reported that chromium have a novel mechanism of action in lipid metabolism. Evidences on chromium efficacy are controversial and benefits are significant only in participants with poor serum chromium (Vincent, 2000). A systematic review in 2007 indicated that chromium can decrease hemoglobin A1c (HbA1c) by 0.6%. The positive effect found in that systematic review was predominantly obtained by inclusion of the study of poor methodological quality in the Chinese patients (Balk *et al*., 2007). As part of the investigation, the Food and Drug Administration (FDA) commissioned a meta-analysis of studies on the effects of chromium on subjects with type 2 DM and reported that chromium supplementation statistically improves glycemic control (FDA, 2005). Some articles have discussed safety of chromium. Chromium III is the usual form of chromium in foods and nutrients known as low toxic minerals

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(Anderson, 1998). The US Environmental Protection Agency established dose (70 mg day^{-1}) for chromium that is 350 times the maximum limit of the estimated safe and adequate daily dietary intake (ESADDI) of 200 μg day^{-1} (Mertz *et al*., 1994). So, for trivalent chromium, this estimate of safety intake is higher than for any other nutrient. Previous clinical studies showed that chromium in form of chloride and picolinate had no toxicity in animals at thousands of times higher (National Research Council, 1989). Supplemental chromium did not show toxicity in human.

Furthermore, efficacy of chromium supplementation in glucose control, insulin sensitivity, lipids modification, weight control and other variables is linked to dose and form of supplement, the severity of glucose intolerance and the period of consumption. People at glucose intolerance state but not diabetes itself usually respond to chromium as picolinate (200 μg day^{-1}) or chloride whereas subjects with good glucose tolerance usually do not respond to chromium with above dose. Meanwhile, patients with diabetes may need more than 200 μg day^{-1} even up to 1000-1500 μg day^{-1}. Studies have reported variable response time from 10 days to more than 3 months in some cases to chromium in DM (Anderson *et al*., 1997). On the other hand, stress and the type of diet could affect chromium efficacy. Conclusively, although chromium would potentially have a role as a treatment to allow the use of lower doses of current medications with severe side effects or to treat subjects at the early stages of type 2 DM to potentially delay the onset of the disease but there is no clear consensus on chromium efficacy in diabetic patients because of little data or poor methodological quality.

With an overview study based on Ministry of Health of Iran data, one may believe that chromium consumptions was 1.1 million tablets with the value of 73 thousand USD in 2010 and 1.7 million tablets with value of 113 thousand USD in 2011. The same rising consume is expected for the future. All of these costs are out of the pocket. This supplement has a high consumer price while other anti-diabetic drugs are inexpensive in Iran, so some challenges for utilization of chromium exist. Very likely, in a recent meta-analysis, use of exenatide as an incretin mimetic that has been approved by FDA as an adjunct to diet and exercise in treating type 2 DM, revealed that not only there is no superiority for exenatide over insulin even in its weight reduction advantage but also the risk of gastrointestinal side effects are of major concerns (Salari *et al*., 2011). In another cost-effectiveness study, it was revealed that cost of drug is the main important element rather than availability or access because some people cannot pay for expensive antidotes even in overdose of their close relatives (Nikfar *et al*., 2011). Therefore comparing every new medication with existing ones can provide more clues about the real benefit of paying extra budget for new drugs. There are few articles which discus cost and benefits of chromium consumption in diabetic patients that do not convince us to conclude use of chromium id type 2 DM is cost-benefit especially when high price of chromium is considered. Therefore, more clinical trials and economic evaluation studies based on a major meta-analysis is very much necessary to clarify place of this supplement in management of DM.

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