

PJN

ISSN 1680-5194

PAKISTAN JOURNAL OF
NUTRITION

ANSI*net*

308 Lasani Town, Sargodha Road, Faisalabad - Pakistan
Mob: +92 300 3008585, Fax: +92 41 8815544
E-mail: editorpjn@gmail.com

Plasma Copper and Zinc in Pregnancy Complicated with Diabetes Mellitus

Emmanuel I. Ugwuja¹, Emmanuel I. Akubugwo² and Boniface N. Ejikeme³

¹Department of Chemical Pathology, Faculty of Clinical Medicine,
Ebonyi State University, P.M.B. 053, Abakaliki, Nigeria

²Department of Biochemistry, Abia State University, Uturu, Nigeria

³Department of Obstetrics and Gynaecology, Faculty of Clinical Medicine,
Ebonyi State University, Abakaliki, P.M.B. 053, Abakaliki, Nigeria

Abstract: To determine the effect of hyperglycaemia on plasma copper and zinc in pregnancy complicated with diabetes mellitus, data for 40 diabetic and 40 non-diabetic pregnant women, matched for age, gestational age, Body Mass Index (BMI), parity and socioeconomic status from a cohort of 349 pregnant women recruited at gestational age of ≤ 25 weeks for the assessment of impacts of trace elements on pregnancy outcomes were analyzed. In addition to plasma copper and zinc which were determined by Atomic Absorption Spectrophotometer (Buck Scientific, Model AVG 210), plasma albumin, glucose, haemoglobin concentration and Total White Blood Cell Count (TWBC) were determined using standard laboratory methods. Although diabetic and non-diabetic pregnant women had comparable ($p > 0.05$) age, gestational age, BMI and plasma copper, the former had significantly ($p < 0.05$) lower plasma zinc (16.49 ± 4.74 vs. 25.31 ± 7.07 $\mu\text{mol/l}$) with significantly higher plasma glucose concentration (13.19 ± 1.81 vs. 6.23 ± 1.12 mmol/l). The diabetic subjects also had significantly ($p < 0.05$) higher plasma albumin and TWBC when compared to their control counterparts (3.41 ± 0.85 vs. 2.92 ± 0.79 g/dl and 5.72 ± 1.75 vs. $5.10 \pm 1.33 \times 10^9/\text{L}$ respectively), although these were within the reference ranges. Correlation analysis showed that plasma glucose was negatively correlated with plasma zinc concentration ($r = -0.239$; $p = 0.051$). It is therefore concluded that hyperglycaemia in pregnancy complicated with diabetes mellitus impacts negatively on plasma zinc status, but lacks effect on plasma copper. This has important health implications for diabetic pregnant women and their newborns.

Key words: Gestational diabetes mellitus, hyperglycaemia, hypozincuria, metallothionein, antioxidant enzymes, insulin resistance

INTRODUCTION

Both zinc and copper are essential trace elements with wide range of functions in the body including the synthesis of enzymes and nucleic acids (WHO, 1996) and are involved in the functions of several cuproenzymes that are essential for life (Goel and Misra, 1982; Raman and Leela, 1992). Studies have shown that lower consumption of dietary zinc and low serum zinc levels were associated with increased prevalence of Coronary Artery Disease (CAD), diabetes as well as other risk factors including hypertension, hypertriglyceridaemia and other factors suggestive of insulin resistance (Singh *et al.*, 1998). In one study (Simon and Taylor, 2001), zinc supplementation was found to attenuate hyperglycaemia and hyperinsulinaemia in *db/db* mice, suggesting a role for zinc in pancreatic function and peripheral tissue glucose uptake. In developing countries where diet is monotonous and deficient in trace elements, pregnant women are at increased risk of copper and zinc

deficiencies. This is aggravated by increased demand for these trace elements to meet both the maternal and foetal needs. Deficiencies of copper and zinc have been implicated in various reproductive events like infertility, pregnancy wastage, congenital abnormalities (Black, 2001), pregnancy induced hypertension, placental abruption, premature rupture of membranes, still birth and low birth weight (Pathak and Kapil, 2004). Studies of micronutrients (including vitamins and minerals) in diabetes have consistently documented conflicting reports (O'Connell, 2001; Bo *et al.*, 2008; Hussain *et al.*, 2009) and data is scarce on the study of copper and zinc metabolism in pregnancy complicated with diabetes mellitus. The aim of the present study is to determine the plasma levels of copper and zinc in pregnancy complicated with diabetes mellitus.

