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REVIEW ARTICLE **OPEN ACCESS**

Trace element copper in male and female reproduction : A review

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ABSTRACT

Copper is an essential microelement for animals and humans. Evidences indicate its significance being associated with numerous enzymes involved in various pathways. Copper availability in the body depends on soil type, its concentration in food and environment. Absorption occurs through diet and transporters, metallo-chaperones as well as exporters maintain homeostasis. Consequences of copper dyshomeostasis - deficiency and toxicity may lead to abnormalities / dysfunctioning of reproductive organs at some specific stage. Experimental evidence relates copper deficiency to cause oxidative stress altering the functional state of copper dependent enzymes as well as glutathione and enhancing apoptotic genes. Copper deficiency adversely affects GnRH, testosterone level, causes defects in sperms, necrozoospermia, asthenozoospermia and sperm DNA fragmentation. Copper deficiency in females caused inhibition of ovarian function as well as ovum transport through fallopian tube, decreased progesterone level, reduced conception rate, structural and biochemical fetal defects. Impaired spermatogenesis, abnormal spermatozoa, decreased sperm count, motility and viability prostate enlargement, erectile dysfunction, prostate cancer, dysfunction of estrogen receptors, negative effect on ovaries and fetus malformation were evident after copper toxicity. Experimental evidences indicate that both copper deficiency as well as toxicity has detrimental effects on the reproduction.

***Key words**: Trace element copper, absorption and transport mechanism, male and female reproduction.*

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INTRODUCTION

From prokaryotes, eukaryotes as well as plants copper, an essential microelement, is present in three oxidation states Cu (0), Cu (I) and Cu (II) . In human beings, copper exists mainly as Cu^{+}/ Cu^{+2} being involved in redox reactions. Bioinformatics analysis revealed that 1% of total eukaryotic proteome is made up of copper binding proteins [1]. Copper is vital for the optimal activity of more than 30 proteins /cuproenzymes [2] and is involved in iron homeostasis, mitochondrial electron transport chain, hormonal perception, collagen maturation and oxidative stress[3;4]. Copper also has critical role in non-enzymatic functions in angiogenesis, nerve myelination and activity of endorphin, brain development [5]. Authors[6;7] have reported the essentiality of copper in reproduction, regulation of gene expression, signal transduction, growth, pregnancy and development as well as in testosterone biosynthesis[8;9].

ABSORPTION, EXCRETION AND TRANSPORT

Dietary copper absorbed through the stomach as well as small intestine through tight junctions is eliminated by hepatocytes with equivalence between absorption from intestine and excretion into bile. 98% is lost through bile [10] and 2% through urine [11]while Barceloux [12] accounted loss in minute quantities through skin, hair, sweat, salivary and gastric. Copper has redox states and free copper can be toxic to the cell and hence it is bound to proteins /peptides to prevent damage to the cell. Cellular homeostasis is maintained by complex system of import, intracellular distribution and export. Copper transporters – CTR1 (SLC31A1) located in small intestine, liver, kidneys, testes, ovaries and heart is involved in intracellular transport [13] and CTR2 – located in lysosomes and endosomes probably involved in releasing copper from degraded copper dependent enzymes to subsequently release in cytosol to attain intracellular copper homeostasis [13] (ii) metallochaperones –ATOX1 that binds with free copper, and deliver it into the cell for storage or to cuproenzymes and (ii) Cu-exporters - ATP7A and ATP7B a retromer copper [14;15]. Besides these to ensure that copper even in minute amount is utilized effectively by the cells COX 17 (mitochondria1 cytochrome oxidase) transports to mitochondria , ATOX1

transports to CCS (superoxide dismutase), NML45 to nucleus, HAHI which transports both to ATP7A as well as ATP7B [3]. Copper homeostasis appears to be regulated by different mechanisms: (a) activation / repression of transcription (b) posttranslational mechanism, modulation of protein trafficking and (c) changes in protein stabilization [16;17;18].

