The Effect of Zinc Supplementation on Serum Adiponectin Concentration and Insulin Resistance in First Degree Relatives of Diabetic Patients

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Abstract

Objective: Adiponectin (an insulin sensitizing protein) and zinc have insulin like effect. This study was conducted to assess the effect of zinc supplementation on serum adiponectin and insulin resistance in first degree relatives of diabetic patients.

Materials and Methods: This study was a randomized clinical trial performed on 58 first degree relatives of diabetic patients with normal glucose tolerance test and body mass index (BMI) more than 25Kg/m^2. The subjects were divided into two groups: a case group which consumed 50mg zinc orally per day for twelve weeks and another group that was not given zinc but regular exercise and weight control were recommended. Adiponectin, fasting blood glucose, insulin and insulin resistance were calculated by the homeostasis model assessment (HOMA) and lipid profile was measured in both groups before and after treatment.

Results: The mean age and BMI of participants were 37.6±7.4 years and 28.8±3.5 Kg/m^2 respectively. The level of adiponectin increased significantly from 1.67 ±1.29 to 3.67± 3.08 mIU/ml in subjects who received 50 mg zinc compared to the control group (p=0.001). HOMA decreased from 1.89±1.07 to 1.54±1.34 in subjects who consumed zinc, but this reduction was not significant (p=0.13).

Conclusion: Zinc significantly increases the level of adiponectin in first degree relatives of diabetic patients. The level of insulin and HOMA index after zinc supplementation decreased but this reduction was not significant.

Key Words: Adiponectin, Zinc, Insulin Resistance, First degree relatives of type 2 diabetes

Introduction

Adiponectin is a 244-amino-acid-long polypeptide that regulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin is exclusively secreted from adipose tissue into the circulation and is very

plentiful in plasma relative to other hormones. Adiponectin, exhibits insulin sensitizing and anti- inflammatory properties (1). The serum adiponectin levels have a negative correlation with body mass index (BMI) and insulin resistance index (2). The serum adiponectin levels are reduced in patients with type 2 diabetes (3). A reduction in adiponectin expression is associated with insulin resistance in animal models. Administration of adiponectin has been accompanied by a reduction in plasma glucose and an increase in insulin sensitivity. The hormone plays a role in the inhibition of the metabolic disturbance that may end in type 2 diabetes (4), obesity, atherosclerosis (1), non-alcoholic fatty liver diseases (NAFLD) and independent risk factors for metabolic syndrome (5). Adiponectin affects glucose flux through decreasing gluconeogenesis and increasing glucose uptake (1,6,7). Adiponectin has a role in lipid catabolism by β-oxidation and triglyceride clearance (7,6). The other metabolic effects of adiponectin are protection against endothelial dysfunction and improvement of insulin sensitivity and weight loss, and control of energy metabolism (8). Adiponectin has also other effects, including putative insulin-sensitizing, anti-atherogenic and anti inflammatory characteristics (9,10).

Consistent with the low circulating levels of adiponectin observed in type 2 diabetes, adiponectin concentration is negatively related to both insulin resistance and central adiposity (3,11). Low baseline adiponectin concentration can predict the subsequent development of insulin resistance; although elevated baseline levels have been shown to be protective against the succeeding development of type 2 diabetes (12-15).

Zinc is an essential trace element that is very important for the function of more than 300 enzymes (16,17) and it is significant for cellular processes like cell division and apoptosis. Zinc has a role in metabolic pathways of proteins, carbohydrates, lipid and nucleic acid (18). Zinc has been associated with the interaction between hormones and receptors and with the improvement in the post receptor stimulus. In vitro studies demonstrated that insulin combines with zinc and leads to increased solubility of insulin in beta cells of the pancreas and also enhances the binding capacity of insulin to receptors (18). Therefore, the concentration of zinc in the human body is firmly regulated and disturbances of zinc homeostasis have been associated with several diseases including diabetes mellitus. Zinc supplementation of animals and humans has been shown to improve glycemic control in type 1 and 2 diabetes but the basic molecular mechanisms have only slowly been explained. Zinc not only is responsible for the synthesis and action of insulin[16] but also provides insulin-like effects in an insulin independent way (19). Previous studies demonstrated that the serum zinc level is lower in diabetic patients than in non-diabetic subjects (20,21). Some studies have shown that zinc supplementation in type 2 diabetic patients has antioxidant properties (22,23). Another study exhibited that zinc supplementation decreased lipid peroxidation (24).

This study was done to evaluate the effect of zinc sulfate on adiponectin and insulin resistance in first degree relatives of diabetic patients who had BMI>25kg/m^2. These subjects were selected because we expected this group to have insulin resistance.

