Zinc Status among Type (2) Diabetes Mellitus in the State of Qatar

Ghazi Daradkeh, Mahmoud Zerie*, Mohamad Othman, Prem Chandra, Amin Jaiosi, Lubna Mahmood, Buthaina Alowainati, Ibrahim Mohammad, Mohamad Daghash

[1]Dietetics Department, HMC – Qatar, [2,5,7,8,9] Diabetes & Endocrine department. HMC – Qatar,
[3] Laboratory departments. HMC – Qatar,[4] Biostatistics department. HMC – Qatar, [6] Qatar University – Qatar

gdaradkeh@hmc.org.qa ; ghaziffff@gmail.com

***Abstract*- To assess the serum zinc level in Type (2) diabetic patients and their association with both blood glucose level and lipid profile. Methods: The collection of data was carried out during the period from Jan 2007 to Nov 2007 in outpatient diabetic clinic at Hamad General Hospital, state of Qatar. 315 Type (2) diabetic patients (aged 25 65) who were previously diagnosed and attended diabetic clinics were selected by systematic random sampling technique. Anthropometric measurements (weight, height, and BMI) of the patients were recorded and venous blood samples drawn from each subject following an overnight fasting for 12 hours, in tube containing 0.15 % EDTA. Blood samples for Zinc determination were collected in Zinc free polypropylene tubes and the separated serum was stored at -20 o C until being analyzed. Zinc determination was performed in duplicate with an atomic absorption method by using flame atomic absorption. All lab tests were done in the central laboratory at Hamad Medical Corporation. RESULTS: The 315 subjects included, 148 (47 %) males and 167 (53 %) females 25-65 years old with a mean age of 50.04 ± 8.46. 172 (54.6 %). 116 (36.8 %) were overweight and obese and 27 (8.6 %) were with a normal body weight, with a mean body mass index of (29.25 ± 3.50), 214 (67.9 %) had uncontrolled blood sugar of HbA1C >7.5%. 51 (16.9 %) had hypercholesterolemia and 102 (23.4 %) had hypertriglyceridemia. 60 (19%) subjects were zinc-deficient (Zn < 70 µg), and 41 (68.3 %) of them had uncontrolled blood sugar of HbA1c>7.5%. 11(18.3 %) had hypercholesterolemia, and17(28.3 %) had hypertriglyceridemia, 38 (73.1 %) and 6 (10.0 %) of the zinc-deficient patients were with low HDL-c and high LDL-c levels, respectively. CONCLUSIONS: The results showed that zinc deficiency is common among type 2 diabetic patients due to hyperglycemia and polyurea. Periodic serum zinc measurement is recommended for type 2 diabetes mellitus.**

Keywords- Zinc; Diabetes Mellitus; EDTA; HbA1C; BMI

I. INTRODUCTION

Diabetes mellitus is considered as a public health problem in both developing and developed countries. The prevalence of diabetes has been progressive worldwide during the last few decades with serious complications and increased mortality among the affected people as well. The number of people with diabetes is increasing due to population growth, aging, urbanization, increasing prevalence of obesity, and physical inactivity [1].

Type (2) diabetes mellitus accounts for 85 % of all diabetes worldwide [2-4]. Insulin is actually needed for about 35 % of Type (2) diabetic patients above the age of 30 [5]. Good glycemic control can delay and reduce complications in both type [1] and Type (2) diabetes [6, 7]. Meanwhile, poor glycemic control in Type (2) patients should no longer be accepted [8], since it is a cause of macro and micro vascular complications with increased morbidity and mortality in Type (2) diabetic patients. Type (2) diabetes is characterized by an increased risk of the development of macro vascular diseases, including [coronary heart disease, cerebro vascular disease, and peripheral vascular disease] and micro vascular complications, such as [Neuropathy, Nephropathy and retinopathy] [9].

