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Role of Zinc and Copper in Infertility: An Update

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Abstract

Extensive research has been conducted on the role of zinc and copper in the human health and diseases with more emphasis on reproductive health. Deficiency of zinc in men results in reduced libido, low testosterone and sperm count and Cu/Zn ratio in body fluids plays a significant role in this aspect Almost all endocrine glands plays a significant roles in reproductive health with more emphasis on the role of LH, FSH, Prolactin, Testosterone, GH and erythrocyte enzymes of Cu/ Zn. Both Cu/Zn deficiencies have been observed in a host of infectious diseases and these metals are low in diabetes mellitus. This review article is the outcome of extensive literature search and compiling of key findings during the last 15 years. The contents of this paper covers from a simple disease to the advanced cancer depicting the role Zn/Cu in human health and diseases. The content of this review article will serve as an eye opener to undertake more research in this field.

Keywords: *Zn, Cu, Cu/Zn, LH, FSH, PRL, BMI, PCOS.*

1. Introduction

Zinc (Zn) deficiency is a key factor in making many parts of the reproductive system work properly. Zn is just one component, but it works with more than 300 different enzymes in the body to regulate many metabolic pathways. In women, zinc plays a vital role in many key reproductive health areas including egg production, maintaining proper follicular fluid levels and hormone regulation. Zn is an important trace metals that the body uses to keep hormone like estrogen, progesterone and testosterone levels stable throughout the entire menstrual cycle. It is especially important during stage 2 and 4 of a woman's cycle. one of the most important trace minerals to date for male fertility, increasing zinc levels in infertile men has been shown to boost sperm levels; improve the form, function and quality of male sperm and decrease male infertility. Deficiencies of zinc in men result in reduced libido, low testosterone levels, and low sperm courts. Zn administration did not have a definite effect on hemodialysis patients with sexual dysfunction, it can cause increase in the serum level of sex hormones which may improve the sexual function of the patients in some aspects.[(1)] Zn deficiency, although very rare, should be considered in patients with poor growth and hypogonadism associated with skin changes and anemia.[(2)]

Zn deficiency reduces circulating Luteinizing Hormone (LH) and testosterone concentrations, alters hepatic steroid metabolism, and modifies sex steroid hormone receptor levels, thereby contributing to the pathogenesis of male reproductive dysfunction.[(3)] Higher serum testosterone levels and Zn levels were associated with Excessive Erythrocytosis (EE), and low scores of signs/symptoms of Chronic mountain sickness were associated with higher Zn and nitric oxide levels.[(4)] Subjects with normal testosterone group had a significantly higher Zn level compared to low testosterone group. Significant negative correlations were evident between total testosterone and Cu level, and the Cu/Zn ratio. Decreased serum testosterone is significantly associated with a high level of Cu and elevated Cu/Zn ratio in hair tissue.[(5)] There was significant decrease in serum and seminal plasma Zn levels in oligospermic and azoospermia infertile males with significantly low androgen. It indicates that Zn has a possible role for spermatogenesis and steroidogenesis.

Therefore, Zn concentration in seminal plasma should be considered as one of the factors responsible for decreased testicular function in infertile male subjects.[(6)] Plasma LH may be more effective than testosterone on plasma leptin and Zn can be an important mediator of the effect LH exercises on leptin.[(7)] Low serum Zn levels are associated with lymphopenia, whereas low selenium and prolactin levels are not. The implications of these findings and the mechanisms by which they occur merit further study.[(8)]

Body mass index (BMI), smoking and Prolactin (PRL) are all inversely associated with arsenic, cadmium, copper, lead, manganese, molybdenum, and Zn, but positively associated with chromium. Several of these associations (Cadmium, lead, Molybdenum) are consistent with limited studies in humans or animals. Lead and copper were associated with non-monotonic decrease in Thyroid Stimulating Hormone (TSH), while arsenic was associated with a dose-dependent increase in TSH. For arsenic these findings were consistent with recent experimental studies where arsenic inhibited enzymes involved in thyroid hormone synthesis and signaling. More research is needed for a better understanding of the role of metals in neuroendocrine and thyroid function and related health implications.(9) No correlation among blood concentration of Zn and PRL, Parathyroid Hormone (PTH), LH, and Follicle Stimulating Hormone (FSH) were observed in the two modalities of dialysis or between zincemia and Zn ingestion. The occurrence of hyperprolactinemia and hypozincemia were not related to dialysis modality and that zincemia did not reflect the observed low dietary intake of Zn.(10)