The absorption of copper in small intestine is due to the expression of Ctr1 that needs high concentration of copper and low pH [19]. Targeted deletion of the Ctr1 gene leads to a genotype of $Ctr1^{-/-}$mice that died at mid-gestation implicating its importance in embryonic development [20]. CTR1 only transports Cu (I) ions so Cu (II) is first reduced into Cu (I) by cupric reductases for absorption [21] which then gets associated with methionine and histidine rich N-terminal of CTR1 and transported to enterocytes[22]. STEAP family (reductases) reduces Cu (II) into Cu (I). STEAP3 and STEAP4 are present in intra- cellular vesicles[23]. Mammalian homologue of Ctr1 is MURR1 [24]. In humans, the human copper transporter 1 (hCTR1) protein participates in copper influx [25]. hCtr1 and hCtr2 have HCH motif essential for the proper functioning of these transporters and contains cysteines and histidines at C-terminal [26].DMT1 helps in the transportation of numerous metal ions like Cu (II), Fe (II), Zn (II) and Mn (II) [25] although it functions as major transporter of iron required for iron absorption in intestine as well as erythropoiesis [27].Absorbed copper binds with albumin, histidine, peptides and transcuperin [28] forming coordinate bond with N - in histidine-imidazole, α-amino groups of amino acids present peptide bonds to form complex. $Cu\text{-}His_2$ complex crosses the placental barrier and help in the embryonic development [29]. During development copper and Atp7a has an important role in notochord formation [30]. 95% of circulating copper (~ 6/7 molecules of copper) binds with ceruloplasmin [31] which is : (a) responsible for the oxidation of ferrous ion (Fe^{+2}) to ferric ion (Fe^{+3}) that is loaded on transferring [31;32] and (b) also has antioxidant properties synthesized by hepatocytes and activated macrophages which decreased after copper deficiency although its synthesis in liver enhanced [33]. ATP7A and ATP7B are closely related P-type ATPases/ ATP-dependent copper export pumps being involved in the transport of copper into both secretory as well as newly formed cuproenzymes [34] in trans Golgi network [35]. Formation of functional form of tyrosinase, peptidyl-α-monooxygenase, lysyl oxidase, etc., requires ATP7A while in biosynthesis of holo-ceruloplasmin - copper-dependent ferroxidase ATP7B is involved [36] exhibiting association of intestinal copper and iron [37]. ATP7A is present in all organs except liver and ATP7B is present in the intestine, liver, kidney, mammary gland, placenta, heart, brain, lung, muscle and pancreas [12]. Point mutation of ATP7A leads to Menkes disease causing abnormal accumulation/sequestration in intestine and kidney [38]. MURR1, COMMD1 and ATP7B (associated with hepatic copper homeostasis) help to transport copper and also excrete excess amount of copper in bile [39], hence either point mutation / gene inactivation disrupts copper homeostasis that can lead to copper toxicity / Wilson's disease [40]. Three chaperone proteins have been identified: (a) COX17 (cytochrome c oxidase Cu chaperone) transporting copper to mitochondrial intermembrane space with concomitant support of other proteins- SCO1 and SCO2 [16] (b) CCS which delivers copper to cytoplasmic enzyme superoxide dismutase (zinc superoxide dismutase SOD 1) [41] and is known to stabilize the enzyme by oxidizing the intra-subunit disulfide bond in SOD_1 [42] and (c) Atox 1 HAH1 responsible for transferring Cu to ATP7A (Cu-transporting ATPase1) and ATP7B (Cu-transporting ATPase 2). CCS knockdown induces Cu (II) accumulation in cells [43]. Metallothionein induction alters Cu (II) accumulation, decreases Ctr1 expression with consequent increase in Atp7a expression to order to maintain Cu (II) homeostasis [43]. Alteration in copper export in $Atox1^{-/-}$cells results in an increase in intracellular copper level as compared to $Atox1^{+/+}$cells [44]. Experimental evidence revealed the expression of CTR1 in spermatogonial cells and primary spermatocytes with the ability to transport copper to germinal cells as well as basal and adluminal compartment of Sertoli cells [45;46] which was further confirmed using mice with conditional knock out of Slc^{31a1} gene ($CTR1^{\Delta GC}$) in germinal cells [46].