Several studies have demonstrated that even mild increase in chronic (fasting) or acute (postprandial) blood glucose concentration can contribute to macro vascular injury and atherosclerotic changes [10]. Conversely, intensive glycemic control prevents or significantly delays the development of nerve abnormalities and diseases related to micro vascular changes in persons with Type (2) diabetes mellitus [11]. The preponderance of evidence indicates that hyperglycemia increases the oxidative stress, which is, defined as the production of reactive oxygen species (free radical; ROS) beyond the protection capability of the antioxidant defenses.

Hyperglycemia may promote the generation of ROS by the activation of polyol and increased glucose auto oxidation [12]. The role of zinc in carbohydrate metabolism has already been a subject of considerable interest. Approximately 0.5% of crystalline insulin is zinc. Zinc deficiency in some studies has been associated with reduced insulin secretion and increased tissue resistance to insulin action [13-16].

Zinc enhances the binding of insulin to hepatocyte membranes [17] and potentiates the lipogenic effect of insulin in rat adipocytes [18]. The effect of zinc on insulin secretion is biphasic: very high or very low zinc plasma concentrations impair insulin

DOI: 10.5963/PHF0301002

secretion [19-21]. Severed zinc deficiency may cause glucose intolerance. Zinc is involved in the synthesis, storage, release, and conformational integrity of insulin. People with diabetes have altered zinc status, based on some observations including low serum zinc concentration, high zinc excretion, and abnormalities in zinc function [22].

Improving zinc deficiency can lead to an improvement in both glucose and insulin variables and lipid peroxidation as well [23]. A physical chemical relationship between insulin and zinc has been known for decades, it was clear that the addition of zinc to insulin would change the time course of the effect of a given dose of insulin, and prolong the duration of action of the insulin by delaying its absorption from the subcutaneous injection site, thus reducing insulin injections [24]. Furthermore, hyperglycemia is the basis for hyperzincyria; other data suggested that there is also a defect in zinc absorption associated with hyperglycemia [25]. Zinc-deficient diet resulted in decreased ability of the pancreas to secrete insulin in response to glucose load, suggesting that zinc deficiency also reduced the ability of the pancreas to respond appropriately [26]. Zinc plays a role in the regulation of insulin production by pancreatic tissues and glucose utilization by muscle and fat cells. The abilities to synthesize and secrete insulin as well as to use glucose are impaired in zinc – deficient state [27, 28].

Zinc deficiency decreases glucose tolerance [29, 30], insulin content in the pancreas [31] and, the physiological potency of insulin [32], while increases insulin degradation [29]. In many developing countries, zinc deficiency is due to low consumption of animal sources foods, which are rich in zinc, besides the high intake of cereals and legumes, which contain substantial amounts of phytate [myoinositol hexaphosphate], a compound known to inhibit zinc absorption [33]. In addition to the structural role in the storage form of insulin, zinc is also capable of modulating insulin action [34]. Hepatic binding of insulin is enhanced by zinc, and stimulation of lipogenesis in the adipocyte has also been described with synergism between insulin and zinc [35]. Development of glucose intolerance in rats after dietary zinc deprivation has recently been reported [36]. A close structural and functional relationship between zinc and insulin has been recognized since crystalline insulin contains relatively large quantities of zinc [37]. Structurally, the addition of zinc to insulin results in conformational changes, which have been detected by ultraviolet circular dichoric spectroscopy [38]. It has been reported that the removal of zinc alters the ternary structure of insulin and can reduce the immunological insulin activity due to the changes in antigenic determinations of insulin [39, 40]. The zinc contents of diabetic pancreases have been reported to be depressed when compared to normal ones[41], and diabetic children have been shown to have low hair zinc levels, which return to normal after insulin administration [42].

II. OBJECTIVES

The aim of this study is to (i) assess the zinc level of type 2 diabetic patients and (ii) assess the association between zinc level with blood glucose and lipid profile.