Diabetes-induced testicular cell death that may eventually cause men's infertility is predominantly mediated by the oxidative stress and damage. To prevent or delay diabetes-caused infertility, diabetic patients should avoid Zn deficiency, and might consider antioxidant supplementation.(11) Immunohistochemistry studies showed a strong expression for Cu/Zn Superoxide dismutase (SOD) in spermatogonia but weak expression in advanced-stage germ cells. Zn deficiency reduced activity of the recombinant eel Cu/Zn SOD protein. Cu/Zn SOD siRNA decreased Cu/Zn SOD expression in spermatogonia and led to increased oxidative damage.(12) Impairment of spermatogenesis can be attributed to the direct action of Zn on testes or indirectly from Leydig cell degeneration indicating that Zn is a critical component for maintenance of both mitotic and meiotic stages of spermatogenesis.(13) Zn is an essential trace element for the maintenance of germ cells, the progression spermatogenesis, and the regulation of sperm motility.(14)

Although intratesticular Zn gluconate treatment in black bears resulted in testicular degenerative changes detected by ultrasound and histology examinations, sperm production was not completely ablated, and hence that normal fertility might have been compromised, but treatment unlikely resulted in sterility.(15) Copper concentration within normal physiologic range is essential in enzymatic activities, yet high level of copper is detrimental to sperm morphology. A positive correlation between Magnesium (Mg) and Calcium (Ca) that Mg serves as a physiological Ca antagonist.(16) Seminal Zn in fertile and infertile (smokers or nonsmokers) males correlated significantly with sperm count and normal morphology of sperm. There was a significantly positive correlation between seminal Zn with Ca and K levels in all specimens. Poor Zn nutrition may be an important risk factor for low quality of sperm and idiopathic male infertility.(17) Complexes of copper with gonadotropin-releasing hormone (GnRH) are even more effective in the release of LH than native GnRH. Moreover, Cu-GnRH is more potent in inducing in vivo release of FSH than LH. Copper complexes with GnRH interact with GnRH receptors (GnRHR) and modulate intracellular signaling in the gonadotropin cells of the anterior pituitary. Copper also plays a significant role in maintaining normal fetus development in mammals.(18) Subjects with normal testosterone group had a significantly higher Zn level compared to low testosterone group. Significant negative correlations were evident between total testosterone and Cu level, and the Cu/Zn ratio.(19) Serum copper and ceruloplasmin (Cp) are the most commonly used indicators to assess nutritional status of copper.(20)

Plasma LH levels may be more effective than testosterone on plasma leptin and zinc may be an important mediator of the effect LH has on leptin.(21) A significant rise in peripheral blood inhibin B and seminal plasma activity was detected in the zinc sulphate/folic acid group after 6 months. A clinical trial indicates a change in the hormonal status of varicocelectomised patients following long-term administration of zinc sulphate and folic acid.(22) Increased intracellular Reactive Oxygen Species (ROS) impaired luteal formation and progesterone production in the mutant females, thus suggesting that SOD1 plays a crucial role in both the luteal function and the maintenance of fertility in female mice.(23) Marginal Zn nutriture may compromise milk production despite increased prolactin levels. In addition, increased circulating prolactin concentration is not due to altered nursing behavior, but may be due to alterations in the prolactin regulatory pathway in the pituitary gland.(24) Both Zn(2+) and hPRLr binding influence hPRL conformers in an interdependent fashion. Although each of these three lactogenic hormones bind hPRLr and induce a biological response that is sensitive to the presence of increasing concentrations of Zn(2+), each hormone is unique in the mechanistic details of this process.(25) Low serum zinc levels are associated with lymphopenia, whereas low selenium and prolactin levels are not. The implications of these findings and the mechanisms by which they occur merit further study.(26)

The occurrence of hyperprolactinemia and hypozincemia were not related to dialysis modality and that zincemia did not reflect the observed low dietary intake of Zn2+.(27) ZnT2-mediated Zn accumulation in mitochondria was associated with increased mitochondrial oxidation. Our results suggest that PRL-R antagonism in PRL-R over-expressing breast cancer cells may reduce invasion through the redistribution of intracellular Zn pools critical for cellular function.(28) 4-week simultaneous and separately zinc and selenium supplementation had no significant effect on resting testosterone and lactate levels of subjects who consume a zinc and selenium sufficient diet. It might be possible that the effect of zinc supplementation on free testosterone depends on exercise.[29] Zn may therefore modify the anabolic action of phyto-oestrogens, promoting characteristics associated with early rather than late stages of osteoblast differentiation. Our data suggest that while Zn enhances the anti-osteoclastic effect of phyto-oestrogens, it may limit aspects of their anabolic action on bone matrix formation.[30]