Materials and methods

First degree relatives of diabetic patients were recruited to the Yazd Diabetes Research Center from 2009 until 2010. The inclusion criteria were age more than 25 years and BMI more than 25 kg/m^2 with normal 75gr oral glucose tolerance test. First degree relatives of diabetic patients with history of diabetes or subjects who consumed vitamin D or magnesium supplementation in the past 6 months were excluded. From these subjects 58 persons were selected and randomly divided into two groups. All subjects gave written informed consent for participation in the study, which was approved by the local ethic committee. In all subjects BMI was determined by dividing weight by the square

of height. A fasting blood sample was drawn to measure glucose, triglyceride, cholesterol, LDL, HDL, insulin, and adiponectin levels. Another blood sample was obtained for measuring a blood sugar two hours after 75 gm glucose consumption (2hpp). In one group subjects received a capsule of zinc sulfate 220 mg (50 mg elemental zinc) daily for 12 weeks and the other group didn't use zinc sulfate. In both groups regular exercise and weight control were recommended.

Fasting serum glucose was measured by using enzymatic in vitro test. Insulin and adiponectin were analyzed by the Human ELISA kit. The homeostatic model assessment of insulin resistance (HOMA) was used as a surrogate measure of insulin resistance. HOMA is derived from the product of the Fasting Plasma Glucose (FPG) and the Fasting Plasma Insulin (FPI) divided by the constant 22.5.

Statistical analysis

All statistical analyses were performed using SPSS for Windows, version 17. Data of continuous variables were expressed as mean ± standard deviation. For comparison of means of variables between two groups we used the t-test and for comparing means of variables before and after intervention in both groups a paired t-test was used.

Results

In this randomized clinical control study 58 subjects from first degree relatives of diabetic patients with age more than 25 years and BMI above 25kg/m^2 were participated. From these subjects 25 persons from the control and 28 from the case group completed their participation in this study. Of these, 53 subjects (43.4%) were males and 56.6% were females. Mean age of the subjects was 37.6 ±7.4 years and mean of BMI was 28.8±3.5 kg/m^2. The baseline characteristics of subjects in the two groups are shown in table 1. Before intervention the level of adiponectin in case and control groups were 1.89±1.67 and 4.8±4.2 respectively (p=0.001). This study demonstrated that adiponectin concentration significantly increased in the group that received 50 mg zinc sulfate daily in comparison to the control group. The level of adiponectin increased from 1.89±1.67 to 3.78±3.08 mIU/ml in groups who received zinc sulfate (p=0.001) but the level of adiponectin in the control group went from 4.88±4.2 to 3.64±3.2 mIU/ml (p=0.2). Mean difference of adiponectin before and after intervention was significant between the two groups (P=0.003). Insulin level decreased from 8.53±5 to 7.04±6.5 (P=0.1) in the case group but mean difference of insulin was not significant between the two groups after intervention (p=0.59). HOMA index decreased from 1.89±1.07 to1.54±1.3 (p=0.13) in the case group, but this reduction was not significant. FBS decreased from 90.6±9.2 to 84.6±8.9 mg/dl in the case group (P=0.002) and in the control group went from 97.2±10.9 to 92.9±12.9 mg/dl (P=0.04) but the mean difference of FBS between the two groups before and after intervention was not significant (p=0.5). The levels of cholesterol, triglyceride, HDL, LDL were not different between the two groups before and after intervention. (Table 2) shows variables before and after treatment in two groups.

Discussion

Table 1: Baseline characteristic of variables before intervention in two groups

Variables	Case	control	P Value
Adiponectin	1.67±1.29	4.75±4.24	0.001
Insulin	8.5±5	8.4±5.6	0. 93
HOMA	1.89±1.07	1.98±1.51	0.81
FBS	90.6±9.2	97.2±10.9	0.02
2hpp	89.7±20.8	92.16±30.03	0.73
Chol	189.25±39.8	196±31.4	0.5
TG	129.21±46.7	162±58.08	0.02
HDL	42.79±80.2	40.19±8.9	0.32
LDL	117.25±25.69	127.88±21.65	0.17