III. METHODS

The study was carried out within a period of 10 months from January 2007 to November 2007. This study included 315 Type (2) diabetic patients who were selected from adult diabetic patients attending the diabetic clinics at Hamad General Hospital, State of Qatar. Patient were selected by using systematic random sampling technique (every other patient who met the inclusion criteria was chosen). Serum Zinc Level was assessed for the diabetic patients.

The assessing of serum zinc level in type 2 diabetic patients and its relation with blood glucose level and lipid profile were fully explained to the patients and written consent forms were obtained before the patients are included in the study. A total of 374 patients aged 25 – 65 years were selected, while 59 patients were excluded because of their refusal to participate or as a result of their incomplete data such as anthropometric measurements or laboratory results.

Body weight was measured using pre-calibrated SECA - SCALE to the nearest 0.1 kg in outdoor clothes, height was measured with bare feet to the nearest 0.5 cm with a vertical measuring scale fixed to a metal bar connected to weighing scale. While the subject stands with feet fully erect, the back of the head comfortably erect, the lower border of the orbit in the same horizontal plane as the external auditory meatus, and arms hang at the sides in a natural manner, the head plastic bar, was gently lowered crushing the hair and contact with the top of the head.

Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared, i.e. BMI = wt. (kg)/ht (m^2), and was used as an indicator for determining overweight or obesity. According to WHO classification, underweight was defined as BMI < 18.5 kg/m ²; overweight when BMI ranges between 25 and 29.9 kg/m² and obesity when BMI ≥ 30 kg/ m²[43]. Zinc deficiency was defined as serum zinc < 70 μg/dl, while normal zinc ≥ 70 μg/dl [44].

Venous blood samples were drawn from each subject in the study following overnight fasting for 12 hours, in tubes containing 0.15 % EDTA, and the sample were centrifuged at 2599*g for 20 minutes at 4°C to separate serum. Fasting blood glucose, was measured by using a glucose oxidase enzymatic method (Hitachi 917), and HbA1c was measured by using Immunoturbidimetric

DOI: 10.5963/PHF0301002

method (Hitachi 917). Total cholesterol concentration, HDL - c,and LDL - c all were all measured by the enzymatic colorimetric method (Hitachi 917). Blood samples for Zinc determination were collected in Zinc free polypropylene tubes and the separated serums were stored at -20 ^{o}C until analysis. Zinc determination was performed in duplicate through an atomic absorption method by using flame atomic absorption. All lab tests were carried out in the central laboratory at Hamad Medical Corporation.

IV. STATISTICAL ANALYSIS

Categorical and continuous values were expressed as frequency (percentage) and mean ± SD. Descriptive statistics were used to summarize all demographic and other characteristics of the participants. Quantitative variable means between the two independent groups were analyzed using unpaired 't' test. Associations between two or more qualitative or categorical variables were assessed using chi-squared test. For small cell frequencies, chi-squares test with continuity correction factor was used. Pictorial presentations of the key results were made using appropriate statistical graphs. A two-sided P value of .05 was considered to be statistically significant. All statistical analyses were done using statistical packages SPSS 19.0 (SPSS Inc. Chicago, IL).

V. RESULTS

315 Type (2) diabetic patients were included in this study. 148 (47 %) were males and 167 (53%) were females, all aged 25 to 65 with mean age of 50.04 ± 8.46. 172 (54.6 %) and116 (36.8 %) were overweight and obese respectively, whereas 27(8.6 %) patients were with normal weight. 60 (19.0 %) patients were zinc-deficient, 36 (60.0%) were males and 24(40.0 %) were females. 22(11.7 %) of the zinc-deficient patients were classified as obese, while 31 (51.7 %) were classified as overweight and 7 (36.6 %) as normal weight.