MATERIALS AND METHODS

This study which was part of a larger study that investigated the impact of plasma copper and zinc

status on pregnancy outcomes was carried out among pregnant women attending antenatal clinic of the Department of Obstetrics and Gynaecology of the Federal Medical Centre, Abakaliki, one of the referral tertiary health institutions in the South eastern part of Nigeria. Subjects' selection and detailed methodology has been previously described (Ugwuja *et al.*, 2010). Data for forty diabetic and forty non-diabetic pregnant women matched for age, gestational age, parity, anthropometrics and socioeconomic status were analysed. Plasma glucose was determined by glucose oxidase method as previously described (Barham and Trinder, 1972), plasma albumin was determined by bromocresol green as previously described (Hill, 1985), haemoglobin concentration was determined by Cyanmethaemoglobin method while total white blood cell count was estimated as in a standard haematology textbook (Dacie and Lewis, 1994).

Data analysis: Data were analysed for mean and standard deviation while comparison between subjects and controls were analysed using Student's t-test with statistical significance set at $p < 0.05$.

RESULTS

From Table 1, the diabetics and non-diabetics pregnant women had comparable ($p > 0.05$) age, gestational age, body mass index and plasma copper. However, the diabetic pregnant women had significantly ($p < 0.05$) lower plasma zinc (16.49 ± 4.74 vs. 25.31 ± 7.07 mmol/l) with significantly higher plasma glucose concentration (13.19 ± 1.81 vs. 6.23 ± 1.12 mmol/l). The diabetic subjects also had significantly ($p < 0.05$) higher plasma albumin and total white blood cell count when compared to their control counterparts (3.41 ± 0.85 vs. 2.92 ± 0.79 g/dl and 5.72 ± 1.75 vs. $5.10 \pm 1.33 \times 10^9/L$ respectively), although these were still within the reference ranges. Correlation analysis showed that plasma glucose was negatively correlated with plasma zinc concentration ($r = -0.239$; $p = 0.051$).

Table 1: Comparison of biochemical and haematological parameters between diabetic and non-diabetic pregnant women

Parameters	Non-diabetics (n = 40)	Diabetics (n = 40)	p-values
Age (yrs)	27.80±4.59	27.18±4.22	0.890
Gestational age (wks)	21.60±3.79	21.68±3.58	0.112
BMI (Kg/m ²)	28.13±4.14	27.09±3.63	0.233
HBC (g/dl)	10.32±1.28	10.31±1.50	0.861
TWBC (x ⁹ /L)	5.10±1.33	5.72±1.75	0.035*
Albumin (g/dl)	2.92±0.79	3.41±0.85	0.010*
Glucose (mmol/L)	6.23±1.12	13.19±1.81	0.021*
Copper (µmol/L)	9.42±8.33	9.19±9.17	0.809
Zinc (µmol/L)	25.31±7.07	16.49±4.74	0.054*

