REVIEW

The role of zinc in the endocrine system

Abdulkerim Kasim Baltaci[1], Rasim Mogulkoc[1] and Saltuk Bugra Baltaci[1]
Selcuk University, Medical School, Department of Physiology, Konya, Turkey

Abstract: Zinc is essential in the regulation of a variety of physiological and biochemical events in the organism. It plays a critical role in maintaining the cell membrane integrity, protein-carbohydrate-lipid metabolism, immune system, wound injury and in the regulation of a number of other biological processes associated with normal growth and development. Physiological and biochemical levels of many hormones are affected by zinc metabolism. Therefore, growth impairment, hypogonadism, and some endocrine diseases are associated with the deficiency of zinc. These effects of zinc are considered versatile. Zinc increases the synthesis of the growth hormone and its number of receptors; thus, it is an important mediator in the binding of this hormone to its receptor. Found in a large quantity in the pancreas tissue, zinc has a part in the regulation of the effect of insulin. Zinc is involved to much more thyroid hormone metabolism such as hormone synthesis, receptor activity, conversion of T4 to T3, and production of carrier proteins. The low levels of zinc and high levels of leptin in obese individuals point to a critical relationship between zinc and leptin. Zinc is related to enzyme activity to melatonin synthesis. Melatonin has regulatory activity for zinc absorption from gastrointestinal system. Zinc particularly affects the conversion of testosterone to dihydrotestosterone, as 5α-reductase that is involved in this conversion is a zinc-dependent enzyme. In consideration of these relations, zinc is accepted to play critical roles in the endocrine system. The aim of the current review is to draw attention to the effects of zinc on the endocrine system.

Keywords: Zinc, endocrine system, hormones

INTRODUCTION

Although zinc, among other metals, is the 23rd most abundant element in the earth's crust, it enjoys the privilege of being the most commonly used element in biology (Vallee and Auld 1989). Zinc was first described in 1509 and zinc deficiency was first shown in mice in 1934 (Bannister 1988; Prasad 1969). Its biological function was revealed in 1940 when carbonic anhydrase was established to be dependent on zinc for its catalytic activity (Bannister 1988; Prasad 1969). Dietary zinc deficiency in humans was first reported by Dr. Prasad in 1963 (Prasad *et al.,* 1963). When it was suggested that zinc deficiency could be responsible for the growth retardation and hypogonadism in the adolescent boys in Egypt, these cases were supplemented with zinc (12-24 months). After the supplementation, secondary sexual characteristics developed in all cases and both hypogonadism and growth retardation were stamped out. This clinical condition arising from zinc deficiency was included into the body of literature as Prasad's Syndrome (Prasad *et al.,* 1963). In early 1970s, the hereditary disease called acrodermatitis enteropathica was documented to be associated with the impaired intestinal absorption of zinc and studies about this trace element started to grow in number (Barnes and Moynahan 1973).

Zinc and growth
Zinc has a positive influence on growth and development.

*Corresponding author: e-mail: rasimmogulkoc@yahoo.com

One of the main reasons for this positive effect is the involvement of zinc in the bone metabolism. The concentration of zinc in the bones is higher in comparison to other tissues. Zinc increases the production of certain proteins in osteoblast that suppress the osteoclasts production. And also zinc is vehicle D vitamin's affects in bone tissue (Salgueiro ve ark. 2002). Alkaline phosphates is a enzyme that zinc dependent and increases to calcium storage. Zinc is induce to alkaline phosphatase (Brandao-Neto ve ark. 2006). The role of zinc on carbonhydrate, lipid and protein metabolism is critical for increasing bone mass and conservation of the mass (Brandao-Neto *et al.,* 2006). Zinc is related to synthesis and secretion of growth hormone. Insuline like growth (IGF-I) factor is mediated to affect of growth hormone and it a factor that zinc dependent. (Brandao-Neto *et al.,* 2006; MacDonald 2000). Although the amount of protein in the diet is important, it has been suggested that zinc supplementation is much more important to IGF-I synthesis in zinc deficient animals (Brandao-Neto *et al.,* 2006; MacDonald 2000). It was noted that when the animals with zinc deficiency were administered growth hormone, IGF-1 concentration did not change (Oner *et al.,* 1984; Dicks *et al.,* 1993), while zinc potentiated the action of IGF-1 in cultured bone cells (Matsui and Yamaguchi 1995) and increased IGF-1 synthesis (Yamaguchi and Hashizume 1994). In case of zinc deficiency, membrane signal transmission and secondary messengers coordinating the cell proliferation are negatively influenced. It was even argued that zinc could act like IGF-1 and affect growth

(Sandstead *et al.,* 1998). Zinc is necessary for the hormonal functions of hypophysis (Henkin 1976). Zinc deficiency reduces the secretion of the growth hormone from the hypophysis (Roat *et al.,* 1979) and its circulating concentration (Roth and Kirchgessner 1997). Likewise, zinc deficiency results in the development of receptor resistance for both the growth hormone and IGF-1 and the resistance is broken down upon dietary supplementation of zinc (Ripa and Ripa 1996). Thus, zinc plays a crucial part at the receptor level as well (Ripa and Ripa 1996). There is a binding site for zinc in the growth hormone, which requires zinc for optimal functioning (Cunningham *et al.,* 1991). Zinc deficiency has been resulted in decreases the combination of growth hormone receptor, IGF-I synthesis and growth factor binding protein-3 (IGFBP-3) in rat (McNall *et al.,* 1995). However, zinc supplementation has corrected mentioned disturbances (Imamoglu *et al.,* 2005).

Zinc and thyroid

Among the endocrine functions associated with zinc are the alterations in thyroid hormone metabolism and energy consumption (Ganapathy and Volpe 1999). A number of hypotheses have been proposed to explain how zinc impacts thyroid hormone metabolism.

Zinc can directly affect the thyroid hormone synthesis. Gupta and co-worker (1997) has reported that zinc deficient diet caused to disturbance of thyroid hormone synthesis and on thyroid gland structure such as atrophy and degenerative alteration. Zinc is a important antioxidant and zinc deficiency cause to oxidative stress and this condition is lead to dysfunction of thyroid gland eventough mechanism is not clear (Ganapathy and Volpe 1999).

Zinc is considered necessary for the receptor activity of thyroid hormones (T_3 in particular). It was claimed that T_3 hormone receptor needed zinc to preserve its biologically active condition (Freake *et al.,* 2001).

