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Do Not Recommend Chromium Supplements for Diabetic Dialysis Patients

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1. Abstract

1.1. Introduction: Trivalent chromium plays an important role in glucose tolerance factor (GTF). GTF may increase the insulin sensitivity and maintain good blood glucose control. Now, someone has become a habit to use it for diabetic patients. However, some researches did not support the strategy on account of trivalent chromium may convert highly toxic hexavalent chromium. So, the "necessity" of chromium supplements for human is still questioned, especially in hemodialysis patients.

1.2. Materials and Methods: 80 patients (consist of 41 dialysis and 39 non-dialysis) were enrolled. Fasting glycosylated hemoglobin, fasting blood glucose, fasting insulin, insulin resistance index and trivalent chromium and hexavalent chromium were evaluated.

1.3. Results: Correlation analysis of trivalent chromium with insulin resistance in blood glucose and HbA1c concentration showed no statistically significant difference between trivalent chromium, fasting blood glucose, HOMA-IR, and HbA1c.

1.4. Conclusion: Trivalent chromium was not correlated with the decrease of blood glucose, HbA1c and HOMA-IR, but the hexavalent chromium level in dialysis patients is higher than normal control. Then, we do not recommend any type of chromium supplement for diabetic dialysis patients.

2. Introduction

Trivalent chromium (Cr^{+3}) is an essential trace element of the human body and plays an important role in Glucose tolerance factor (GTF) [1]. It participates in glucose metabolism by binding with insulin and receptor then ultimate improves the sensitivity of human tissues to insulin, makes the body's glucose metabolism normal, and maintains the hemostasis of glucose level in blood [2-3]. Studies showed that plasma chromium concentration was negatively correlated with glucose level among type 2 diabetes (T2DM) patients [4]. Now the trivalent chromium supplement has been became a habit for diabetic patients and emphasizes the benefits in diabetes [5]. Although chromium is considered to be an enhancer of insulin action, but it has not been consistently supported good for diabetes patients by most researches [6], so the role of chromium in T2DM is still controversial. Due to the widespread presence of chromium, it's extremely low nutritional requirement and lacks of reliable markers, the "necessity" of chromium is even more questioned [5-6].

The insulin resistance (IR) usually means that the decrease in insulin response in diabetic patients. However, Investigation found that chronic kidney diseases (CKD) had insulin resistance and hyperinsulinemia also exist in non-diabetic patients. The blood level of insulin, Haemoglobin A1C (HbA1c) and insulin resistance (HOMA-IR) are increasing significantly by the gradual declination of renal function, even though the non-diabetic dialysis patients may appear slight insulin resistance also [7-8]. Most of the trace elements are excreted by the kidney, so, they will be accumulated while the renal function deterioration. Some trace elements are not biodegradable, and have a long biological half-life, it may poison to the human body even at low doses [9]. Trivalent chromium

will be accumulated due to reduced elimination in patients with chronic kidney disease [10]. It is interesting that trivalent chromium can enhance the metabolism of glucose, but excessive trivalent chromium can be naturally oxidized to toxic hexavalent chromium [11]. So, we want to know the relationship among the concentrations of trivalent chromium, hexavalent chromium, blood glucose and HbA1c. In the meanwhile, we also evaluate the necessity of chromium supplement in diabetic dialysis patients.

3. Materials and Methods

Experimental group (hemodialysis patients, eGFR<10ml/min/1.73 m^2): consist of 21 diabetes (Group A) and 20 non-diabetes (Group B); Control group (non-dialysis patients, eGFR>90ml/min/1.73 m^2): consist of 20 diabetes (Group C) and 19 non-diabetes (Group D). Totally 80 volunteers are enrolled with informed consent, all patients were assessed fasting HbA1C, fasting plasma glucose (FPG), fasting insulin (FINS) and homeostasis model assessment of insulin resistance (HOMA-IR) [12], in the meanwhile, we also collected another 5ml whole blood with anticoagulant-free test tube, centrifuge at 3000rpm, store the serum at -70℃ until with the graphite furnace atomic absorption spectrometer for trivalent chromium and hexavalent chromium [13-14]. This study protocol was approved by the Institutional Review Board of Ping-tung Christian Hospital (IRB No. A10915), and retrospective analysis using anonymous test data. The results are shown in mean ± SD. All statistical analyses are performed with SPSS 25.0. Statistical analysis was using independent sample t test and Pearson correlation analysis. P <0.05 indicates statistical significance.

4. Result

There were 41 hemodialysis and 39 non-dialysis subjects. The basic analysis is shown in Table 1. The systolic blood pressure and I-PTH of the hemodialysis group were significant higher than those of the non-dialysis group. We compared the values of fasting blood glucose, insulin resistance and insulin in the diabetic hemodialysis group whose results were also lower than those in the diabetic non-dialysis group, but there was no statistically significant difference.