TABLE 1 SUBJECTS CHARACTERISTICS (ZINC STATUS, SEX, AND BODY MASS INDEX)

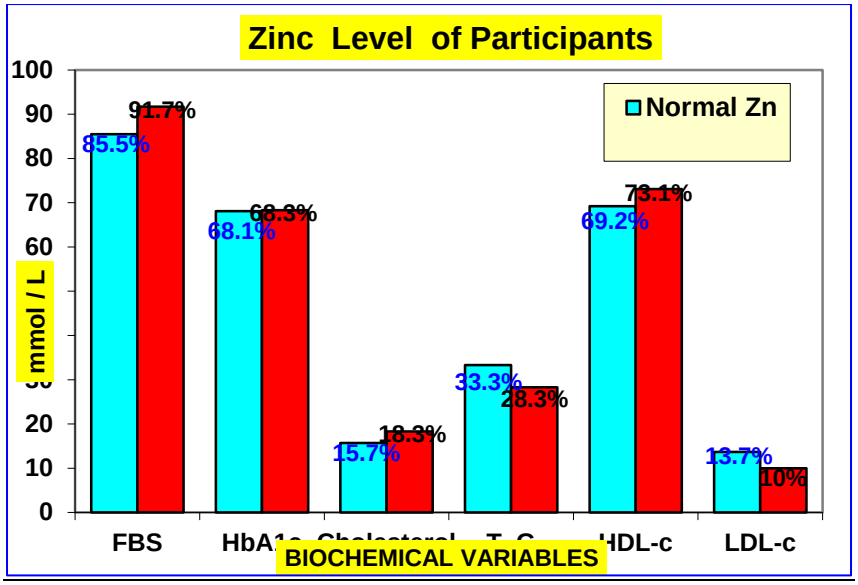
	Normal Zinc n = 255, (81.0%)	**Zn – Def. n =60, (19%)**
Sex Male Female	 112 (43.9) 143 (56.1)	 36 (60.0) 24 (40.0)
BMI 18.5-24.9 25.0-29.9 ≥30	 20 (8.0) 141 (55.3) 94 (36.7)	 7 (11.7) 31 (51.7) 22 (36.6)

Table 2. shows biochemical results of Type (2)diabetic patients. 214(67.9%) of the participants had uncontrolled blood sugar of Hb A1c > 7.5 %. 51 (16.2%) had high cholesterol level, while 111 (35.2%) were on border line. 102 (32.4 %) were with high triglyceride level and 58 (18.4%) were on border line. 41 (13.0%) were with high risk of LDL - C ≥ 4.11 mmol/L, and 93(29.5 %) were on border line. Comparison between normal zinc and zinc-deficient groups shows that there is no significant difference regarding glucose and lipid profile.

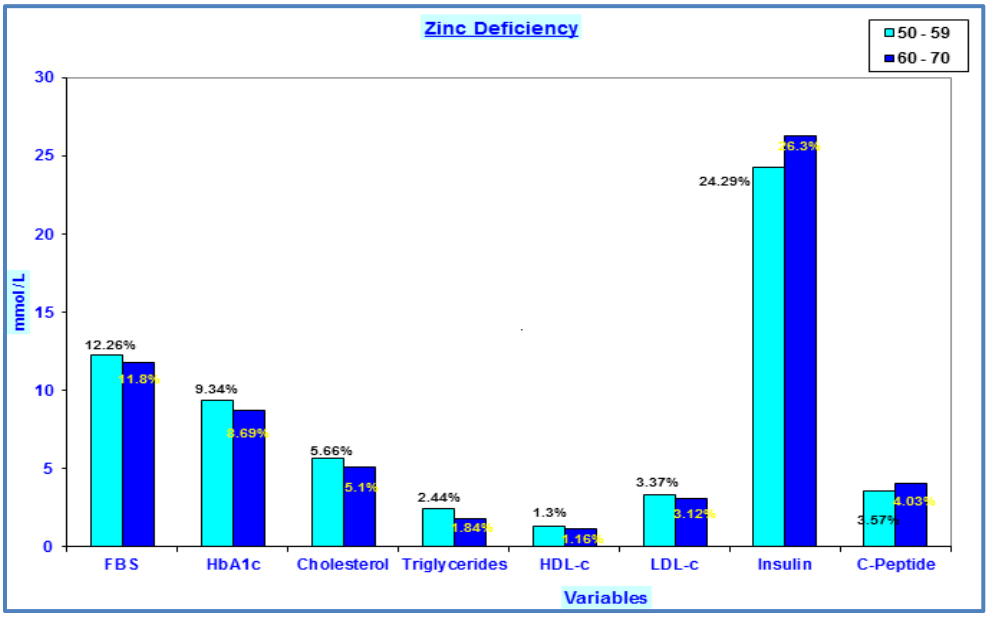
TABLE 2 BIOCHEMICAL RESULTS OF WHOLE SAMPLE