Table2: Mean±SD of variables before and after intervention in two groups

Variables	Case				Control				
	Before	After	Pvalue[1]	Mean dif	Befor	After	Pvalue[1]	Mean dif	P value[2]
Adiponectin	1.67±1.29	3.67±3.08	0.001	2±2.7	4.75±4.24	3.64±3.2	0.2	-1.2±4.6	0.003
Insulin	8.5±5	7.04±6.59	0.1	-1.49±4.75	8.4±5.6	7.9±6.68	0.77	-0.48±8.4	0.59
HOMA	1.89±1.07	1.54±1.34	0.13	-0.35±1.21	1.98±1.51	1.81±1.45	0.67	-0.16±1.9	0.66
FBS	90.6±9.2	84.6±8.9	0.002	-0.33±0.51	97.2±10.9	92.9±12.9	0.04	-0.23±0.55	0.5
2hpp	89.7±20.8	85.75±13.39	0.33	-3.9±21.3	92.16±30.03	100.8±26.54	0.09	8.6±24.6	0.05
Chol	189.25±39.8	189.5±34.26	0.96	0.25±26.7	196±31.4	199.76±31.03	0.43	3.76±23.8	0.61
TG	129.21±46.7	130.39±34.4	0.85	1.17±32.8	162±58.08	160.24±37.24	0.88	-1.7±61	0.82
HDL	42.79±80.2	42.57±9.33	0.91	-0.21±10.1	40.19±8.9	40.25±8.47	0.71	0.06±0.67	0.91
LDL	117.25±25.69	119.71±24.5	0.6	2.4±25.1	127.88±21.65	127.06±21.44	0.09	-0.81±1.7	0.6

1p value of variables before and after intervention within groups

2p va lue of mean difference of variables before and after intervention between groups

Adiponectin has a role in glucose control by increasing insulin sensitivity, decreasing gluconeogenesis and increasing glucose uptake.

Some studies have exhibited that a low level of adiponectin can predict the succeeding development of insulin resistance although elevated baseline levels have been shown to be protective against consequent development of type 2 diabetes (12-15). Our study showed that zinc significantly increases the level of adiponectin, but the level of insulin and HOMA decrease though this reduction was not significant.

Yoshikawa et al. demonstrated that Zn (II)-dithiocarbamate complexes increase adiponectin level and decrease insulin resistance in mice (25). Adachi et al. showed that supplementation with 30 mg zinc daily for 4 weeks significantly decreased the insulin level; ameliorated hyperglycemia; impaired glucose tolerance and insulin resistance and increased depressed adiponectin level in mice[19]. Our results are consistent with these animal studies that demonstrated zinc supplementation increases adiponectin levels.

Mracek et al. showed that zinc-alpha$_2$-glycoprotein (ZAG*)* gene expression in adipose tissue is down-regulated with increased adiposity and circulating insulin. Negative associations were also found between ZAG mRNA and insulin resistance parameters including plasma insulin and homeostasis model of insulin resistance. However, ZAG mRNA was positively correlated with adiponectin, and ZAG enhances adiponectin production by human adipocytes (26). We didn't find any human studies about the effect of zinc supplementation on adiponectin level.

The result of one study in the Cochrane Systematic Review demonstrated no significant difference in insulin concentration and insulin resistance in subjects who received zinc supplementation compared to the placebo group and this finding is in concordance with our results (27). Chen et al. evaluated the effect of zinc supplementation on plasma glucose and insulin levels in genetically obese mice and their lean controls. The result of this study demonstrated that zinc supplementation reduced fasting plasma glucose in both obese and lean mouse by 51% and 25%, respectively. Fasting plasma insulin levels were significantly decreased by 42% in obese mice after zinc (28). Kelishadi et al. showed that after receiving zinc supplementation, markers of insulin resistance among prepubescent children with metabolic syndrome decreased significantly (29). In our study we found that the level of insulin and insulin resistance after zinc supplementation decreased but this reduction was not significant. This difference may be due to the small number of subjects in our study. We demonstrated that the level of triglyceride, cholesterol, HDL and LDL did not decrease after zinc supplementation and this is inconsistent with the result of Pyrianka Gunasekara et al. who showed that zinc supplementation lowered serum cholesterol in adult diabetes (30). We did not find any human studies about the effect of zinc supplementation on adiponectin levels, but

there were some studies that showed adiponectin reduced the risk of type 2 diabetes. Our study demonstrated increasing levels of adiponectin after zinc supplementation. However a cohort study in a large population to assess the protective effect of zinc supplementation on insulin resistance and developing of diabetes is needed.

Conclusion

Our study exhibited a significant increase in the level of adiponectin after zinc supplementation (50 mg element of zinc sulfate) daily for 12 weeks, but the level of insulin and HOMA index did not significantly change compared with the control group.