Higher levels of Mg and Zn were found in blood plasma of women who used menopausal hormone therapy (MHT). The mean concentration of Cd in the blood of women in both groups was similar, and in women who use MHT the level of Pb in whole blood was lower, compared to the rest of the women.[31] Serum Mg and Zn concentrations in postmenopausal women, not using MHT, were low. The average serum Mg levels decreased considerably with the time since the final menstruation. No correlation between BMI and worsening of climacteric symptoms and serum Mg and Zn concentrations in postmenopausal women, not using MHT was found.[32] Urinalyses did not suggest need of additional supply of Ca, Mg or Zn at advanced ages. Correction for creatinine (CR) or Specific gravity (SG) may induce a bias in evaluation of age-dependent changes in mineral concentrations, because CR and SG decrease in accordance with age.[33] Serum Copper levels of both the pre- and the post-menopausal groups were significantly correlated with mean and diastolic B.P. while the serum Zn levels of the pre-menopausal group was significantly correlated solely with diastolic BP, implying that the metal plays a physiological role in some mechanism of blood pressure regulation. In the pre-menopausal non-smokers subgroup and the post-menopausal group, there was a weak, but statistically significant, correlation between systolic and mean BP, and blood lymphocytes levels. These data may be explained by a neuroendocrine influence, related partially to the morning hours.[34]

There was no correlation between Se, Cu, Zn, P and lipid parameters. Although BMI has a positive effect on Bone Mineral Density (BMD), trace elements and lipids, except Zn and TG, did not directly and correlatively influence BMD. Further studies are needed to clarify the role and relationship of trace elements and lipid parameters in postmenopausal osteoporosis.[35] Hormonal replacement therapy provides beneficial effects on trace mineral status related to menopause.[36] Reduction in zinc and copper levels was observed in the bone tissues and serum of the ovariectomy group. Zinc administration restored these levels to normal. Electron microscopic studies revealed a looser structure and resorbed areas in ovariectomized rat cortical bone. Zinc administration restored bone tissue morphology. These findings suggest that changes in cortical bone attributed to estrogen deficiency are arrested by zinc supplementation, which can be a sustainable approach to improving bone health.[37] Zinc levels are lower in the erythrocyte compartment of pre-menopausal women with breast cancer.[38] Urine Zn level could be considerable an appropriate marker for bone absorption, usage of Zn supplements in postmenopausal women may result a beneficial reduction in osteoporotic risk.[39]

No significant correlation was found between urinary zinc and BMD in postmenopausal osteopenic women indicating that hyperzincuria is associated with loss of bone mineral density, as is seen in osteoporotic women. Estimation of urinary zinc appears to be valuable marker for the assessment of increased bone resorption as seen in postmenopausal osteoporotic women.[40] No correlation between BMI and worsening of climacteric symptoms and serum Mg and Zn concentrations in postmenopausal women, not using MHT was found.[41] Mean serum zinc levels tended to be lower in patients with polycystic ovarian syndrome with impaired glucose tolerance than patients with normal glucose tolerance, but the difference was not statistically significant. In conclusion, zinc deficiency may play a role in the pathogenesis of polycystic ovarian syndrome and may be related with its long-term metabolic complications.[42] Imbalanced element status may be a key foundation for insulin resistance in Poly Cystic Ovarian Syndrome (PCOS). The findings in this study should be investigated with further trials in order to obtain new insights into PCOS.[43] The serum levels of trace elements and heavy metals might change in patients with PCOS. The findings in this study should be investigated with further trials in order to obtain new insights into PCOS.[44] Zinc supplementation may be considered as an inexpensive adjunct to treatments in patients with polycystic ovary syndrome in the hope of reducing cardiovascular disease risk factors, particularly inflammation.[45]

Cu levels were correlated with a change in carotid intima-media thickness and brachial artery flow mediated dilation in PCOS patients were related to Cu levels as well as several cardiovascular risk factors. Thus, increased Cu levels may be responsible for the increased risk of early vascular disease in women with PCOS.[46] The timing of breast and of pubic hair development is moderately correlated and remain so when it is stratified by characteristics associated with puberty.[47]

The places of residence sex and age were variables that significantly affected copper and zinc concentrations. Men's had more copper and zinc in their hair than women's, whereas hair zinc and copper levels were significantly correlated with the place of the residence and age. The methods were free from interferences, reliable and reproducible. For all metals present in real samples, precision was better than 0.4% (RSD).[48] High-dose oral $Zn2+$ is a potent down regulator of eumelanin content in murine hair shafts in vivo. The C57BL/6 mouse model offers an excellent tool for further dissecting the as yet unclear underlying molecular basis of this phenomenon, while electron paramagnetic resonance technology is well suited for the rapid, qualitative and quantitative monitoring of hair pigmentation changes.[49]