REPRODUCTION

Copper deficiency

Males: Regulation of copper in testes is achieved by complex network of importers, chaperones, recipient proteins, and exporters as they are localized in germinal cells and Sertoli cells [47]. Copper has the ability to react with superoxide anion and hydrogen peroxide which leads to the formation of hydroxyl radical [48;49] which has the potential to cause oxidative damage. Al-Bayati et al., [50] reported enhanced mitochondrial damage probably due to low copper level as well as activity of superoxide dismutase (SOD). SOD1 mutant mice shows higher level of superoxide radicals hence increase in DNA damage and apoptosis of spermatozoa was reported [51]. Duan et al., [52] reported decreased activity with enhanced malondialdehyde, the condition reversed with copper intake. Glutathione (GSH), – an antioxidant binds

majority of cytoplasmic copper in eukaryotic cells, has an specific role in the mechanism of trafficking copper into the human cells [53] which at low level causes spermatozoa mid piece instability and reduced motility[54]. Experimental evidence revealed the expression of CTR1 in spermatogonial cells and primary spermatocytes with the ability to transport copper to germinal cells as well as basal and adluminal compartment of Sertoli cells [45;46] which was further confirmed using mice with conditional knock out of Slc31a1 gene(CTR1ΔGC) in germinal cells[46].Studies using $CTR1^{\Delta GC}$ (conditional knockout in Slc31a1 in germinal cells) showed reduced testicular size, increase in spermatogenic abnormalities-residual germ cells specifically primary spermatocyte stage- preleptotene and leptotene and absence of germ cells - pachytene spermatocytes as well as round spermatids [46]. Ogórek *et al.,* [55] studied the expression in epididymal epithelium and spermatozoa of copper exporters /importers and observed copper transfer to SOD1 through chaperones, the cooperative action not only was responsible for attaining the proper copper balance but simultaneously in preventing copper toxicity .

Apoptosis and oxidative stress are associated with DNA damage in the germ line. Increase in nuclear enzymes related with DNA repair in rats consuming low Cu diets was reported [56]. Copper deficiency also causes sperm DNA damage induced by oxidative stress leading to necrozoospermia, asthenospermia and sperm DNA fragmentation [57]. Oxidative stress induced sperm DNA damage are: (a) DNA single and double strand breaks (b) an abasic site generation (iii) base oxidation/ modification (iv) inter- and intra-strand crosslinking of DNA strands and (v) cross-linking of DNA-protein [58]. Infertile men contain high level of 8-hydroxy-2'-deoxyguanosine in ejaculates due to oxidative stress [59]. Major causes for the generation of defective sperms are :(i) neutrophil invasion or contamination (ii) decrease in seminal antioxidants and (iii) overproduction of ROS [60]. These factors appear to affect the fertilizing capacity and genetic integrity, which would account for sub-fertility / infertility in copper deficient animals. Experiments on male copper deficient rat, mouse, goat and ram revealed a decline in spermatozoa concentration as well as motility with altered morphology and less developed seminiferous tubules which was correlated to functional inactivation of Sertoli cells[61]. Tsunoda *et al.,* [62] observed that copper deficient mice with poor semen quality caused decreased *in vivo* oocyte fertilization. Approximately 80% of ceruloplasmin which has six copper atoms in its structure is located in the Sertoli cells [63] so decline would affect Sertoli cell function while remaining is bound to metallothionein.The structure of metallothionein as well as glutathione may be altered due to lack of copper with subsequent loss of in its functionality [64]. Reactive oxygen species(ROS) mainly superoxide anion and hydrogen peroxide not only produce DNA damage but also damage mitochondrial and nuclear genomes of human spermatozoa[65;66].Sperm parameters – count, motility and morphology are susceptible to free radicals and reduces fertility – causative factor for male infertility[59]. Sperms attain their motility in epididymis hence sperm protection is essential to preserve sperm DNA. Cu-Zn SOD expressed at very high levels along the length of epididymis[67]. The abnormal level of copper, may affect spermatogenesis, sperm maturation and motility. Semen contains ceruloplasmin that is involved in normal seminiferous tubular growth and development [61]. High level of ROS in semen induces apoptosis and decreases sperm count in infertile men. Infertile patients have high levels of Cyt. c, caspase 9 and caspase 3 in their ejaculates [68].Copper homeostasis in testes is also due to the presence of copper transporter ATP7A localized in Sertoli cells near the basolateral region of seminiferous tubules Study on mosaic mutation (Atp7amo-ms) mouse revealed mainly atrophic and vacuolation in gonads although few mouse exhibited sclerotic seminiferous tubules although live spermatozoa and motile sperms were observed but the number compared to controls were less along with effect on plasma membrane of spermatozoa[69;70].