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References

1. Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. European Journal of Endocrinology 2003;148(3):293-300.
2. Havel PJ. Update on adipocyte hormones regulation of energy balance and carbohydrate/lipid metabolism. Diabetes 2004;53(Suppl 1):S143–S151.
3. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochemical and Biophysical Research Communications 1999;257(1):79-83.
4. Ukkola O, Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities? Journal of molecular medicine 2002;80(11):696-702.
5. Renaldi O, Pramono B, Sinorita H, Purnomo LB, Asdie RH, Asdie AH.. Hypoadiponectinemia: a risk factor for metabolic syndrome. Acta Med Indones 2009;41(1):20-4.
6. Nedvidkova J, Smitka K, Kopsky V, Hainer V. Adiponectin, an adipocyte-derived protein. Physiol Res 2005;54(2):133-40.
7. Vasseur F, Leprwtre F, Lacquemant C, Froguel P. The genetics of adiponectin. Current Diabetes Reports 2003;3(2):151-8.
8. Vasseur F, Meyre D, Froguel P. Adiponectin, type 2 diabetes and the metabolic syndrome: lessons from human genetic studies. Expert Rev Mol Med 2006;8(27):1-12
9. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends in Endocrinology and Metabolism 2002;13(2):84-9.
10. Ukkola O, Santaniemi M. Adiponectin: a link between excess adiposity and associated comorbidities? Journal of molecular medicine 2002;80(11):696-702.
11. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. Journal of Clinical Endocrinology & Metabolism 2001;86(5):1930-5.
12. Daimon M, Oizumi T, Saitoh T, Kameda W, Hirata A, Yamaguchi H, et al. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese Population The Funagata study. Diabetes Care 2003;26(7):2015-20.
13. Lindsay RS, Funahashi T, Hanson RL ,Matsuzawa Y, Tanaka S, Tataranni PA, et al.Adiponectin and development of type 2 diabetes in the Pima Indian population. The Lancet 2002;360(9326):57-8.
14. Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner SM, Ramachandran A. Plasma adiponectin is an independent predictor of type 2 diabetes in Asian Indians. Diabetes care 2003;26(12):3226
15. Spranger J, Kroke A, Mhlig M, hlig M, Bergmann MM, Ristow M, Boeing H, et al.Adiponectin and protection against type 2 diabetes mellitus. The Lancet 2003;361(9353):226-8.
16. Yanagisawa H, Nodera M. Zinc physiology and clinical practice. Biomed Res Trace Elements 2007;18(1):3-9.
17. Vallee BL, Falchuk KH. The biochemical basis of zinc physiology. Physiological reviews 1993;73(1):79-118.
18. Marreiro DN, Geloneze B, Tambascia MA, Ler_rio AC, Halpern A, Cozzolino SMF. Participation of zinc in insulin resistance. Arquivos Brasileiros de Endocrinologia & Metabologia 2004;48(2):234-9.
19. Adachi Y, Yoshida J, Kodera Y, Kiss T, Jakusch T, Enyedy EA, et al. Oral administration of a zinc complex improves type 2 diabetes and metabolic syndromes. Biochemical and Biophysical Research Communications 2006;351(1):165-70.

20. Kinlaw WB, Levine AS, Morley JE, Silvis SE, McClain CJ. Abnormal zinc metabolism in type II diabetes mellitus. The American journal of medicine 1983;75(2):273-7.
21. Niewoehner CB, Allen JI, Boosalis M, Levine AS, Morley JE. Role of zinc supplementation in type II diabetes mellitus. The American journal of medicine 1986;81(1):63-8.
22. Roussel AM, Kerkeni A, Zouari N, Mahjoub S, Matheau JM, Anderson RA. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. Journal of the American College of Nutrition 2003;22(4):316-321.
23. Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. Journal of the American College of Nutrition 2001;20(3):212-8
24. Faure P, Benhamou PY, Perard A, Halimi S, Roussel AM. Lipid peroxidation in insulin-dependent diabetic patients with early retina degenerative lesions: effects of an oral zinc supplementation. European journal of clinical nutrition 1995;49(4):282-8
25. Yoshikawa Y, Adachi Y, Sakurai H. A new type of orally active anti-diabetic Zn (II)-dithiocarbamate complex. Life sciences 2007;80(8):759-66
26. Mracek T, Ding Q, Tzanavari T, Kos. K, Pinkney.J,Wilding. J,et al. The adipokine zinc-α 2 -glycoprotein (ZAG) is downregulated with fat mass expansion in obesity. Clinical endocrinology 2010;72(3):334-41.
27. Beletate V, El Dib RP, Atallah AN. Zinc supplementation for the prevention of type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;1
28. Chen MD, Liou SJ, Lin PY, Yang VC, Alexander PS, Lin WH. Effects of zinc supplementation on the plasma glucose level and insulin activity in genetically obese (ob/ob) mice. Biological trace element research 1998;61(3):303-11
29. Kelishadi R, Hashemipour M, Adeli K, Tavakoli N, Movahedian-Attar A, Shapouri J, et al.Effect of zinc supplementation on markers of insulin resistance, oxidative stress, and inflammation among prepubescent children with metabolic syndrome. Metabolic Syndrome and Related Disorders 2010;8(6):505-10
30. Gunasekara P, Hettiarachchi M, Liyanage C, Lekamwasam S. Effects of zinc and multimineral vitamin supplementation on glycemic and lipid control in adult diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2011;4:53-60.