Zinc can affect T_4 hormone levels by increasing the production of thyroxin-binding protein (Hartoma *et al.*, 1979).

Type I-5' deiodinase is a dependent-zinc enzyme and is required to conversion of T4 hormone to T3 (Wada and King 1986). The activity of type I-5'deiodinase enzyme and consequently conversion of T_4 to T_3 is curbed in zinc deficiency (Wada and King 1986).

Both the hypothalamus and hypophysis are susceptible to zinc deficiency (Pakary *et al.,* 1991). Consequently, it was suggested that zinc could be necessary for the enzymes involved in TRH and TSH synthesis (Pakary *et al.,* 1991). However, this result is contentious. It was reported by Brandao-Neto *et al.,* (2006) that zinc did not alter TRH and/or TSH synthesis in healthy males.

It can be said that the relationship between zinc and thyroid hormones is not unidirectional, as impaired thyroid functions affect body zinc levels (Maxwel and Volpe 2007). That zinc concentrations were found lower in hypothyroidism and higher in hypothyroidism, both of which are thyroid gland diseases (Imamoglu *et al.,* 2005), substantiates the fact that the relation between zinc and thyroid hormones is not a one-way relation.

Pawan *et al.,* (2007) reported that both intestinal and renal zinc uptake was significantly elevated in hyperthyroid rats and therefore rats with hyperthyroidism had higher zinc levels than their controls. It is accepted that the chief reason of this condition is that Zip 10, a zinc-transporting protein, is positively correlated with thyroid hormones in the intestines and kidneys (Pawan *et al.,* 2007).

However, it was revealed in a study of 34 hyperthyroid patients that serum zinc content decreased considerably in hyperthyroidism (Buchinger *et al.,* 1988). It was reported that the reduced serum zinc levels had two main reasons: lower zinc absorption and increased urinary zinc excretion (Kandhro *et al.*, 2009).

Low serum zinc levels in thyroid cancer patients were shown to be restored to normal after the operation (Al-Sayer *et al.,* 2004). It was stated that elevated serum zinc levels after the operation in thyroid cancer patients was an indicator of the success of the surgery and long-term monitoring of zinc levels in patients with thyroid cancer could be important (Al-Sayer *et al.,* 2004).

Zinc and insulin

Zinc fulfills one of the major biochemical functions in the organism through its effects on the carbohydrate metabolism. Insulin is stored in the β cells of pancreas in the form of crystals containing zinc (Scott 1934; Qadir *et al.,* 2015). Zinc is not only involved in the structure of insulin, but also has critical effects on its activity (Jansen *et al.,* 2009).

That the glycemic control of diabetic individuals and animals was maintained through zinc supplementation attests to the insulin-like properties of zinc (Adachi *et al.,* 2004; Yoshikawa *et al.,* 2001). Insulin-like effects of zinc ions were first identified in isolated rat fat cells in 1982 (May and Contoreggi 1982). Basis of this affect which zinc is lead to glucose entry to cells (May and Contoreggi 1982). Enhancer affect of zinc at the entry of glucose into cell is a enzyme is present that called as insulin-responsive aminopeptidase (IRAP). This molecule has been expressed in muscle and adipose tissue (Keller *et al.,* 1995). This zinc-dependent molecule (IRAP) is required for the maintenance of the glucose transporter 4 (GLUT 4) levels IRAP is important to regulation of GLUT 4 levels that a glucose transporter protein (Keller *et al.,* 1995). Ezaki (1989) has show that zinc provides

settlement to GLUT 4 to cell membrane, consequently accelerate to glucose entry to cell. The other molecule glycogen syntesis kinase (GSK-3β) is affectted by zinc and this molecule is affect insuline mechanism. The level and the activity of this molecule is elevated particularly in type II diabetes patients. Elevated levels of GSK-3β in type II diabetes patients disrupt the glycogen level and cause insulin resistance (Ilouz *et al*., 2002). Zinc inhibits glycogen synthase kinase 3β and reduces blood glucose by increasing glucose intake of the cell (Ilouz *et al*., 2002). Consequently, zinc affects the insulin pathway in several ways (Attia *et al.,* 2015):

1. By stimulating the phosphorylation of insulin receptor beta subunit
2. By causing the inhibition of GSK-3β, zinc produces insulin-like effects. This makes zinc a treatment option in diabetes mellitus or insulin resistance. Oral or intraperitoneal administration of zinc as a GSK-3β inhibitor in animal models rapidly lowered the blood glucose level and restored both insulin responses and insulin sensitivity (Henriksen *et al.,* 2003; Plotkin *et al.,* 2003).

A high number of studies investigating the zinc metabolism in diabetic humans and animals reveal that urinary zinc excretion is higher in diabetic humans and animals in comparison to the controls (Awadallah *et al.,* 1978; Canfield *et al.,* 1984). Although the cause of the increase in urinary zinc excretion in diabetic humans and animals has not been conclusively explained, some reports point to a correlation between urine volume and increased urinary zinc (Awadallah *et al.,* 1978; Canfield *et al.,* 1984). Increased blood glucose concentration, higher glycose and protein excretion through the urine, and elevated urinary zinc are further factors (McNair *et al.,* 1981; Quilliot *et al.,* 2001). One of the reasons for the increase in the urinary excretion of zinc in diabetes is caused by high blood glucose osmotic diuresis. These results are also supported by the observation of reduced urinary zinc loss when blood glucose is reduced with insulin therapy (Lau and Failla 1984; McNair *et al.,* 1981). Besides urinary zinc excretion, another possible mechanism to explain zinc loss in diabetes is increased intestinal zinc secretion. Calcium, magnesium, phytate, phosphates and other chelating agents prevent intestinal zinc absorption and then lead to increased intestinal zinc secretion (Jansen *et al.,* 2009). Increased urinary zinc loss commonly found in diabetic patients suggests that if the zinc they lose through the urine is not compensated, these patients develop zinc deficiency.

Type II diabetes is usually associated with lower plasma or serum zinc, whereas plasma or serum zinc in type I diabetes is commonly higher, especially at the outset (Aguilar *et al.,* 2007; Pedrosa *et al.,* 1999). At the onset of type I diabetes, when the beta cells are destroyed, zinc levels are found higher, but after hyperzincuria offsets zinc secretion from the beta cells, zinc levels drop. This hypothesis is supported by the duration of type I diabetes and the negative correlation between plasma and serum zinc (Jansen *et al.,* 2009; Pedrosa *et al.,* 1999).