Only an insignificant rise of the copper content in the hair was found in all three groups of patients. The content of zinc in the hair did not differ significantly in any of the groups in comparison with the control group.[50]

For copper, the variations in concentration with age were similar to zinc. Regarding the age variations for manganese, hGHD had lower concentrations in hair compared to the normal subjects throughout adolescence (11-18 yrs.). We have studied the effects between the hair and these trace element concentrations in hGHD before and after hGH administration. These results suggest that hGH affects the metabolism of these trace elements.[51] Preeclampsia (PE) patients have considerably lower level of serum zinc, copper, manganese, and iron compared to the healthy pregnant women.[52] The serum zinc and calcium were 43% and 10% lower in the PE women, respectively, whereas the magnesium concentration showed nonsignificant differences between the two groups. Measurement of these elements may be useful for the early diagnosis of a preeclamptic condition.[53] The serum levels of ceruloplasmin appear to be invariable during pregnancy. Moreover, we noted a disturbance of these parameters in preeclampsia (hypozincemia, hypocupremia and a significant increase of ceruloplasmin). Zinc and copper are essential for the development and fetal growth. Their involvement in several maternal-fetal complications is not currently in any doubt.[54]

PE might be associated with hyperhomocysteinemia and elevated blood levels of zinc and copper. Furthermore, elevated blood levels of zinc were significantly associated with hyperhomocysteinemia in preeclampsia. More studies are warranted to investigate further any relationship between altered homocysteine metabolism and levels of zinc and copper in PE.[55] Severe PE is associated with abnormal concentrations of Zn, Cu and Se. Therefore, trace elements may have a crucial role in the pathogenesis of severe PE.[56] In placental zinc also plays a role in the biosynthesis of connective tissue, maintaining its integrity, which might have an impact on the structure of the spiral arteries.[57]Low levels of maternal copper and zinc are related to preeclampsia and might have a causal role in this disease. Further investigation is needed to establish the role of these elements in this dangerous condition of pregnancy.[58] Wasting and lethality in acrodermatitis enteropathica patients reflects the loss-of-function of the intestine zinc transporter ZIP4, which leads to abnormal Paneth cell gene expression, disruption of the intestinal stem cell niche, and diminished function of the intestinal mucosa. These changes, in turn, cause a switch from anabolic to catabolic metabolism and altered homeostasis of several essential metals, which, if untreated by excess dietary zinc, leads to dramatic weight loss and death.[59]

A more acute 3-d treatment with a zinc-deficient diet did not block ovulation but did increase the number of oocytes trapped in luteinizing follicles. Moreover, 23% of ovulated oocytes did not reach metaphase II due to severe spindle defects. Thus, acute zinc deficiency causes profound defects during the periovulatory period with consequences for oocyte maturation, cumulus expansion, and ovulation.[60] Most women with POI are deficient in vit D. Zinc, copper, and vitamin D seems to correlate with hormonal status in the participants. The present study may generate hypotheses for future studies that will investigate the possible mechanisms behind alterations in trace elements and vit D deficiency in women with POI and whether these changes could be used for screening the risk of developing POI.[61] Increased intracellular ROS impaired luteal formation and progesterone production in the mutant females, thus suggesting that SOD1 plays a crucial role in both the luteal function and the maintenance of fertility in female mice.[62]

Zinc therapy improves sexual competence of male rats; the effect is dose dependent. Increase in the T levels is beneficial in this regard. However, increase in PRL is responsible for the reduced libido index. Further studies on pigs and monkeys are needed for evaluating the therapeutic use of zinc in sexual dysfunction.[63] There was a significantly positive correlation between seminal Zn with Ca and K levels in all specimens. In conclusion, poor Zn nutrition may be an important risk factor for low quality of sperm and idiopathic male infertility.[64] Assessing the relationship between seminal plasma zinc and semen quality using two markers; zinc concentration (Zn-C) and total zinc per ejaculate (Zn-T).Count, motility, viability, pH and viscosity are affected by variations of seminal plasma zinc. Seminal plasma Zn-T is the better marker for assessing the relationship between zinc and semen quality.[65]

A significant positive correlation was observed between zinc levels and sperm count and zinc and alpha-glucosidase activity in seminal plasma. These results suggest that zinc and neutral alpha-glucosidase seems to play an important role in human reproduction.[66] When serum zinc concentration was low, the risk of asthenozoospermia was higher. The ratio of Cu/Zn was higher in the progressive motility abnormal group than in the normal group.[67] Correlation analysis showed significant positive correlation between copper and lead . High correlation between small head and knob twisted tail , small head and broken flagellum as well as between small head and total number of pathological spermatozoa was determined.[68]

Conclusion

This review article has brought out may important role of zinc and copper in a variety of human disorders particularly in reproductive health of both sexes. The role played by zinc is predominates that of copper. The contents of this paper depicts each and every possible are of the functional roles of these metals. This articles covers the research works undertaken during the last 15 years and have been complied using more than 60 research papers. Each and every important findings brought out in this article may serve as a source for further experimental work on laboratory diagnosis related to these two trace metals for the benefits of humanity.

