Role of zinc in diabetes mellitus, oxidative stress and other human healthy: a review article

Alemayehu Toma[1*], Eyasu Makonnen[2], Getnet Yimer [2]

[1]Pharmacology unit, school of medicine, Hawassa University, PO Box 1560, Hawassa, Ethiopia
[2]Pharmacology department, school of medicine, Addis Ababa University, Addis Ababa, Ethiopia
*Corresponding Author: Alemayehu Toma
Email: alexpharma99@yahoo.com , mobile; +251913259141
P O box 1560, Hawassa University, Hawassa, Ethiopia

ABSTRACT

Diabetes mellitus is a leading cause of morbidity and mortality worldwide, with an estimated 346 million adults being affected in year 2011. The prevalence is expected to double between years 2025–2030. Some of the minerals are the essential part of some of the enzymes for their biological activities. As diabetes mellitus is a disease of metabolic abnormality so minerals as such or as a component of enzymes may be playing a significant role in development and control of diabetes mellitus. Amongst minerals, zinc is involved in the development and control of diabetes mellitus. Zinc has been shown to have an antioxidant potential through the non-enzymatic stabilization of biomembrane and biostructures. A recent finding indicated that there is a direct relationship between low zinc levels, greater body fat content, and insulin resistance. The individuals who were classified as zinc deficient had poorer insulin sensitivity and greater glucose intolerance. Zinc plays multiple roles in the body, affecting numerous chemical messengers that play complex, essential, interconnected biological activities in human beings. Zinc is involved in synthesis, secretion and storage of insulin and has antioxidant activity which makes zinc vital trace element in management of blood glucose level and its associated complication's.

Key words: Zinc, diabetes mellitus, glycemic control, antioxidant effect, oxidative stress

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1. Introduction

The number of people with diabetes and pre-diabetes are exponentially increasing worldwide due to population growth, aging, urbanization, unhealthy eating habits, increasing prevalence of obesity and physical inactivity [1]. Diabetes mellitus is a leading cause of morbidity and mortality worldwide, with an estimated 346 million adults being affected in year 2011. The prevalence is expected to double between years 2025–2030, with the greatest increases expected in low- and middle-income developing countries of the African, Asian, and South American regions. At present, 80% of the worlds' populations with diabetes live in low- and middle-income countries [2]. Diabetes is also associated with a host of life threatening and potentially disabling macro- and micro-vascular complications [3]. Hence, there is also a much larger burden in the form of lose of productivity as a result of restricted daily activity.

Minerals are essential component of diets and hence of life. They perform important functions in the various biochemical processes of the body. Some minerals, particularly the trace minerals are active participants of metabolism. Some of the minerals are the essential part of some of the enzymes for their biological activities. As diabetes mellitus is a disease of metabolic abnormality so minerals as such or as a component of enzymes may be playing a significant role in development and control of diabetes mellitus. Amongst minerals, zinc is involved in the development and control of diabetes mellitus. Zinc is a multi functional nutrient involved in glucose and lipid metabolism, hormone function and wound healing. Zinc is known to be an essential trace mineral which is necessary for health and growth and is also essential for the function and activity of enzymes [4].

The complexity of zinc in adult humans (2.5 g per individual person) is testimony to the critical role it plays in normal health and development. Improve all aspects of health and well-being. Zinc was known for its immune boosting properties, but this mineral is actually a wonder of health benefits: - zinc is such a critical element in human health that even a small deficiency is a disaster [5].