Females: Michaluk & Kochman [71] reported the role of copper for normal development of mammalian fetus being principally stored in liver and brain [72]. Poor body condition score, ovarian inactivity, low progesterone level-luteal phase, enhanced lipid peroxidation, altered antioxidant enzymes in hypocuperimic animals [73],inhibition of ovum transport through fallopian tube, infertility in humans [74], abnormality in connective tissue in copper deficient animals[75] has been observed. Risk of congenital defects of heart i.e. Kawasaki disease enhances in pregnant women deficient in copper with structural and biochemical abnormalities in fetus [71].Alavi- Shoushtari *et al.,* [76] reported high uterine copper concentration (269.40± 9.40 µg/dl) during cyclic period as against pre pubertal period (133.40±5.70 µg/dl), high value in serum during diestrous phase (89±2.10 µg/dl) while concentration was high in uterine period during proestrous (395.40±6.50 µg/dl) in buffalos. Roychoudhary *et al.,* [77] reported loss of functional ovaries , decline in serum progesterone level during luteal phase (estrous cycle) in buffalo due to copper deficiency. Relation of copper with different phases of estrous cycle and hormone has been reported [78]. Studies conducted on Sod1-deficient female mice revealed impairment of luteal formation and of progesterone due to increased intracellular ROS and apoptotic cells[79]. Mudgal et al. [80] associated the occurrence of retained placenta and decreased conception rates and anoestrus due to copper deficiency. Ahmed *et al.,* [73] examined buffalo –cows and reported that 19.12 %

of the examined animals exhibited hypocuprosis and during luteal phase (estrous cycle) 21.84 % of these hypocupremic animals had inactive ovaries and low serum progesterone level. Patterson *et al.,* [81] from copper deficient studies observed early embryonic death along with embryo resorption, enhanced placentas retention as well as necrosis of the placenta.

Copper deficiency induced endocrinopathy

In vitro studies using pituitary cells of immature female rat showed stimulatory effect on basal and GnRH-stimulated LH release due to copper ions [82]. Gonadotrophic releasing hormone (GnRH) injected into the rats with normal levels of copper enhanced the liberation of LH and FSH from the hypophysis as compared to copper deficient animals [83]. Studies suggested that complexes of copper (Cu^2+) with gonadotropin-releasing hormone (GnRH) increases the release of LH than native GnRH. Cu-GnRH complexes are more effective inducers for the release of FSH than LH (Hazum 1983). Authors [83;84] revealed that Cu-GnRH is more effective than native GnRH for LH secretion *in vivo*. Copper also plays an essential role in amidation of GnRH [85]. Activation of GnRH in turn increases the LH and estrogen levels. Cu-GnRH complexes interact with GnRH receptors (GnRHR) which in turn affects intracellular signaling in the gonadotrope cells of the adenohypophysis[71]. Another cupro-enzyme dopamine-β-monooxygenase catalyzes the conversion of dopamine to noradrenaline, an essential neurotransmitter involved in GnRH release signaling [85]. Therefore, copper deficiency leads to endocrinopathy that directly affects apoptosis of cells during gametogenesis as well as reproduction.