Conflict of Interest : None

Reference

[1]. Jalali GR, Roozbeh J, Mohammadzadeh A, Sharifian M, Sagheb MM, HamidianJahromi A, Shabani S, Ghaffarpasand F, Afshariani R. (2010), Impact of oral zinc therapy on the level of sex hormones in male patients on hemodialysis. Ren Fail. May ;32(4):417-9.

[2]. ZuleyhaKaraca, FatihTanriverdi, SelimKurtoglu, SerifeTokalioglu, Kur sadUnluhizarci, FahrettinKelestimur.(2007), Pubertal arrest due to Zn deficiency The effect of zinc supplementation.Erciy ; Hormones, 6(1):71-74

[3]. Ae-son Omoeng-Who Chung (2013), Zinc Deficiency Alters 5a-Reduction and AEsrtormogaetinzatRioencepotforTsesitnosRteartonLeivear1nd Androgen and jn.nutrition.org by guest on November 21, 2013.

[4]. Gonzales GF, Tapia V, Gasco M, Rubio J, Gonzales-Castañeda C (2011), High serum zinc and serum testosterone levels were associated with excessive erythrocytosis in men at high altitudes.Endocrine. 40(3):472-80.

[5]. Chang CS, Choi JB, Kim HJ, Park SB (2011), Correlation between serum testosterone level and concentrations of copper and zinc in hair tissue.Biol Trace Elem Res. 144(1-3):264-71.

[6]. Ali H, Baig M, Rana MF, Ali M, Qasim R, Khem AK. (2005) Relationship of serum and seminal plasma zinc levels and serum testosterone in oligospermic and azoospermic infertile men.J Coll Physicians Surg Pak. 15(11):671-3.

[7]. Ozturk A, Baltaci AK, Mogulkoc R, Oztekin E, Kul A (2005), The effects of zinc deficiency and testosterone supplementation on leptin levels in castrated rats and their relation with LH, FSH and testosterone.NeuroEndocrinolLett.26(5):548-54.

[8]. Heidemann SM, Holubkov R, Meert KL, Dean JM, Berger J, Bell M, Anand KJ, Zimmerman J, Newth CJ, Harrison R, Willson DF, Nicholson C, CarcilloJ (2013), Baseline serum concentrations of zinc, selenium, and prolactin in critically ill children. PediatrCrit Care Med. 14(4):e202-6

[9]. Meeker JD, Rossano MG, Protas B, Diamond MP, Puscheck E, Daly D, Paneth N, Wirth JJ (2009). Multiple metals predict prolactin and thyrotropin (TSH) levels in men.Environ Res. 109(7):869-73.

[10]. Castro AV, Caramori J, Barretti P, Baptistelli EE, Brandão A, Barim EM, Padovani CR, Aragon FF, Brandão-Neto J (2002). Prolactin and zinc in dialysis patients.Biol Trace Elem Res. 88(1):1-7.

[11]. Zhao Y, Zhao H, Zhai X, Dai J, Jiang X, Wang G, Li W, Cai L (2013). Effects of Zn deficiency, antioxidants, and low-dose radiation on diabetic oxidative damage and cell death in the testis.ToxicolMech Methods. 23(1):42-7.

[12]. Celino FT, Yamaguchi S, Miura C, Ohta T, Tozawa Y, Iwai T, Miura T (2011). Tolerance of spermatogonia to oxidative stress is due to high levels of Zn and Cu/Zn superoxide dismutase. PLoS One. 6(2):e16938.

[13]. Kumari D, Nair N, Bedwal RS (2011). Effect of dietary zinc deficiency on testes of Wistar rats: Morphometric and cell quantification studies.J Trace Elem Med Biol. 25(1):47-53.

[14]. Yamaguchi S, Miura C, Kikuchi K, Celino FT, Agusa T, Tanabe S, Miura T(2009). Zinc is an essential trace element for spermatogenesis.ProcNatlAcadSci U S A. 106(26):10859-64.

[15]. Leonardo F.C. Brito, Patricia L. Sertich, William Rives, Marc Knobbe, Fabio Del Piero,Gordon B. Stull (2011). Effects of intratesticular zinc gluconate treatment on testicular dimensions, echodensity, histology, sperm production, and testosterone secretion in American black bears (Ursusamericanus). Theriogenology. 75 (8) :1444-1452.