Biochemical Variables	**Normal Zn [n=255]**		**Zn Deficiency [n=60]**		**P-Value**
	n	**%**	**n**	**%**	
FB mmol/l					
≤ 6.4 controlled	37	14.5	5	8.3	0.20
> 6.4 uncontrolled	218	85.5	55	91.7	
HbA1c (%)					
≤ 7.5 controlled	81	31.9	19	31.7	0.97
> 7.5 uucontrolled	173	68.1	41	68.3	
Cholesterol mmol/l					
< 5.17 Desirable	119	46.7	34	56.7	
5.17-6.18 Borderline	96	37.6	15	25.0	0.18
> 6.18 High Risk	40	15.7	11	18.3	
Triglycerides mmol/l					
< 1.7 Desirable	122	47.9	33	55.0	
1.7- 2.2 Borderline	48	18.8	10	16.7	0.62
> 2.2 High Risk	85	33.3	17	28.3	
HDL mmol/l					
≤ 1.0 Low	64	30.8	14	26.9	0.58
> 1.0 Normal	144	69.2	38	73.1	
LDL mmol/l					
< 3.36 Normal	141	55.3	40	66.7	
3.36- 4.11 Borderline	79	31.0	14	23.3	0.31
> 4.11 High Risk	35	13.7	6	10.0	

DOI: 10.5963/PHF0301002



60 (19.0 %) of the participant were zinc-deficient with zinc level < 70 µgm/dL, while 55 (91.7 %) of them were with uncontrolled FBS and 41(68.3%) were with uncontrolled HbA1c. 11(18.3 %) and 6(10.0 %) of the zinc-deficient participant were with high blood cholesterol or high risk of LDL-c respectively, while 17(28.3 %) of the zinc-deficient patients were with hypertriglyceridemia. The results in Table 2showsthat there is no significant difference within the zinc-deficient group, indicating that severity of zinc deficiency has no effect on both the glucose and lipid levels Table 3.



VI. DISCUSSION

As it was seen before, zinc deficiency, among Type (2) diabetic patients has an inverse effect on blood sugar control and it leads to increasing development of the diabetic complications. This study shows the prevalence of zinc deficiency among Type (2) diabetic patients is 19.0%, which is nearly the same as what was founded by Niewoenher et al. [45]. This may be because of the polyuria and zinc loss through the urine. William et al., [46, 47] reported that zinc level in diabetic patients was lower than control group by 13%.

This study shows an inverse, yet not significant relationship between FBS and zinc level. FBS was uncontrolled among 91% of the zinc-deficient group, and this can be explained as after prolonged hyperglycemia and inability of the islet cell to make enough insulin for controling the glucose, there was a loss of islet cell in the meantime and this provides a mechanism by which zinc

DOI: 10.5963/PHF0301002

deficiency might affect the progress of Type (2) diabetes [48]. Because the role of zinc in the regulation of insulin production via pancreatic tissue as well as glucose utilization through muscles and fat cells, zinc deficiency would lead to elevated blood sugar i.e. (hyperglycemia) and the abilities to synthesizes and secret insulin as well as to use glucose are impaired in zinc-deficient state [27,28].