Zinc and thymuline
A great many of the diseases that develop in humans bring about changes in the zinc metabolism (Salguerio *et al.,* 1999; Salguerio *et al.,* 2000). Zinc has a critical role in regulation of cellular immune function (Tipu *et al.,* 2012). Thereafter, zinc deficiency has increases trend to infections in human and animals (Prasad 2009; Salguerio *et al.,* 2000). One of the important roles of zinc is induce DNA, RNA and protein synthesis for required immunologic reactions. This effect of zinc is provided by zinc include enzymes such as DNA-RNA polymerase and thymidine kinase (Salguerio *et al.,* 1999; Salguerio *et al.,* 2000). Therefore, the effects of zinc are sure to be seen in immunological reactions (Prasad 2009; Salguerio *et al.,* 2000). Currently, it is a widely accepted view that the deficiency of no other element can cause as much damage as zinc deficiency, which is the most common cause of immunodeficiency (El- Fekih *et al.,* 2011; Prasad 2009; Salguerio *et al.,* 2000). Therefore, zinc deficiency in diet lead to inhibition of T-cell activity, thus cell immunity and its products sitokin secretion is affected by adversely (Kahmann *et al.,* 2006). Zinc is an essential element for the thymus endocrine activity. Thymuline is known to be important in cellular immune function and this molecule is zinc-dependent hormone (Hadden 1988). When it is not bound to zinc, thymuline is not only inactive, but also exercises inhibiting effects on active thymuline (Hadden 1988; Mocchegiani *et al.,*1995). Zinc-thymuline complex is formed by TEC (Thymic Epithelial Cells) (Hadden 1988). TEC uptakes zinc from the circulation (Hadden 1988). Thymuline is provides to zinc transport to T-lymphocyte (Hadden 1988; Mocchegiani *et al.,*1995). The secretion of zinc-thymuline complex by TEC is stimulated by zinc and Interleukin-1 (IL-1) (Hadden 1988; Mocchegiani *et al.,*1995). Together with working by coordination IL-1 and zinc-thymuline complex increases sitokin production of T-lymphocyte and support receptor activity. (Hadden 1988; Mocchegiani *et al.,*1999). As a consequent, immune function of thymus is controlled by sensitive neuroendocrine mechanism (Hadden 1988). Apart from the Th1 cells and the cytokines they secrete, zinc also affects the activation of Natural Killer (NK) cells (Bao *et al.,* 2003; Hadden 1988).

Zinc and neuropeptide-y (NPY)
Zinc plays a key role in the regulation of nutrition. It has been shown that zinc supplementation prevents reduce food intake and body weight is seen zinc deficiency (Jing *et al*., 2008). The significant effects of zinc on appetite include changes in the sense of taste (Jing *et al*., 2008).

The mechanism that enjoys widest recognition is the one by which the taste changes result from altered neurotransmitter concentrations at the general or local hypothalamic level due to changed zinc status (Birmingham and Gritzner 2006). In anorexia caused by due to zinc deficiency has been shown that significant reductions in body weight in rats. However, zinc supplementation to these animals has prevented anorexia and weigth loss (Birmingham and Gritzner 2006, Jing *et al.,* 2008). Similar findings have been reported in patients with anorexia nervousa (Safai-Kutti 1990). Therefore, zinc deficiency was reported to contribute to AN symptoms (Safai-Kutti 1990). In order to restore the normal body weight in the process of recovery from AN, the diet must certainly contain an adequate amount of zinc. It was already shown that the hypothalamic zinc levels dropped in AN, and zinc supplementation increased the body weight (Safai-Kutti 1990).

In anorexia associated with zinc deficiency, there is a significant relation between zinc, and NPY and galanin regulation (Selvais *et al.,* 1997). Selvais *et al.* (1997) demonstrated that NPY mRNA was elevated in the hypothalamus of rats fed on a zinc-deficient diet, but no similar increase was established in NPY levels. Likewise, Lee *et al.,* (1998) found a 100% increase in NPY mRNA, but a 50% increase in NPY levels in zinc deficiency. Actually, there is not any study reporting a decrease in NPY levels in zinc deficiency (Lee *et al.,* 1998; Selvais *et al.,* 1997). Therefore, zinc may be responsible for NPT resistance in anorexia nervousa (Lee *et al.,* 1998; Selvais *et al.,* 1997). It is suggested that this resistance may be caused by factors such as disruption of the conversion process of pro-NNPY to active NPY, reduced NPY secretion from the neurons, and a decrease in NPY signal formation (Lee *et al.,* 1998; Selvais *et al.,* 1997). The concentration of galanin, an appetite-stimulating peptide like NPY, falls significantly in zinc deficiency (Lee *et al.,* 1998; Selvais *et al.,* 1997). Galanin mRNA in the hypothalamus was reported to be low in zinc deficiency, while Kennedy *et al.,* (1998) showed that the galanin concentration in the paraventricular nucleus (PVN) of the rats without zinc deficiency was 120 times higher than that in the zinc-deficient rats. Galanin mitigates the effect of NPY during anorexia (Kennedy *et al.,* 1998). The failure of the body to increase food intake despite elevated NPY levels in zinc deficiency may be attributed to the suppression of galanin concentration.

Zinc and leptin
Recent studies about the relation between zinc and leptin indicate that zinc may have a critical effect on leptin secretion (Baltaci *et al.,* 2005; Chen *et al.,* 2000). Chen and co-worker (2000) have reported high leptin and lower zinc levels in obese mice. Zinc supplementation to these animals has increased leptin levels and treatment to obesity. In the light of mentioned findings they postulated