The concentrations of trivalent chromium are shown in Table 2A. Dialysis patients whose results were significantly higher than those of non-hemodialysis patients (6.8 ± 7.8 *vs*. 1.5 ± 2.7, p <0.001); and all diabetic patients' data were higher than those of normal population (2.4 ± 3.1 *vs*. 0.5 ± 1.7, p <0.05); in addition, trivalent chromium level in diabetic dialysis patients was higher than in non-diabetic dialysis patients.

In Table 2B are shown the analysis of correlation between trivalent chromium and HOMA-IR, there were no statistically significant difference (r = 0.001, p = 0.992).

Table 1: Characteristics of all tested patients

		dialysis(41)		Non-dialysis(39)		
Catalog	reference	DM	Non-DM	DM	Non-DM	P value
		Group A	Group B	Group C	Group D	A *vs.* C
Number		21	20	20	19	
Age	years	59.8±9.7	54.1±15.4	55.1±12.2	52.8±6.8	0.177
eGFR(MDRD)	>90ml/min/1.73M^2	7.0±3.2	5.4±2.1	107.4±18.3	96.5±6.4	<0.001
Systolic pressure	<140mmHg	161.1±18.3	141.9±23.1	137.8±20.4	132.0±12.1	<0.001
Diastolic pressure	<90mmHg	90.0±10.3	83.3±11.2	84.3±12.2	84.7±9.7	0.113
Creatinine	44-133 μmol/L	789.4±264.2	963.2±303.4	67.8±10.2	72.0±8.1	<0.001
Albumin	>38g/L	39.9±4.2	42.9±3.9	43.1±4.0	43.3±2.0	0.019
Ca	mmol/L	2.32±0.21	2.14±0.33	2.31±0.07	2.33±0.08	0.904
P	mmol/L	1.62±0.47	1.65±0.55	1.16±0.15	1.44±0.29	<0.001
Ca * P	<55$(mg/dl)^2$	45.1±14.0	42.2±16.4	32.3±4.6	40.5±8.8	0.001
I-PTH	<100pg/ml	283.7±176.5	465.7±342.0	43.1±10.0	42.5±14.7	<0.001
Cr^{+3}	0.12~0.67μg / L	7.6±5.0	6.0±10.0	2.4±3.1	0.5±1.7	<0.001
Cr^{+6}	μg / L	1.1±2.8	0.6±1.1	0.4±0.8	0.1±0.0	0.308
Sugar (Fast)	<7.0mmol/L	10.5±6.9	5.1±1.5	12.2±5.9	4.8±0.7	0.381
Insulin (Fast)	5～20mU/L	17.6±18.2	9.8±4.7	19.9±20.2	6.1±3.7	0.701
HOMA-IR	<2.8	7.68±7.85	2.19±1.32	10.47±11.03	1.33±0.86	0.354
HbA1c	< 7%	8.01±1.89	5.50±1.96	8.55±2.07	5.69±0.38	0.384
hematocrit	40～50%	36.9±6.3	34.6±7.6	43.7±3.6	40.7±4.7	<0.001

If P<0.05, was show statistically significant difference.

Table 2A: The concentrations of trivalent chromium and hexavalent chromium.

	All	Non-dialysis	dialysis	Non-dialysis (39)		dialysis (41)	
N=	80	39	41	Non-DM(19)	DM(20)	Non-DM(20)	DM(21)
Cr^{+6}	0.6±1.6	0.2±0.6	0.8±2.1	0.1±0.0	0.4±0.8	0.6±1.1	1.1±2.8
Cr^{+3}	4.2±6.4	1.5±2.7	6.8±7.8*	0.5±1.7	2.4±3.1*	6.0±10.0	7.6±5.0

*P<0.05

Table 2B: Correlation analysis between chromium and insulin resistance parameters.

	Trivalent chromium		Hexavalent chromium	
	r	P	r	P
HOMA-IR	0.001	0.992	-0.041	0.718
Blood glucose	0.003	0.981	0.059	0.604
HbA1c	0.015	0.892	0.062	0.585

5. Discussion

Insulin may turn glucose into energy in cells; the blood sugar will rise if glucose can't enter the cells. Then, the body will produce more insulin compensatory in order to control blood sugar [15-16]. GTF or Chromudulin is a complex that consisting of Trivalent chromium. GTF increases insulin sensitivity *via* activation and binding to insulin receptors [17-18], which can enhance glucose transport through the cell membrane, increase insulin signal sensitivity and regulate blood glucose balance, therefore it improves the T2DM patients to enhance insulin signal transmission in skeletal muscles and well blood glucose control [19-21]. Despite the increased insulin in the body while the chromium deficiency, it still reduces the effectiveness of insulin and impairs glucose intolerance. The increase in circulating insulin and fasting blood glucose will occur [15].