* $p < 0.05$ is considered statistically significant

DISCUSSION

This study has shown that while plasma zinc concentration was significantly lower in diabetic pregnant women in comparison to their non diabetic counterparts, the level of copper was comparable between the two groups. We have previously reported significantly higher prevalence of Diabetes Mellitus (D/M) in zinc-deficient than in zinc-adequate pregnant women (Ugwuja *et al.*, 2010). Again, decreased serum zinc had been reported in type I diabetes mellitus (Isbir *et al.*, 1994; Garg *et al.*, 1994). Hyperglycaemia from either type 1 or 2 DM has been found to cause physiologically important loss of zinc from the body via the urine by interference with active transport of zinc into the renal tubular cells (Chausmer, 1998). Although study has suggested that tissue and plasma zinc loss via urine may be ameliorated by a compensatory increase in gastrointestinal absorption of zinc (Chausmer, 1998), down regulation of zinc transport due to increased production of metallothioneine (MT), a cation binding protein with high affinity for zinc has been reported in diabetes mellitus (Escobar *et al.*, 1995). However, abnormality in zinc metabolism in diabetes cannot be solely attributed to hyperzincuria (Cunningham *et al.*, 1994) as zinc may be lost from cells as glucose is translocated into the muscle (Cordova, 1994). Although results from micronutrients studies in diabetes mellitus have been conflicting (O'Connell, 2001; Bo *et al.*, 2008; Hussain *et al.*, 2009) and data is scarce on the study of zinc metabolism during pregnancy complicated with diabetes mellitus, the present finding suggests that zinc plays an important role in the pathogenesis of diabetes mellitus in pregnant women. Studies have suggested roles for zinc in the aetiology and progression of diabetes mellitus (Sumovski *et al.*, 1992; Chausmer, 1998; Spreitsma and Schuitemaker, 1994; Faure *et al.*, 1995). For example, *in vitro* studies have found that zinc enhances the effectiveness of insulin in non-insulin dependent diabetes mellitus (Arquilla *et al.*, 1978). Again, the development of glucose intolerance in animals deprived of zinc together with the occurrence of zinc deficiency in type 2 diabetes mellitus suggests a role for zinc deficiency in the pathogenesis of gestational DM. Zinc is required for the assemblage of insulin into structurally stable and functional hexameric structure (Brange and Langkjoer, 1993). Also, video fluorescence analysis has shown that zinc concentrated in the islet cells was related to the synthesis, storage and secretion of insulin (Zalewski *et al.*, 1994). Additionally, zinc is a cofactor of antioxidant enzymes, Superoxide Dismutase (SOD) and catalase that are involved in the protection of pancreatic beta cells from reactive oxygen species (Chausmer, 1998). Hence in zinc deficiency, the synthesis, secretion and functions of insulin may be

affected. The significantly negative correlation between plasma glucose and zinc in the present study corroborates earlier studies (El-Yazigi *et al.*, 1993; Williams *et al.*, 1995). Decreased plasma zinc in diabetic subjects has implications for pregnant women with diabetes mellitus. Zinc is an essential trace element with diverse cellular functions, especially in rapidly dividing cells as that of the foetus (WHO, 1996). Therefore, it is speculated that pregnancy complications such as macrosomia, congenital foetal abnormalities spontaneous abortion and miscarriage associated with gestational diabetes mellitus may be mediated at least in part through zinc deficiency. Also, diabetic complications such as dehydration and susceptibility to infections may be exacerbated by zinc deficiency as evidenced by significantly ($p < 0.05$) higher plasma albumin (a measure of dehydration) and total white blood cell count (index for infection), although the two parameters were still within the reference ranges in the present study. We therefore concluded that hyperglycaemia of gestational diabetes mellitus is associated with reduced plasma zinc without effect on plasma copper. This has important health implications both for the diabetic pregnant mothers and their newborns.