[16]. Wong, W.Y., Flik, G., Groenena, P.M., Swinkels, D.W., Thomas, C.M., Copius-Peereboom, J.H.J., Merkus, H.M.W.M. and Steegers-Theunissen, R.P.M. (2001) The impact of calcium, magnesium, zinc, and copper in blood and seminal plasma on semen parameters in men. Reproduc-tive Toxicology, 15, 131-136.

[17]. Abasalt Hosseinzadeh Colagar, Eisa Tahmasbpour Marzony, Mohammad Javad Chaichi (2009). Zinc levels in seminal plasma are associated with sperm quality in fertile and infertile men Nutrition Research. 29(2): Pages 82–88

[18]. Michaluk A, Kochman K(2007). Involvement of copper in female reproduction. Reprod Biol. 7(3):193-205.

[19]. Chang CS, Choi JB, Kim HJ, Park SB (2011). Correlation between serum testosterone level and concentrations of copper and zinc in hair tissue. Biol Trace Elem Res. 144(1-3):264-71.

[20]. Arredondo M, Núñez H, López G, Pizarro F, Ayala M, Araya M (2010). Influence of estrogens on copper indicators: in vivo and in vitro studies. Trace Elem Res. 134(3):252-64.

[21]. Baltaci AK, Mogulkoc R, Ozturk A (2006).Testosterone and zinc supplementation in castrated rats: Effects on plasma leptin levels and relation with LH, FSH and testosterone. ife Sci. 78(7):746-52.

[22]. Nematollahi-Mahani SN, Azizollahi GH, Baneshi MR, Safari Z, Azizollahi S (2014). Effect of folic acid and zinc sulphate on endocrine parameters and seminal antioxidant level after varicocelectomy. Andrologia. 46(3):240-5.

[23]. Yoshihiro Noda, Kuniaki Ota, Takuji Shirasawa and Takahiko Shimizu (2012). Copper/Zinc Superoxide Dismutase Insufficiency Impairs Progesterone Secretion and Fertility in Female Mice[1] Biology of Reproduction. 86(1) 1-8.

[24]. Chowanadisai W, Kelleher SL, Lönnerdal B (2004). Maternal zinc deficiency raises plasma prolactin levels in lactating rats. J Nutr. 134(6):1314-9.

[25]. Voorhees JL, Rao GV, Gordon TJ, Brooks CL (2011). Zinc binding to human lactogenic hormones and the human prolactin receptor. EBS Lett. 23;585(12):1783-8.

[26]. Heidemann SM, Holubkov R, Meert KL, Dean JM, Berger J, Bell M, Anand KJ, Zimmerman J, Newth CJ, Harrison R, Willson DF, Nicholson C, Carcillo J (2013) . Baseline serum concentrations of zinc, selenium, and prolactin in critically ill children. Pediatr Crit Care Med. 14(4):e202-6.

[27]. Castro AV, Caramori J, Barretti P, Baptistelli EE, Brandão A, Barim EM, Padovani CR, Aragon FF, Brandão-Neto J (2002). Prolactin and zinc in dialysis patients. Biol Trace Elem Res. 88(1):1-7.

[28]. Bostanci Z, Alam S, Soybel DI, Kelleher SL (2014). Prolactin receptor attenuation induces zinc pool redistribution through ZnT2 and decreases invasion in MDA-MB-453 breast cancer cells. xp Cell Res. 321(2):190-200.

[29]. Shafiei Neek L, Gaeini AA, Choobineh S (2011). Effect of zinc and selenium supplementation on serum testosterone and plasma lactate in cyclist after an exhaustive exercise bout. Biol Trace Elem Res. 144(1-3):454-62.

[30]. Karieb S, Fox SW (2012).Zinc modifies the effect of phyto-oestrogens on osteoblast and osteoclast differentiation in vitro. Br J Nutr. 108(10):1736-45.

[31]. Jurczak A, Brodowski J, Grochans E, Karakiewicz B, Szkup-Jabłońska M, Wieder-Huszla S, Mroczek B, Włoszczak-Szubzda A, Grzywacz A (2013).Effect of menopausal hormone therapy on the levels of magnesium, zinc, lead and cadmium in post-menopausal women. Ann Agric Environ Med. 20(1):147-51.

[32]. Grochans E, Karakiewicz B, Kozielec T, Brodowska A, Brodowski J, Starczewski A, Laszczyńska M, Noceń I, Grzywacz A, Samochowiec A, Chlubek D.Serum Mg and Zn levels in postmenopausal women. Magnes Res. 2011 Dec;24(4):209-14

[33]. Ikeda M[1], Ezaki T, Moriguchi J (2007). Levels of calcium, magnesium and zinc in urine among adult women in relation to age with special reference to menopause. Nutr Health Aging. 11(5):394-401.