On the other hand, this study shows an association between the FBS and the degree severity of zinc deficiency, but this relation does not reach the significance level as shown in table [3]. In addition, the same relation is observed in this study between the severity of zinc deficiency and glycolated hemoglobin (HbA1c), triglyceride (TG), cholesterol level, LDL-c, and HDL-c.

Moreover, the study shows insignificant relation between zinc level and glycolated hemoglobin (HbA1c) concentration (p=0.97). This can be explained by that zinc absorption has been defected or reduced by uncontrolled blood sugar (hyperglycemia), and it would lead to an elevation of HbA1c, the same as reported by Kinlaw et al [26].

TABLE 3 BIOCHEMICAL RESULTS IN ZINC-DEFICIENT GROUP

Zinc deficiency group	**50-59 n = 11**	**60-70 n = 49**	**P-value**
FBS	12.26 ±4.41	11.08 ± 3.89	0.380
HbA1C	9.34 ± 2.11	8.69 ± 2.10	0.358
Cholesterol	5.66 ± 1.54	5.10 ±1.02	0.143
Triglycerides	2.44 ± 1.50	1.84 ±1.11	0.140
HDL	1.30 ± 0.43	1.16 ±0.27	0.181
LDL	3.37 ± 1.10	3.12 ± 0.98	0.468
Insulin	24.29 ± 17.49	26.30 ± 39.64	0.870
C-Peptide	3.57 ± 1.86	4.03 ± 4.81	0.758

This study shows a positive relationship between zinc level and triglyceride level but this relation is not statistically significant (p value =0.09). Hypertriglyceridemia was present in both normal and zinc-deficient groups, few reports have been published supporting a direct relation between zinc and triglyceride level, but these observations may depends on the severity of the zinc depletion. This increase is represented by endogenous triglycerides transported by VLDL and IDL fractions. This explanation is in agreement with those of Petering et al. [49], who reported a variation in triglyceridemia from 52 mg /100 ml in zinc-deficient subjects to 28.8 mg / 100 ml in control subjects. In the same way, Clejan et al. observed a 200 % increase in triglyceride level of zinc-deficient rats and put forward the hypothesis that zinc-deficient rats have a high endogenous production of lipid.

In addition, an inverse relation between HDL-c level and zinc deficiency was reported by this study also, but this relation didnt reach the significant level with p value at > 0.05, this result is agreed with other reports. 91.6% of the zinc-deficient group were uncontrolled blood sugar FBS> 6.4 mmol/l and 68.3% were uncontrolled glycolated hemoglobin HbA1c >7.5%, this can be due to low zinc level.

VII. CONCLUSION

Zinc deficiency is common in Type (2) diabetes mellitus, due to chronic hyperglycemia and polyurea, which cause zinc loss. Periodic serum zinc determination is mostly recommended for Type (2) diabetic patients.

REFERENCES

[1] King H, Rewers M : Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults: WHO Ad Hoc Diabetes Reporting Group. Diabetes Care 16; 157-177, 1993.

[2] Gatling W, Houston AC. Hill RD, An epidemiological survey: the prevalence of diabetes mellitus in a typical English community. JR Coll Phys London 1985; 4 : 248-250.

[3] Neil HAW, Gatling W, Mather H M et al. The Oxford community diabetes study – evidence for an increase in the prevalence of known diabetes in Great Britain. Diabet Med 1987; **4 :** 539 – 543 .

[4] Zimmer P. Type 2 (non-insulin dependent diabetes mellitus) – AN Gatling W, Houston AC. Hill RD, An epidemiological survey: the prevalence of diabetes mellitus in a typical English community. J R Coll phys London 1985 ; **4:** 248 – 250.

[5] Klein R, Klein BE, Anderson S, Moss SE. Hypoglycemic therapy in-patient diagnosed to have diabetes at 30 years of age . J Chron Dis 1984; **37:** 159 – 165.

[6] Diabetes control and complications trial research group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med 1993; **329 :** 977-986.

[7] UKPD 33. Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes mellitus. Lancet 1998; **352:** 837-853.