Copper toxicity

Males : In mammals, copper ions at high dose effects fertility due to its effect on the testes, especially late stage of sperm maturation, epididymis as well as scrotum [86]. Máchal et al., [87] observed that high copper concentration not only effects testicular and ovarian structure but also functional aspect of spermatozoa. Study conducted by Canadian Centre for Occupational Health and Safety [88] revealed a significant decrease in sperm cell count/ml along with significant increase in the percentage of morphological abnormal spermatozoa indicative of detrimental effect of copper. Khushboo *et al.,* [89] exposed three-month-old male Wistar rats to CuSO4 200 mg/kg for 30 days (chronic exposure) and observed decreased testicular weight, decrease in tubules size, germ cells, Leydig cells and Sertoli cells, over expression of HSP70, enhanced lipid peroxidation, sloughed cells in the lumen, vacuolization, cellular debris, degeneration and depletion of germ cell with deleterious effect on spermatogonia and Sertoli cells, increase of head and tail morphologic abnormalities and DNA fragmentation index, formation of immature sperm, decreased sperm count, viability and motility. Copper administered for 56 days impaired testes with significant decrease in diameters of seminiferous tubules, Sertoli cell nuclei, epithelial height, meiotic index as well as the percentage of spermatogenesis [90]. *In vivo* copper administration by gavage in rats resulted in increased testicular apoptosis and structural abnormalities - atrophic and sclerotic tubules along with decreased spermatogonial and Sertoli cells [91] Adverse effect on sperm motility at high concentration of copper was also reported [92;93]. Wong et al., [94] correlated high concentration of copper in seminal plasma with reduced sperm motility due to in lipid peroxidation in sperm plasma membrane. Sakhaee *et al.,* [95] administered copper (100 mg/kg/day ; 200mg/kg/day) for a period of eight weeks to Wistar rats which resulted in significant decrease in sperm concentration, motility, and viability.Concommitant with these observation Romaniuk *et al.,* [96] reported enhanced occurrence of morphologically abnormal sperms. Study of 232 subfertile/ infertile men (oligozospermic, asthenozospermic and azospermic) revealed that the seminal plasma copper concentrations in oligozospermic, asthenozospermic and azospermic groups are significantly higher than normozospermic group and there was negative correlations between seminal plasma copper concentration and sperm coun,, sperm motility, sperm vitality and normal morphology reflecting the detrimental effect of excess copper [97]. Badiye et al., [98] reported copper toxicity also causes prostate enlargement and infections, erectile dysfunction and to some extent prostate cancer. Using variable concentrations of $CuSO_4$/ml (3.57 to 4.85 µg) morphological abnormalities in rabbit spermatozoa after Giemsa stain revealed small head, acrosomal changes and knob-twisted flagellum. Further analysis carried out using annexin revealed positive reaction in acrosome and mid piece of spermatozoa which indicates alteration in these regions. [99].

Females : Murawski *et al.,* [100] studied reproduction in ewes and observed that disturbances in wavy pattern of follicles, altered number of corpora lutea along with disorders in fecundity, prolificacy and pregnancy occurred. Dysfunction of estrogen receptors due to excess of copper concentration might be one of the cause for reproductive disorders and pathological changes during pregnancy [101].Increased copper levels can be correlated to premature births and low birth weight [102]. Mouse intracellular organelles in ovarian cells showed degenerative changes even at 100mg/kg dose of copper for 35 days. [103].The average numbers of antral follicles decreased after 100 mg /kg copper sulfate on day 14 with some ultrastructural cell damages - decrease of zona pellucida thickness, appearance of vacuolated areas,

dilation of nuclear envelop dilation were seen on day 14. With administration of 200 mg/kg copper sulfate / long duration for 35 days the detrimental effects enhanced with occurrence of more vacuolated areas, secondary lysosomes, irregular cell shape and segmented nuclei with condensed and marginated chromatin as well as enlarged and damaged mitochondria [103]. Studies on mice revealed decreased litter size fetal mortality with only 2–9% of the surviving fetuses showing skeletal and soft tissue malformations after 3000 and 4000 mg/kg copper sulfate per kg of diet for 1 month [104]. Case studies have shown that spontaneous miscarriage and subfertility occurs in untreated Wilsons disease and has to be monitored regularly even after treatment as some may be asymptomatic [105;106].

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