[34]. Di Gioacchino M, Forcucci R, Tiboni GM, Kouri S, Di Gioacchino F, Boscolo P (2000).The influence of menopause and habitual smoking upon serum zinc, serum copper and the cardiovascular and immune parameters of women. Int J Immunopathol Pharmacol. 13(2):91-97.

[35]. Arikan DC, Coskun A, Ozer A, Kilinc M, Atalay F, Arikan T (2011). Plasma selenium, zinc, copper and lipid levels in postmenopausal

Turkish women and their relation with osteoporosis. Biol Trace Elem Res. 2011 Dec;144(1-3):407-17.
[36]. Bureau I[1], Anderson RA, Arnaud J, Raysiguier Y, Favier AE, Roussel AM. Trace mineral status in post menopausal women: impact of hormonal replacement therapy. J Trace Elem Med Biol. 2002;16(1):9-13.
[37]. Bhardwaj P, Rai DV, Garg ML (2013). Zinc as a nutritional approach to bone loss prevention in an ovariectomized rat model. Menopause. 20(11):1184-93.
[38]. Tinoco-Veras CM, Bezerra Sousa MS, da Silva BB, Franciscato Cozzolino SM, Viana Pires L, Coelho Pimentel JA, do Nascimento-Nogueira N, do Nascimento-Marreiro D (2011).Analysis of plasma and erythrocyte zinc levels in premenopausal women with breast cancer. Nutr Hosp. 26(2):293-7
[39]. Rezvan Razmandeh, Ensieh Nasli-Esfahani, Reza Heydarpour, Farnoush Faridbod,Mohammad Reza Ganjali, Parviz Norouzi, Bagher Larijani and Davood Khoda-amorzideh (2014). Association of Zinc, Copper and Magnesium with bone mineral density in Iranian postmenopausal women – a case control study.Journal of Diabetes & Metabolic Disorders. 13:43.
[40]. Rafat Murad, Murad Qadir, Mukhtiar Baig (2012).Association of urinary zinc with bone mineral density in postmenopausal women. RMJ. 37(4): 429-432.
[41]. Serum Mg and Zn levels in postmenopausal women. Magnesium Research : Official Organ of the International Society for the Development of Research on Magnesium 2011, 24(4):209-214.
[42]. Guler , Himmetoglu O, Turp A, Erdem A, Erdem M, Onan MA, Taskiran C, Taslipinar MY, Guner H. Zinc and homocysteine levels in polycystic ovarian syndrome patients with insulin resistance (2014). Biol Trace Elem Res.158(3):297-304. doi: 10.1007/s12011-014-9941-7. Epub 2014 Mar 26.
[43]. Chakraborty P, Ghosh S, Goswami SK, Kabir SN, Chakravarty B, Jana K. Altered trace mineral milieu might play an aetiological role in the pathogenesis of polycystic ovary syndrome (2013). Biol Trace Elem Res. 152(1):9-15.
[44]. Kurdoglu Z, Kurdoglu M, Demir H, Sahin HG (2012).Serum trace elements and heavy metals in polycystic ovary syndrome. Hum Exp Toxicol. 31(5):452-6.
[45]. F Pourteymour Fard Tabrizi , B Alipoor , AR Ostadrahimi , and M Mehrzad Sadagiani (2010). Effect of Zinc Supplementation on Inflammatory Markers in Women with Polycystic Ovary Syndrome. Shiraz E-Medical Journal. 12(1): 30-38.
[46]. Celik C, Bastu E, Abali R, Alpsoy S, Guzel EC, Aydemir B, Yeh J (2013).The relationship between copper, homocysteine and early vascular disease in lean women with polycystic ovary syndrome. Gynecol Endocrinol. 29(5):488-91
[47]. Christensen KY, Maisonet M, Rubin C, Flanders WD, Drews-Botsch C, Dominguez C, McGeehin MA, Marcus M (2010). Characterization of the correlation between ages at entry into breast and pubic hair development. Ann Epidemiol. 20(5):405-8.
[48]. Srogi K (2005).Zinc and copper contents in the hair as the test of environmental pollution of Gliwice. Rocz Panstw Zakl Hig. 2005;56(2):189-98.
[49]. Plonka PM, Handjiski B, Michalczyk D, Popik M, Paus R (2006). Oral zinc sulphate causes murine hair hypopigmentation and is a potent inhibitor of eumelanogenesis in vivo. Br J Dermatol. 155(1):39-49.
[50]. Dastych M, Procházková D, Pokorný A, Zdrazil L (2010). Copper and zinc in the serum, urine, and hair of patients with Wilson's disease treated with penicillamine and zinc. Biol Trace Elem Res. 133(3):265-9.