REFERENCES

- Arquilla, E.R., S. Packer, W. Tarmas and S. Miyamoto, 1978. The effect of zinc on insulin metabolism. *Epidemiology*, 103: 1440-1449.
- Barham, D. and P. Trinder, 1972. An improved colour reagent for the determination of blood glucose by oxidase system. *Analyst*, 27: 142-145.
- Black, R.E., 2001. Micronutrients in pregnancy. *Br. J. Nutr.*, 85 (Suppl. 2): S193-7.
- Bo, S., M. Durazzo, R. Gambino, C. Berutti, N. Milanesio, A. Caropreso, L. Gentile, M. Cassader, P. Cavello-Perin and G. Pagano, 2008. Associations of dietary and serum copper with inflammation, oxidative stress and metabolic variables in adults. *J. Nutr.*, 138: 305-310.
- Brange, J. and L. Langkjoer, 1993. Insulin structure and stability. *Pharm Biotechnol.*, 5: 315-350.
- Chausmer, A.B., 1998. Zinc, insulin and diabetes. *J. Am. Coll. Nutr.*, 17: 109-115.
- Cordova, A., 1994. Zn content in selected tissues in streptozotocin diabetic rats after maximal exercise. *Biol. Trace Elem. Res.*, 42: 209-215.
- Cunningham, J., A. Fu, P. Mearkle and R. Brown, 1994. Hyperzincuria in individuals with insulin dependent diabetes mellitus: concurrent zinc status and the effect of high dose zinc supplementation. *Metabolism*, 43: 1558-1562.
- Dacie, J.V. and S.M. Lewis, 1994. *Practical Haematology*, 8th Edn., Churchill Livingstone, Edinburgh, pp: 49-59.
- El-Yazigi, A., N. Hannan and D. Raines, 1993. Effect of diabetic state and related disorders on the urinary excretion of magnesium and zinc in patients. *Diabetes Res.*, 22: 67-75.
- Escobar, O., M. Sandoval, A. Vargas and J. Hempe, 1995. Role of metallothionein and cysteine rich intestinal protein in the regulation of Zn absorption by diabetic rats. *Paed Res.*, 37: 321-327.
- Faure, P., H.P. Ben, A. Perard, S. Halimi and A. Rousset, 1995. Lipid peroxidation in insulin dependent diabetic patients with early retinal degenerative lesions: Effects of an oral Zn supplementation. *Eur. J. Clin. Nutr.*, 49: 282-288.
- Garg, V., R. Gupta and R. Goal, 1994. Hypozincaemia in diabetes mellitus. *J. A.P.I.*, 42: 720-721.
- Goel, R. and P.K. Misra, 1982. Study of plasma zinc in neonates and their mothers. In: *Paediatrics*, 19: 611-614.
- Hill, P.G., 1985. The measurement of albumin in serum and plasma. *Ann. Clin. Biochem.*, 22: 565-578.
- Hussain, F., M.A. Maan, M.A. Sheikh, H. Nawaz and A. Jamil, 2009. Trace elements status in type 2 diabetes. *Bangladesh J. Med. Sci.*, Vol. 8.
- Isbir, T., A. Tamer, A. Taylor and M. Isbir, 1994. Zinc, copper and magnesium status in insulin dependent diabetes. *Diabetes Res.*, 26: 41-45.
- O'Connell, B.S., 2001. Selected vitamins and minerals in the management of diabetes. *Diabetes Spectrum*, 14: 133-148.
- Pathak, P. and U. Kapil, 2004. Role of trace elements zinc, copper and magnesium during pregnancy and its outcome. In: *Paediatrics*, 71: 1003-1005.
- Raman, L. and J. Leela, 1992. Role of maternal nutrition. In: *PIH Annual report*, National Institute of Nutrition, 93: 47-50.
- Simon, S.F. and C.A. Taylor, 2001. Dietary zinc supplementation attenuates hyperglycaemia in *db/db* mice. *E.B.M.*, 226: 43-51.
- Singh, R.B., M.A. Niaz, S.S. Rastogi, S. Bajaj, Z. Gaoli and Z. Shoumin, 1998. Current zinc intake and risk of diabetes and coronary artery disease and factors associated with insulin resistance in rural and urban populations of North India. *J. Am. Coll. Nutr.*, 17: 564-570.
- Spreitsma, J. and G. Schuitemaker, 1994. Diabetes can be prevented by reducing insulin production. *Med. Hypotheses*, 42: 15-23.
- Sumovski, W., H. Baquerizo and A. Rabinovich, 1992. Oxygen free radical scavenger protect rat islet cells from damage by cytokines. *Diabetologia*, 32: 792-796.

- Ugwuja, E.I., E.I. Akubugwo, U.A. Ibiam and O. Obidoa, 2010. Impact of maternal copper and zinc status on pregnancy outcomes in a population of pregnant Nigerians. *Pak. J. Nutr.*, 9: 678-682.
- Williams, N.R., J. Rajput-Williams, J. West, S. Nigdikar, J. Foote and A. Howard, 1995. Plasma, granulocyte and mononuclear cell copper and zinc in patients with diabetes mellitus. *Analyst*, 120: 887-890.
- World Health Organisation, 1996. Zinc. In: Trace elements in human nutrition and health (World Health Organisation, ed.), WHO, Geneva, Switzerland, pp: 72-104.
- Zalewski, P., S. Millard, I. Forbes, O. Kapaniris, S. Slavotinek, W. Betts, A. Ward, S. Lincoln and I. Mahadevan, 1994. Video analysis of labile Zn in viable pancreatic islet cells using specific fluorescent probe for Zn. *J. Histochem. Cytochem.*, 42: 877-884.