DOI: 10.5963/PHF0301002

[8] Panzram G. Mortality and survival in type II non-insulin dependent diabetes mellitus. Diabetologia 1987; **30:** 123-131.

[9] Hsueh WA, Law RE: Cardiovascular risk continuum: implications of insulin resistance and diabetes. Am J Med 105:4S-24S, 1998.

[10] Kawamori R: Asymptomatic hyperglycemia and early atherosclerotic changes. Diabetes Res Clin Pra 40 (Suppl):35S-42S, 1998.

[11] Fedele D, Giugliano D: Peripheral diabetic neuropathy. Current recommendations and future prospects for its prevention and management. Drugs 54:414-421, 1997.

[12] Watts GF, Playford DA: Dyslipoproteinemia and hyperoxidative stress in the pathogenesis of endothelial dysfunction in non-insulin dependent diabetes mellitus : a hypothesis. Atherosclerosis 141:17-30, 1998.

[13] Hendricks DG, Mahoney AW: Glucose tolerance in zinc deficient rats. J Nutr 102:1079-1084, 1972.

[14] Huber AM, Gershoff SN: Effect of zinc deficiency in rats on insulinrelease from the pancreas. J Nutr 103:1739-1744, 1973.

[15] Kirchgessner, Roth HP, Weigand E: Biochemical changes in zinc deficiency. In Trace Elements in Humans Health and Disease:Zinc and Copper. Vol 1. Prasad AS, Oberleas D, Eds. New York, Academic Press, 1976, P. 189-266.

[16] Arquilla ER, Packer S, Tarmas W, Miyamoto S: The effect of zinc on insulin metabolism. Endocrinology 103:1440-1449, 1978.

[17] Coulston L, Dandona P: Insulin-like effect of zinc on adipocytes. Diabetes 29: 665-667, 1980.

[18] Ghalghazi T, Ludvigsen CW, McDaniel ML, Lacy PE: The inhibitory effect of zinc on insulin secretion. IRCS J Med Sci 7:122, 1979.

[19] Figlewicz DP, Formby B, Hodgson AT, Schmid FG, Grodsky GM: Kinetic of zinc uptake and distribution in fractions from cultured rat islets of Langerhans. Diabetes 29: 767-773, 1979.

[20] Figleswicz DP, Held A, Forhan se, Grodsky GM: Effect of exogenous zinc on insulin secretion in vivo. Endocrinology 108:730-732, 1980.

[21] Levine AS, McClain CJ,Handwerger BS, Brown DM, Morley JE: Tissue zinc status of genetically diabetic and streptozotocin-induced diabetic mice . Am j Clin Nutr 37: 382-386, 1983.

[22] Kinlaw WB, Levine AS, Morley HE, Silvis SE, McClain CJ: Abnormal zinc metabolism in type II diabetes mellitus. Am J Med 75:273-277.

[23] Faure P, Benhamou PY, Perard a, et al. Lipid peroxidation in insulin –dependent diabetic patients with early retina degenerative lesions; effects of an oral zinc supplementation. Euro J Clin Nutr; 49 : 282-8,1995.

[24] Zalewski P, Millard S, Forbes I, Kapaniris O,Slavotinek, Betts W, Ward A, Lincolin S, Mahadevan I : Video image analysis of liable Zn in viable pancreatic islet cells using specific fluorescent probe for Zn. J Histochem Cytochem 42 :877-884, 1994.

[25] Williams NR, Rajput-Williams J, West J, Nigdikar S, Foote J, Howard A: Plasma,granulocyte and mononuclear cell copper and zinc in patients with diabetes mellitus. Analyst 120:887-890, 1995.

[26] Engelbart K, Kief H: The functional behavior of zinc and insulin contain in the pancreatic islet cells of rats. Virchows Archives, Cell Pathol 4:294-302, 1970.

[27] Ezaki O :IIb group metal ions (Zn++,cd++,Hg++) stimulate glucose transporter activity by post- insulin receptor kinase mechanism in rat adipocytes . J Biol Chem 264:16118-16122, 1989.