that zinc deficiency may lead to leptin resistance (Chen *et al.,* 2000). Zinc may either directly affect the leptin gene expression or indirectly cause leptin production by increasing the glucose utilization of the fat tissue. It was reported that zinc deficiency in mice which had hyperglycemia induced by streptozotocin (STZ) inhibited leptin secretion, whereas supplementation of zinc at a physiological dose might cause an increase in both leptin levels and glucose intake (Chen *et al.,* 2001). Zinc deficiency also inhibited the secretion of interleukin-6 (IL-6) from adipose tissue in the same rats (Chen *et al.,* 2001). This result is of particular interest as the structure of leptin and leptin receptors is similar to that of IL-6 (Chen *et al.,* 2001). Consequently, it was demonstrated in the concerned study that metabolic defects that developed in hyperglycemic mice induced by STZ could be corrected by zinc supplementation at a physiological dose (Chen *et al.,* 2001). Perhaps the most remarkable study about the relationship between zinc and leptin is the study by Ott and Shay (2001). The researchers explored how zinc deficiency influenced leptin gene expression and leptin secretion in adipose tissue. They found a reduced amount of Ob mRNA in the fatty tissue, as well as significantly lower leptin secretion from the adipose tissue in rats fed on a zinc-deficient diet (Ott and Shay 2001). Interestingly, they observed an important decrease in the leptin secretion from each gram of fatty tissue of zinc-deficient rats, in comparison to their controls (Ott and Shay 2001). In relation to the significantly inhibited insulin levels in zinc-deficient rats, the authors concluded that reduced insulin levels and the weaker insulin response might be responsible for the decrease in Ob gene expression (Ott and Shay 2001). The major question that needs to be answered is whether the decrease in leptin gene expression is caused by a decrease in transcription, as zinc is involved in the structure and function of RNA polymerase (Mohommad *et al.,* 2012). Zinc deficiency principally alters the composition of the cell's mRNA synthesis (Mohommad *et al.,* 2012). Proteins are found in smaller amounts, or are not found at all, in zinc-deficient systems, relative to zinc-sufficient ones (Mohommad *et al.,* 2012).

The relationship between zinc and leptin was investigated in 9 healthy individuals in whom zinc-deficiency was induced (Chen *et al.,* 2001; Mohommad *et al.,* 2012). It was established that zinc deficiency critically inhibited leptin secretion from the adipose tissue and IL-2 and TNF-α levels displayed a significant fall parallel to the inhibited leptin levels (Mantzoros *et al.,* 1998). The individuals in the study were seen to have a significant increase in leptin secretion, as well as remarkable elevations in IL-2 and TNF-α concentrations after zinc supplementation (Mantzoros *et al.,* 1998). It was concluded in the study that there was a positive correlation between zinc and leptin and that elevated IL-2 and TNF-α levels might be mediating this effect of zinc

on leptin (Mantzoros *et al.,* 1998). This claim suggesting that zinc is a regulator of leptin concentration in humans was supported by various results, including those obtained by Chen *et al*. (2000).

In a study which examined the effects of zinc and testosterone supplementation on plasma leptin levels of castrated rats, zinc supplementation was found to increase plasma leptin and LH levels of castrated rats, relative to their controls (Baltaci *et al.,* 2006). Zinc supplementation was also established to prevent the suppression caused by testosterone supplementation in leptin and LH levels (Baltaci *et al.,* 2006).

The study suggests that leptin secretion is related to LH at the hypophyseal level and zinc has a critical part in this relation (Baltaci *et al.,* 2006).

In conclusion, there is a proven positive correlation between zinc and leptin. These results may have major clinical implications.

Zinc and testosterone
It has been accepted that zinc is present almost each enzyme system and has a critical role in male reproduction system (Stallard ve ark 1997, Vallee and Falchuk 1993). It has been known zinc has provide sperm membrane integrity, increases sperm motility, helezonic movement of sperm tail (Omu ve ark 2015; Wong ve ark 2001). In varicole patients, zinc supplementation for 6 months has been resulted in seminal plasma activity (Nematollahi-Mahani ve ark. 2014). Prostate is the organ that has the highest zinc concentration in the body and testis tissue also contains high concentrations of zinc (Bedwal and Bahuguna 1994). Thus, zinc is closely related to the male reproductive hormones. Severe and moderate zinc deficiency in males causes hypogonadism (Prasad *et al.,* 1996). Zinc may have functional effects on the male reproductive system in two ways:
1. Zinc affects the testis tissue (Ozturk *et al.,* 2005).
2. Zinc influences the male reproductive system through the gonadotropic hormones (Baltaci *et al.,* 2006).

Zinc deficiency disrupts the activity of angiotensin converting enzyme (ACE) which is involved in the production of adrenal androgens (Kwok *et al.,* 2010) and this disruption results in reduced testosterone production and the inhibition of spermatogenesis (Bedwall and Bahuguna 1994). Zinc is required for the conversion of testosterone to its active form, dihydrotestosterone (Om and Chung 1996). The 5α-reductase enzyme that has a part in this conversion is a zinc-dependent enzyme (Om and Chung 1996).

Zinc influences the male reproductive system by way of gonadotropic hormones as well (Mantzoros *et al.,* 1998; Ozturk *et al.,* 2006). It was shown that zinc deficiency in male rats considerably inhibited not only testosterone, but also LH and FSH secretion (Ozturk *et al.,* 2006), while zinc supplementation brought about an increase in LH and FSH levels (Baltaci *et al.,* 2006).

It is acknowledged that zinc deficiency suppressed the receptor activity of androgenic hormones and thus zinc had a critical part in the regulation of male reproductive functions (Om and Chung 1996).

Zinc and estrogen
Zinc plays a critical role in the reproductive physiology of females (Akhtar *et al.,* 2014; Stallard and Reeves 1997). It was shown in a study that LH and FSH levels were significantly inhibited in female rats fed on a zinc-deficient diet (Vallee and Falchuk 1993). Besides, it was reported that disrupting the production and secretion of LH and FSH in females, zinc deficiency gave rise to an abnormal ovarium, reduced estrogen secretion, and thus disturbed the estrus cycle (Stallard and Reeves 1997).

Maybe the fundamental mechanism underlying the effects of zinc on the female and male reproductive systems is based on the relationship between zinc and hormone receptors (Om and Chung 1996; Vallee and Falchuk 1993). Sex hormones secreted by the female and male reproductive system are bound to their specific receptors (Dylewski *et al.,* 1986; Vallee and Falchuk 1993). The hormone-receptor complex is bound to RNA polymerase, a zinc metalloenzyme, and a specific DNA segment in the nucleus (Dylewski *et al.,* 1986). Zinc deficiency prevents the binding of the hormone-receptor complex to DNA. Thus, the activation of the genes regulated by these receptors is blocked (Dylewski *et al.,* 1986). This event provides at least a partial explanation for the endocrinological abnormalities associated with zinc deficiency (Dylewski *et al.,* 1986; Vallee and Falchuk 1993). Furthermore, zinc has a direct effect on the activity of RNA polymerase (Dylewski *et al.,* 1986). This can be considered a mechanism explaining the unresponsiveness of zinc-deficient animals to estrogens (Dylewski *et al.,* 1986; Vallee and Falchuk 1993).