[51]. Miki F, Sakai T, Wariishi M, Kaji M (2002). Measurement of zinc, copper, manganese, and iron concentrations in hair of pituitary dwarfism patients using flameless atomic absorption spectrophotometry. Biol Trace Elem Res. 85(2):127-36.
[52]. Sarwar MS, Ahmed S, Ullah MS, Kabir H, Rahman GK, Hasnat A, Islam MS (2013). Comparative study of serum zinc, copper, manganese, and iron in preeclamptic pregnant women. Biol Trace Elem Res. 154(1):14-20.
[53]. Kumru S, Aydin S, Simsek M, Sahin K, Yaman M, Ay G (2003). Comparison of serum copper, zinc, calcium, and magnesium levels in preeclamptic and healthy pregnant women. Biol Trace Elem Res. 94(2):105-12.
[54]. Monia MM, Fethi BA, Wafa LB, Hédi R (2012). Status of zinc and copper in pregnant women and their changes during preeclampsia. Ann Biol Clin (Paris). 70(4):423-9.
[55]. Harma M, Harma M, Kocyigit A (2005). Correlation between maternal plasma homocysteine and zinc levels in preeclamptic women. Biol Trace Elem Res. 104(2):97-105.
[56]. Katz O, Paz-Tal O, Lazer T, Aricha-Tamir B, Mazor M, Wiznitzer A, Sheiner E. Severe pre-eclampsia is associated with abnormal trace elements concentrations in maternal and fetal blood (2012). J Matern Fetal Neonatal Med. 25(7):1127-30.
[57]. Açikgoz S, Harma M, Harma M, Mungan G, Can M, Demirtas S (2006).Comparison of angiotensin-converting enzyme, malonaldehyde, zinc, and copper levels in preeclampsia. Biol Trace Elem Res. 113(1):1-8.
[58]. Deepa V. Kanagal, Aparna Rajesh, Kavyarashmi Rao, Harish Shetty, Prasanna Kumar Shetty, Harshinidevi Ullal (2014).Zinc and copper levels in preeclampsia: a study from coastal South India.Int J Reprod Contracept Obstet Gynecol. 3(2): 370-373.
[59]. Geiser J, Venken KJ, De Lisle RC, Andrews GK (2012).A mouse model of acrodermatitis enteropathica: loss of intestine zinc transporter ZIP4 (Slc39a4) disrupts the stem cell niche and intestine integrity. PLoS Genet. 8(6):e1002766.
[60]. X. Tian and F. J. Diaz (2012).Zinc Depletion Causes Multiple Defects in Ovarian Function during the Periovulatory Period in Mice. Endocrinology. 153(2): 873–886.
[61]. Kebapcilar AG, Kulaksizoglu M, Kebapcilar L, Gonen MS, Unlü A, Topcu A, Demirci F, Taner CE (2013). Is there a link between premature ovarian failure and serum concentrations of vitamin D, zinc, and copper? Menopause. 20(1):94-9.
[62]. Noda Y, Ota K, Shirasawa T, Shimizu T (2012). Copper/zinc superoxide dismutase insufficiency impairs progesterone secretion and fertility in female mice. Biol Reprod. 19;86(1):1-8.
[63]. Dissanayake D, Wijesinghe PS, Ratnasooriya WD, Wimalasena S (2009). Effects of zinc supplementation on sexual behavior of male rats. J Hum Reprod Sci.2(2):57-61.
[64]. Colagar AH, Marzony ET, Chaichi MJ (2009).Zinc levels in seminal plasma are associated with sperm quality in fertile and infertile men. Nutr Res. 29(2):82-8
[65]. Dissanayake D, Wijesinghe P, Ratnasooriya W, Wimalasena S (2010).Relationship between seminal plasma zinc and semen quality in a subfertile population. J Hum Reprod Sci. 3(3):124-8.
[66]. Mankad M, Sathawara NG, Doshi H, Saiyed HN, Kumar S (2006). Seminal plasma zinc concentration and alpha-glucosidase activity with respect to semen quality. Biol Trace Elem Res. 110(2):97-106.
[67]. Yuyan L, Junqing W, Wei Y, Weijin Z, Ersheng G (2008). Are serum zinc and copper levels related to semen quality? fertil Steril. 89(4):1008-11.
[68]. Massányi P, Trandzík J, Nad P, Koréneková B, Skalická M, Toman R, Lukác N, Strapák P, Halo M, Turcan J (2003).Concentration of copper, iron, zinc, cadmium, lead, and nickel in boar semen and relation to the spermatozoa quality. J Environ Sci Health A Tox Hazard Subst Environ Eng. 38(11):2643-51.