Chromium is commonly found in water, soil and biological systems, which consists of three forms (metal chromium, trivalent chromium and hexavalent chromium). Among them, trivalent chromium is considered to be an essential nutrient element for animals and humans [22]. There are articles showed that daily supplementation with 25-35 micrograms of trivalent chromium per day may improve glucose utilization by cells, reduce the need for exogenous insulin in diabetic patients, and reduce cholesterol and triglyceride low-density lipoprotein (LDL), thereafter reducing the risk of heart attack [23]. People who take chromium supplements have a lower risk of developing T2DM and can reduce insulin resistance in offspring [24-25]. There are studies compared serum chromium concentration between HbA1c> 7.0% and HbA1c ≤7.0% in T2DM patients, the former in serum chromium was significantly lower than the last did, and a linear inverse correlation between HbA1c and serum chromium concentration, which indicated that chromium was helpful for blood glucose control [26, 27]. These studies supported the benefits of adding chromium supplements in the diet [28]. So far chromium has been used as an enhancer of insulin action [4]. Especially in diabetic patients or elderly people are often supplemented with chromium-containing formula in milk powder or Supplement nutrition [5].

However, the role of chromium supplements in T2DM is still controversial, because not all the researches' reports which were consistent with the benefits for DM patients [6]. Although potential benefits in vitro and small-scale in vivo studies have been reported, but the safety and effectiveness of chromium in human being have not yet being reported in large studies [21, 24]. Moreover, some studies have shown that trivalent chromium supplementation will not only significantly improve blood biochemical indicators, but also cannot improve insulin resistance or glucose metabolism in people with T2DM, and even won't reduce the risk of diabetes [5, 29-31]; The actual effect of GTF in humans is not clear as animal experiments, and Chromium deficiency is very rare in humans. So, the recommendation for diabetic patients who use the chromium supplements to help control blood glucose is still controversial [32].

Chromium is not reabsorbed by the kidney, it is lost through the urine, and it may be deficient in diabetic patients with normal renal function, resulting in reduced storage of chromium [33-34]. But the ability of eliminate metal elements declined, then the blood

level of trivalent chromium in chronic renal failure patients will higher than normal populations, even 2.6 times higher than normal people [10, 35].

Even though trivalent chromium can enhance the metabolism of glucose, but hexavalent chromium (Cr^{+6}) is highly toxic [11, 33], when the amount of trivalent chromium was excess of naturally oxidized to hexavalent chromium [11]. Hexavalent chromium owns a strong oxidative stress that will destroy DNA and induces apoptosis in liver cells [36-37]. It also causes malignant tumors [36, 38-41] and damage kidney tissue while hexavalent chromium accumulation [36, 39]. Therefore, the safety of chromium supplements is more doubtful for diabetic patients in dialysis, and so far no reliable references.

We found that fasting blood glucose, insulin and insulin resistance in diabetic dialysis patients (group A) were lower than the diabetic non-dialysis patients (group C). It seemed that blood glucose is better controlled in diabetic dialysis patients than diabetic non-dialysis. Clinical findings showed that the prevalence of chronic kidney disease patient is significantly increased in serum insulin, HbA1c, and insulin resistance [7, 9], although patients with CKD will initially increase β-cell secretion to compensate for decreased insulin sensitivity [8], However, insulin resistance will still increase with the severity of chronic kidney disease [8, 42], and hemodialysis treatment will not change the islet β-cell secretion capacity [42].

According to the literature, plasma insulin concentration will be reduced during the HD or DHF treatment after the second hour to ending [43], that can remove a lot of ineffective insulin, then improves the activity of insulin receptor and reduces insulin resistance. Those make dialysis patients easier to control blood sugar and further reduce the hypoglycemic agent dose. Therefore, the theories included the accumulation of uremic toxin caused hypoglycemia , renal gluconeogenesis decreased and insulin clearance during dialysis. Therefore, patients who are treated by dialysis should decrease insulin dosage or little insulin usage, because of the normal blood glucose happened [43].

However, diet control, proper exercise and reasonable medications are still necessary for blood glucose control in diabetic dialysis patient. At the same time, blood glucose shall be monitored regularly; HbA1c and HOMA-IR shall be detected at least every 3 months [44].

6. Conclusion

Trivalent chromium supplements are over-the-counter medications, and some hypoglycemic drugs per se also contain trivalent chromium [45], therefore, diabetic patients might be intake under habitual or uninformed conditions [24], so the trivalent chromium and hexavalent chromium in diabetic patients are higher than those of non-diabetic dialysis patients and the normal population. This result is different from the previous study that the trivalent chromium in the blood of normal people is higher than diabetic patients [4] (Table 2A).

Here, there are no correlations among trivalent chromium and blood glucose, HbA1c and insulin resistance in all patients (Table 2B). Based on xxx hexavalent chromium is a risk of cancer, we consider that patients with diabetic dialysis are not advised to take the chromium supplements.

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