Zinc and melatonin
Pineal gland is the brain region which is richest in zinc (Fabris *et al.,* 1991). Plasma melatonin levels drop by aging (Reiter *et al.,* 1981). Similarly, it was shown that gastrointestinal zinc absorption was reduced and plasma zinc levels decreased with aging in both humans (Turnlund *et al*., 1986) and animals (Sugarman and Munro 1980). In a study by Mocchegiani *et al.,* (1996), one-month melatonin administration (100μg/mouse) to pinealectomized mice converted the body zinc content values from negative to positive. Interruption of the melatonin administration for one month brought the negative body zinc content values back in the same mice. Another round of one-month melatonin administration to

these mice corrected the negative zinc pool. Similar results were put forward in aged mice (Mocchegiani *et al.,* (1994). The aforementioned studies suggest that zinc absorption in the digestive system may be related to melatonin. The presence of melatonin receptors in the digestive system strengthens this idea (Lee 1992, Lee ve Pang 1993). The relation between zinc and melatonin is not one-way. Zinc is involved in the synthesis of melatonin synthesis in pineal gland (Johnson 2001). Serotonin synthesis is a important step in melatonin synthesis and the role of zinc is critical in this process. Especially in serotonin formation, in reaction catalyzed by L-amino acid decarboxylase zinc has play as a cofactor (Johnson 2001). Already, it has been reported that zinc deficiency caused to decrease in melatonin levels, but zinc supplementation led to significantly increases in melatonin production (Bediz ve ark. 2003).

CONCLUSION

Zinc, which plays a key role in growth, development, and the reproductive system, is the only metal found in almost all enzyme classes. Physiological and biochemical levels of many hormones are affected by the zinc metabolism. In consideration of these relations, zinc is accepted to play critical roles in the endocrine system.

When the considered relationship between zinc and endocrine system it can be postulated that

1. Zinc is effective on growth via growth hormone, IGF-1, insuline and thyroid hormones.
2. Pubertal period, zinc plays a critical role in the development of gonadal function.
3. IGF-like affects of zinc show that it is important for prevents of diabetes and importance of the carbohydrate metabolism.
4. Zinc affect thymic function, thereafter it has regulatory function in cellular immunity.
5. Relationship among the zinc, leptin and NPY show that zinc has a role in regulation of body weigth and feeding.
6. Because of the relationship between zinc and pineal gland-melatonin synthesis, zinc may be a potantial significant for saving brain function and delays of aging.

REFERENCES

Adachi Y, Yoshida J, Kodera Y, Kato A, Yoshikawa Y, Kojima Y and Sakurai H (2004). A new insulin-mimetic bis(allixinato)zinc(II) complex: Structure-activity relationship of zinc(II) complexes. *J. Biol. Inorg. Chem.,* **9**: 885-893.

Aguilar MV, Saavedra P, Arrieta FJ, Mateos CJ, González MJ, Meseguer I and Martínez-Para MC (2007). Plasma mineral content in type-2 diabetic patients and their association with the metabolic syndrome. *Ann. Nutr. Metab.,* **51**: 402-406.

Akhtar T, Khan MH, Zahoorullah, Hussain H, Nazli R and Lutfullah G (2014). Prevalence of zinc deficiency among rural women during childbearing age in Peshawar, Pakistan. *Pak. J. Pharm. Sci.,* **27**: 173-177.

Al-Sayer H, Mathew TC, Asfar S, Khourshed M, Al-Bader A, Behbehani A and Dashti H (2004). Serum changes in trace elements during thyroid cancers. *Mol. Cell. Biochem.,* **260**: 1-5.

Attia H, Al-Rasheed N, Al-Rasheed N and Faddah L (2015). The combination of zinc and glibenclamide limits cardiovascular complications in diabetic rats via multiple mechanisms. *Pak. J. Pharm. Sci.,* **28**: 499-508.

Awadallah R, El-Dessoukey EA, Doss H, Khalifa K and el-Hawary Z (1978). Blood-reduced glutathione, serum ceruloplasmin and mineral changes in juvenilediabetes. *Z. Ernährungswiss.,* **17**: 9-83.

Baltaci AK, Mogulkoc R and Halifeoglu I (2005). Effects of zinc deficiency and supplementation on plasma leptin levels in rats. *Biol. Trace Elem. Res.,* **104**: 41-46.

Baltaci AK, Mogulkoc R and Ozturk A (2006). Testosterone and zinc supplementation in castrated rats: Effects on plasma leptin levels and relation with LH, FSH and testosterone. *Life Sci.,* **11**: 746-752.

Bannister WH (1988). From haemocuprein to copper-zinc superoxide dismutase: A history on the fiftieth anniversary of the discovery of haemocuprein and the twentieth anniversary of the discovery of superoxide dismutase. *Free Radic. Res. Commun.,* **5**: 35-42.

Bao B, Prasad AS, Beck FW and Godmere M (2003). Zinc modulates mRNA levels of cytokines. *Am. J. Physiol. Endocrinol. Metab.,* **285**: E1095-E1102.

Barnes PM and Moynahan EJ (1973). Zinc deficiency in acrodermatitis enteropathica: multiple dietary intolerance treated with synthetic diet. *Proc. R. Soc. Med.,* **66**: 327-329.

Bediz CS, Baltaci AK and Mogulkoc R (2003). Both zinc deficiency and supplementation effect plasma melatonin levels in rats. *Acta. Physiol. Hung.,* **90**: 335-339.

Bedwal RS and Bahuguna A (1994). Zinc, copper and selenium in reproduction. *Experientia.,* **50**: 626-640.

Birmingham CL and Gritzner S (2006). How does zinc supplementation benefit anorexia nervosa? *Eat. Weight Disord.,* **11**: e109-e111.

Brandao-Neto J, Saturnino ACRD and Leite LD (2006). Lack of acute zinc effect on thyrotropin-releasing hormone-stimulated thyroid-stimulating hormone secretion during oral zinc tolerance test in healthy men. *Nutr. Res.,* **26**:493-496.