[28] Chooi mk, Todd JK, Boyd ND: Influence of age and sex on plasma zinc levels in normal and diabetic individuals. Nutr Metab 20: 135-142, 1976.

[29] Quarterman J, Florence E: Observations on glucose tolerance and plasma levels of free fatty acids and insulin on the zinc –deficient rat Br J Nutr 28:75-86, 1972.

[30] Hubar AM, Gershoff SN: Effect of zinc deficiency in rats on insulin release from the pancreas. J Nutr 103:1739-1744, 1973.

[31] Levine AS, Mcclain CJ, Handwerger BS, et al: Tissue zinc status of genetically diabetic and streptozotocin- induced diabetic mice. Am J Clin Nutr 37:382-386, 1983.

[32] hograth, f. w.: j. hum. nutr. 35: 379-382, 1981.

[33] Boosalis MG, Evans GW, McClain CJ: Impaired handling of orally administered zinc in pancreatic insufficiency . Am J Clin Nutr 37:268-271, 1983.

[34] Coulston L, Dandonna P: Insulin-Kike effect of zinc on adipocytes. Diabetes 1980; 29:665-667.

[35] Roth H, Kirchgessner M: Zinc and insulin metabolism. Bio Tr El Res 1981; 3: 13-32.

[36] Scott DA. Crystalline insulin. Bioche J 1934; 28: 1592-8.

[37] Goldman J, Carpenter FH. Zinc binding, circular dichroism and equilibrium sedimentation studies on insulin (bovine) and several of its derivatives. Biochemistry 1974; 13: 4566-74.

[38] Arquilla ER, Thiene P, Miyamotos, Dial L.Modulation by zinc of binding and degradation by two liver plasma membrane receptors. Proceeding of the Ninth Congress of the International Diabetes Federation. Amsterdam: Excerpta Medica, International Congress Series no 413.

[39] Arquilla ER, Thiene P, Brugman T, Ruess W, Sugiyama R. Effect of zinc on conformation of antigenic determinants on insulin. Biochem j 1978; 175: 289-97.

[40] Scott DA, Fisher AM. The insulin and the zinc cotent of normal and diabetic pancreas. J Clin Invest 1938; 17: 725-728.

[41] Baerlocher K, Weissert W. Zinc, ein Spruerelement von Klinischer Bedeutung Heiv. Pediatr Acta 1976; 31:99-107.

[42] King h, rewers m: global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults: WHO Ad Hoc Diabetes Reporting Group. Diabetes Care 16; 157-177, 1993.

DOI: 10.5963/PHF0301002

[43] WHO, 1995, WHO, 2000, and WHO 2004.

[44] King, J C, Hambidge K M, Westcott JL, Kern DL, Marshall G, 1994. Daily variation in plasma zinc concentration in women fed meals at six hour intervals. J Nutr 124: 508 – 516.

[45] Degle PS, Partly RE, Hagberg JM, Rogus EM, Goldberg AP: Distinct effect of aerobic execise training and weight loss on glucose homestasis in obese sedentary me. J Applphysiol 81:318-325, 1996.

[46] Isbir T, Tamer A, Taylor A, Isbir M: Zinc,copper and magnesium status in insulin dependent diabetes. Diabetes Res 26:41-45, 1994.

[47] McNair p, kiilerich S, Christiansen M, Madsbad S, Transbol I: Hyperzincuria in insulin treated diabetes mellitus –its relation to glucose homeostasis and insulin administration. Clinica Chemica Acta 112:343-348, 1981.

[48] Huber AM, Gershoff SN: effect of zinc deficiency in rats on insulin release from the pancreas. J Nutr 103:1739-1744, 1973.

[49] Hsueh WA, Law RE: Cardiovascular risk continnum: implications of insulin resisitance and diabetes. AM J Med 105:4S-24S, 1998.

DOI: 10.5963/PHF0301002