Buchinger W, Leopold B, Lind P, Langsteger W, Klima G, Költringer P, Wawschinek O and Eber O (1988). Changes in zinc level in the serum, whole blood and erythrocytes in disorders of thyroid function. *Wien Klin. Wochenschr.,* **100**: 619-621.

Canfield WK, Hambidge KM and Johnson LK (1984). Zinc nutriture in type I diabetes mellitus: Rrelationship

to growth measures and metabolic control. *J. Pediatr. Gastroenterol. Nutr.,* **3**: 577-5884.

Chen MD and Lin PY (2000). Zinc-induced hyperleptinemia relates to the amelioration of sucrose-induced obesity with zinc repletion. *Obes. Res.,* **8**: 525-529.

Chen MD, Song YM and Lin PY (2000). Zinc may be a mediator of leptin production in humans. *Life Sci.,* **66**: 2143-2149.

Chen MD, Yang VC, Alexander PS, Lin PY and Song YM (2001). Effects of selected minerals on leptin secretion in streptozotocin-induced hyperglycemic mice. *Exp. Biol. Med. (Maywood).,* **226**: 836-840.

Cunningham BC, Mulkerrin MG and Wells JA (1991). Dimerization of human growth hormone by zinc. *Science.,* **253**: 545-548.

Dicks D, Rojhani A and Cossack ZT (1993). The effect of growth hormone treatment on growth in zinc deficient rats. *Nutr. Res.,* **13**: 701-713.

Dylewski DP, Lytton F and Bunce GE (1986). Dietary zinc and parturition in the rat II. Myometrial gap junctions. *Biol. Trace Elem. Res.,* **9**: 165-175.

El Fékih N, Monia K, Schmitt S, Dorbani I, Küry S and Kamoun MR (2011). Transient symptomatic zinc deficiency in a breast-fed infant: relevance of a genetic study. *Nutrition.,* **27**: 1087-1089.

Ezaki O (1989). IIb group metal ions (Zn2+, Cd2+, Hg2+) stimulate glucose transport activity by post-insulin receptor kinase mechanism in rat adipocytes. *J. Biol. Chem.,* **264**:16118-16122.

Fabris N, Mocchegiani E, Muzzioli M and Provinciali M (1991). The role of zinc in neuroendocrine-immune interactions during aging. *Ann. N. Y. Acad. Sci.,* **621**: 314-326.

Freake HC, Govoni KE, Guda K, Huang C and Zinn SA (2001). Actions and interactions of thyroid hormone and zinc status in growing rats. *J. Nutr.,* **131**: 1135-1141.

Ganapathy S and Volpe SL (1999). Zinc, exercise and thyroid hormone function. *Crit. Rev. Food Sci. Nutr.,* **39**: 369-390.

Gupta RP, Verma PC and Garg SL (1997). Effect of experimental zinc deficiency on thyroid gland in guinea-pigs. *Ann. Nutr. Metab.,* **41**: 376-381.

Hadden JW (1998). Thymic endocrinology. *Ann. N. Y. Acad. Sci.,* **840**: 352-358.

Hartoma TR, Sotaniemi EA and Määttänen J (1979). Effect of zinc on some biochemical indices of metabolism. *Nutr. Metab.*, **23**: 294-300.

Henkin RI (1976). Trace metals in endocrinology. *Med. Clin. North. Am.,* **60**: 779-797.

Henriksen EJ, Kinnick TR and Teachey MK (2003). Modulation of muscle insulin resistance by selective inhibition of GSK-3 in Zucker diabetic fatty rats. *Am. J. Physiol. Endocrinol. Metab.,* **284**: E892-E900.

Ilouz R, Kaidanovich O, Gurwitz D and Eldar-Finkelman H (2002). Inhibition of glycogen synthase kinase-3beta

by bivalent zinc ions: Insight into the insulin-mimetic action of zinc. *Biochem. Biophys. Res. Commun.*, **295**:102-106.

Imamoğlu S, Bereket A, Turan S, Taga Y and Haklar G (2005). Effect of zinc supplementation on growth hormone secretion, IGF-I, IGFBP-3, somatomedin generation, alkaline phosphatase, osteocalcin and growth in prepubertal children with idiopathic short stature. *J. Pediatr. Endocrinol. Metab.,* **18**:69-74.

Jansen J, Karges W and Rink L (2009). Zinc and diabetes--clinical links and molecular mechanisms. *J. Nutr. Biochem.,* **20**:399-417.

Jing MY, Sun JY and Wang JF (2008). The effect of peripheral administration of zinc on food intake in rats fed Zn-adequate or Zn-deficient diets. *Biol. Trace Elem. Res.,* **124**:144-156.

Johnson S (2001). Micronutrient accumulation and depletion in schizophrenia, epilepsy, autism and Parkinson's disease? *Med. Hypotheses.,* **56**:641-645.

Kahmann L, Uciechowski P, Warmuth S, Malavolta M, Mocchegiani E and Rink L (2006). Effect of improved zinc status on T helper cell activation and TH1/TH2 ratio in healthy elderly individuals. *Biogerontology.,* **7**:429-435.

Kandhro GA, Kazi TG and Afridi HI (2009). Effect of zinc supplementation on the zinc level in serum and urine and their relation to thyroid hormone profile in male and female goitrous patients. *Clin. Nutr.,* **28**:162-168.

Keller SR, Scott HM, Mastick CC, Aebersold R and Lienhard GE (1995). Cloning and characterization of a novel insulin-regulated membrane aminopeptidase from Glut4 vesicles. *J. Biol. Chem.,* **270**: 23612-23618.

Kennedy KJ, Rains TM and Shay NF (1998). Zinc deficiency changes preferred macronutrient intake in subpopulations of Sprague-Dawley outbred rats and reduces hepatic pyruvate kinase gene expression. *J. Nutr.,* **128**:43-49.

Kwok T, Ohlsson C, Vandenput L, Tang N, Zhang YF, Tomlinson B and Leung PC (2010). ACE inhibitor use was associated with lower serum dehydroepian drosterone concentrations in older men. *Clin. Chim. Acta.,* **411**:1122-1125.

Lau AL and Failla ML (1984).Urinary excretion of zinc, copper and iron in the streptozotocin-diabetic rat. *J. Nutr.,* **114**:224-233.

Lee PP and Pang SF (1992). Identification and characterization of melatonin binding sites in the gastrointestinal tract of ducks. *Life Sci.,* **50**:117-125.

Lee PP and Pang SF (1993).Melatonin and its receptors in the gastrointestinal tract. *Biol. Signals.,* **2**:181-193.

Lee RG, Rains TM, Tovar-Palacio C, Beverly JL and Shay NF (1998). Zinc deficiency increases hypothalamic neuropeptide Y and neuropeptide Y mRNA levels and does not block neuropeptide Y-induced feeding in rats. *J. Nutr.,* **128**:1218-1223.

Pak. J. Pharm. Sci., Vol.32, No.1, January 2019, pp.231-239

237

MacDonald RS (2000). The role of zinc in growth and cell proliferation. *J. Nutr.,* **130**:1500S-1508S.

Mantzoros CS, Prasad AS, Beck FW, Grabowski S, Kaplan J, Adair C and Brewer GJ (1998). Zinc may regulate serum leptin concentrations in humans. *J. Am. Coll. Nutr.,* **17**: 270-275.

Matsui T and Yamaguchi M (1995). Zinc modulation of insulin-like growth factor's effect in osteoblastic MC3T3-E1 cells. *Peptides.,* **16**:1063-1068.

Maxwell C and Volpe SL (2007). Effect of zinc supplementation on thyroid hormone function. A case study of two college females. *Ann. Nutr. Metab.,* **51**: 188-194.

May JM and Contoreggi CS (1982). The mechanism of the insulin-like effects of ionic zinc. *J. Biol. Chem.,* **257**: 4362-4368.

McNair P, Kiilerich S, Christiansen C, Christensen MS, Madsbad S and Transbol I (1981). Hyperzincuria in insulin treated diabetes mellitus-its relation to glucose homeostasis and insulin administration. *Clin. Chim. Acta,* **112**: 343-348.

McNall AD, Etherton TD and Fosmire GJ (1995). The impaired growth induced by zinc deficiency in rats is associated with decreased expression of the hepatic insulin-like growth. *J. Nutr.,* **125:** 874-879.

Mocchegiani E, Bulian D, Santarelli L, Tibaldi A, Muzzioli M, Pierpaoli W and Fabris N (1994). The immuno-reconstituting effect of melatonin or pineal grafting and its relation to zinc pool in aging mice. *J. Neuroimmunol.,* **53**: 189-201.

Mocchegiani E, Bulian D, Santarelli L, Tibaldi A, Muzzioli M, Lesnikov V, Pierpaoli W and Fabris N (1996). The zinc pool is involved in the immune-reconstituting effect of melatonin in pinealectomized mice. *J. Pharmacol. Exp. Ther.,* **277**: 1200-1208.

Mocchegiani E, Perissin L and Santarelli L (1999). Melatonin administration in tumor-bearing mice (intact and pinealectomized) in relation to stress, zinc, thymulin and IL-2. *Int. J. Immunopharmacol.,* **21**: 27-46.

Mocchegiani E, Santarelli L, Muzzioli M and Fabris N (1995). Reversibility of the thymic involution and of age-related peripheral immune dysfunctions by zinc supplementation in old mice. *Int. J. Immunopharmacol.,* **17**: 703-718.

Mohommad MK, Zhou Z, Cave M, Barve and McClain CJ (2012). Zinc and liver disease. *Nutr. Clin. Pract.,* **27**: 8-20.

Nematollahi-Mahani SN, Azizollahi GH, Baneshi MR, Safari Z and Azizollahi S (2014). Effect of folic acid and zinc sulphate on endocrine parameters and seminal antioxidant level after varicocelectomy. *Andrologia.,* **46**: 240-245.

Om AS and Chung KW (1996). Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. *J. Nutr.,* **126**: 842-848.

Omu AE, Al-Azemi MK, Al-Maghrebi M, Mathew CT, Omu FE, Kehinde EO, Anim JT, Oriowo MA and Memon A (2015). Molecular basis for the effects of zinc deficiency on spermatogenesis:An experimental study in the Sprague-dawley rat model. *Indian J. Urol.,* **31**: 57-64.

Oner G, Bhaumick B and Bala RM (1984). Effect of zinc deficiency on serum somatomedin levels and skeletal growth in young rats. *Endocrinology.,* **114**: 1860-1863.

Ott ES and Shay NF (2001). Zinc deficiency reduces leptin gene expression and leptin secretion in rat adipocytes. *Exp. Biol. Med. (Maywood).,* **226**: 841-846.

Ozturk A, Baltaci AK, Mogulkoc R, Oztekin E and 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. *Neuro Endocrinol. Lett.,* **26**: 548-554.

Pawan K, Neeraj S, Sandeep K, Kanta Ratho R and Rajendra P (2007). Upregulation of Slc39a10 gene expression in response to thyroid hormones in intestine and kidney. *Biochim. Biophys. Acta.,* **1769**: 117-123.

Pedrosa LFC, Ferreira SRG, Cesarini PR and Cozzolino SMF (1999). Influence of glycemic control on zinc urinary excretion in patients with type 1 diabetes. *Diabetes Care.*, **22**: 362-363.

Pekary AE, Lukaski HC, Mena I and Hershman JM (1991). Processing of TRH precursor peptides in rat brain and pituitary is zinc dependent. *Peptides.* **12**: 1025-1032.

Plotkin B, Kaidanovich O, Talior I and Eldar-Finkelman H (2003). Insulin mimetic action of synthetic phosphorylated peptide inhibitors of glycogen synthase kinase-3. *J. Pharmacol. Exp. Ther.,* **305**: 974-980.

Prasad AS (1969). A century of research on the metabolic role of zinc. *Am. J. Clin. Nutr.,* **22**: 1215-1221.

Prasad AS (2009). Impact of the discovery of human zinc deficiency on health. *J. Am. Coll. Nutr.,* **28**: 257-265.

Prasad AS, Mantzoros CS, Beck FW, Hess JW and Brewer GJ (1996). Zinc status and serum testosterone levels of healthy adults. *Nutrition.,* **12**: 344-348.

Prasad AS, Schulert AR, Maile Jr, Farid Z and Sandstead HH (1963). Zinc and iron deficiencies in male subjects with dwarfism and hypogonadism but without ancylostomiasis, schistosomiasis or severe anemia. *Am. J. Clin. Nutr.,* **12**: 437-444.

Qadir MA, Ahmed M, Haq I and Ahmed S (2015). Improved limit of detection and quantitation development and validation procedure for quantification of zinc in Insulin by atomic absorption spectrometry. *Pak. J. Pharm. Sci.,* **28**: 875-879.

Quilliot D, Dousset B, Guerci B, Dubois F, Drouin P and Ziegler O (2001). Evidence that diabetes mellitus favors impaired metabolism of zinc, copper, and selenium in chronic pancreatitis. *Pancreas.,* **22**: 299-306.

238

Pak. J. Pharm. Sci., Vol.32, No.1, January 2019, pp.231-239

Reiter RJ, Craft CM and Johnson JE Jr (1981). Age-associated reduction in nocturnal pineal melatonin levels in female rats. *Endocrinology.,* **109**: 1295-1297.

Ripa S and Ripa R (1996). Zinc and the growth hormone system. *Minerva Med.*, **87**: 25-31.

Root AW, Duckett G, Sweetland M and Reiter EO (1979). Effects of zinc deficiency upon pituitary function in sexually mature and immature male rats. *J. Nutr.,* **109**: 958-964.

Roth HP and Kirchgessner M (1997). Course of concentration changes growth hormone, IGF-1, insulin and C-peptide in serum, pituitary and liver of zinc-deficient rats. *J. Anim. Phys. Anim. Nutr.,* **77**: 91-101.

Safai-Kutti S (1990). Oral zinc supplementation in anorexia nervosa. *Acta Psychiatr. Scand.,* **361**: 14-17.

Salgueiro J, Zubillaga M, Lysionek A, Sarabia MI, Calmanovici G, Caro R, De Paoli T, Hager A, Weill R and Boccio J (1999). Zinc: Concepts on an essential micronutrient. *Acta. Physiol. Pharmacol. Ther. Latinoam.,* **49**: 1-12.

Salgueiro MJ, Zubillaga M, Lysionek A, Cremaschi G, Goldman CG, Caro R, De Paoli T, Hager A, Weill R and Boccio J (2000). Zinc status and immune system relationship: A review. *Biol. Trace Elem. Res.,* **76**: 193-205.

Salgueiro MJ, Zubillaga MB, Lysionek AE, Caro RA, Weill R and Boccio JR (2002). The role of zinc in the growth and development of children. *Nutrition.,* **18**: 510-519.

Sandstead HH, Penland JG and Alcock NW (1998). Effects of repletion with zinc and other micronutrients on neuropsychologic performance and growth of Chinese children. *Am. J. Clin. Nutr.,* **68**: 470S-475.

Scott DA (1934). Crystalline insulin. *Biochem. J.*, **28**: 1592-1602.

Selvais PL, Labuche C, Nguyen XN, Ketelslegers JM, Denef JF and Maiter DM (1997). Cyclic feeding behaviour and changes in hypothalamic galanin and neuropeptide Y gene expression induced by zinc deficiency in the rat. *J. Neuroendocrinol.,* **9**: 55-62.

Stallard L and Reeves PG (1997). Zinc deficiency in adult rats reduces the relative abundance of testis-specific angiotensin-converting enzyme mRNA. *J. Nutr.,* **127**: 25-29.

Sugarman B and Munro HN (1980). Altered [65Zn]chloride accumulation by aged rats' adipocytes in vitro. *J. Nutr.,* **110**: 2317-2320.

Tipu MK, Saleem U, Hussain K, Muhammad K, Hashmi FK, Islam M and Ahmad B (2012). The role of zinc on anti-Newcastle disease virus specific antibody response and agranulocytes count in rabbits treated with methotrexate and prednisolone. *Pak. J. Pharm. Sci.,* **25**: 845-849.

Turnlund JR, Durkin N, Costa F and Margen S (1986). Stable isotope studies of zinc absorption and retention in young and elderly men. *J. Nutr.,* **116**: 1239-1247.

Vallee BL and Auld DS (1989). Short and long spacer and other features of zinc binding sites in zinc enzymes. *FEBS Lett.,* **257**: 138-140.

Vallee BL and Falchuk KH (1993). The biochemical basis of zinc physiology. *Physiol. Rev.*, **73**: 79-118.

Wada L and King JC (1986). Effect of low zinc intakes on basal metabolic rate, thyroid hormones and protein utilization in adult men. *J. Nutr.,* **116**: 1045-1053.

Wong WY, Flik G, Groenen PM, Swinkels DW, Thomas CM, Copius-Peereboom JH, Merkus HM and Steegers-Theunissen RP (2001). The impact of calcium, magnesium, zinc, and copper in blood and seminal plasma on semen parameters in men. *Reprod. Toxicol.,* **15**: 131-136.

Yamaguchi M and Hashizume M (1994). Effect of beta-alanyl-L-histidinato zinc on protein components in osteoblastic MC3T3-El cells: Increase in osteocalcin, insulin-like growth factor-I and transforming growth factor-beta. *Mol. Cell Biochem.,* **136**: 163-169.

Yoshikawa Y, Ueda E, Miyake H, Sakurai H and Kojima Y (2001). Insulinomimetic bis (maltolato)zinc(II) complex: blood glucose normalizing effect in KK-A(y) mice with type 2 diabetes mellitus. *Biochem. Biophys. Res. Commun.,* **281**: 1190-1193.

Akhtar T, Khan MH, Zahoorullah, Hussain H, Nazli R and Lutfullah G (2014). Prevalence of zinc deficiency among rural women during childbearing age in Peshawar, Pakistan. *Pak. J. Pharm. Sci.,* **27**: 173-177.

Attia H, Al-Rasheed N, Al-Rasheed N and Faddah L (2015). The combination of zinc and glibenclamide limits cardiovascular complications in diabetic rats via multiple mechanisms. *Pak. J. Pharm. Sci.,* **28**: 499-508.

Qadir MA, Ahmed M, Haq I and Ahmed S (2015). Improved limit of detection and quantitation development and validation procedure for quantification of zinc in Insulin by atomic absorption spectrometry. *Pak. J. Pharm. Sci.,* **28**: 875-879.

Tipu MK, Saleem U, Hussain K, Muhammad K, Hashmi FK, Islam M and Ahmad B (2012). The role of zinc on anti-Newcastle disease virus specific antibody response and agranulocytes count in rabbits treated with methotrexate and prednisolone. *Pak. J. Pharm. Sci.,* **25**: 845-849.