1.1 Zinc and Zinc-Containing Biomolecules

In biological systems, zinc always occurs in its only stable ionic state of +2. This is physiologically significant because, unlike copper and iron, it cannot participate in electron transfer (redox) chemistry. Redox has the potential undesirable consequences of forming free radicals and damaging reactive oxygen species. In fact, many of the myriad biomolecules that require zinc for their function appear to have evolved to zinc specifically to avoid the complicating side effects of redox chemistry [6]. In the human genome, the prevalence of genes encoding for zinc proteins (over 3% of the 32,000 identified genes) is so large that it has led to the concept of the "galvanization of biology." Zinc biomolecules include over 300 characterized zinc enzymes including carbonic anhydrase, alcohol dehydrogenase, carboxypeptidase, glutamic dehydrogenase, lactic dehydrogenase, and alkaline phosphatase as well as hormones, such as thymulin, testosterone, prolactin, and somatomedin, as well as one of the largest classes of eukaryotic proteins, called zinc finger proteins [7, 12].

The zinc finger proteins are involved in regulation of gene expression. Two of the most important proteins of this class relevant to biological activities of zinc are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) polymerases, which catalyze the replication of DNA and its transcription. These are critically important in the highly proliferative environment of the tissues. Another important family of zinc finger proteins is the steroid or thyroid hormone receptors. These receptors bind hormone molecules and facilitate the wide range of effects of these molecules, often through transcription control [8].

1.2 Deficiency of Zinc

Zinc deficiency makes both men and women infertile and causes low libido. Low zinc also exacerbates the effects of stress on the body and accelerates aging, due to lack of antioxidant activities of zinc. Additionally, adequate zinc is necessary for optimal physical performance, energy levels, and body composition. Zinc affects protein synthesis and is required for proper function of red and white blood cells. It is highly concentrated in our bones, pancreas, kidneys, liver, and retina [9].

Zinc deficiency occurs from not eating enough zinc-rich foods. Zinc is found in large concentrations in meat, some seafood—oysters contain the largest concentration of all known foods—and dairy. Whole grains and legumes contain zinc, but it is bound to phytates in these plant-based foods, making the zinc inaccessible by the body. Vegetarians are at greatest risk of zinc deficiency, but alcoholics and people with digestive issues and poor stomach acid are also highly susceptible. Medications may produce zinc deficiency and low levels of almost all essential nutrients. Women on the birth control pill or on hormone replacement therapy are at greater risk of deficiency [10].

Low zinc may produce an altered sense of taste leading to cravings of saltier, sweeter food. Deficiency can also be indicated by diarrhea, low energy, chronic fatigue, infertility, poor immunity, bad memory, and inability to focus, attention deficit disorder (ADD) symptoms, slow wound healing, nerve dysfunction, and ringing in the ears. These symptoms may be present, but because they are so diverse and associated with other health conditions, it is difficult to correlate to zinc deficiency without a test 11, 12].

1.3 Determination of Zinc level in human

The simplest way to test for zinc is a taste test that works because it was known that taste and smell are dependent on there being adequate zinc in the body. To do this test, put zinc sulfate of about 1-2 teaspoons in a cup and sip it, holding it in the mouth. If it tastes just like water, it shows very zinc deficiency. If it tastes something slightly metallic, it shows moderately zinc deficient. If it tastes disgusting—strongly metallic and unpleasant—it shows probably adequate. This test is subject to individual taste perception and it is not 100 percent valid, but it is a good place to start. Other test options are a serum zinc test, but there are factors that can cause inaccuracies such as fluctuations from meals, stress, diurnal variations, and complications from other nutrient deficiencies. A plasma zinc test is another option and it may pick up severe zinc deficiencies, but it may not indicate a more moderate deficiency. It should not be relied on because even a moderate deficiency may negatively influence health. Serum and plasma zinc concentrations in adults range from 80 to 150 micromg/dL [12].

2. Role of Zinc on Diabetes Mellitus

Ninety percent of those with diabetes have type-2 diabetes, characterized by insulin resistance, hyper insulinaemia, β-cell dysfunction and subsequent β–cell failure [13]. Insulin is stored as a hexamer containing two Zinc ions in β-cells of the pancreas and released into the portal venous system at the time of β-cells de-granulation [14]. The Zn(II) ions which are co-secreted with insulin suppress inherent amyloidogenic properties of monomeric insulin [15]. It was indicated that high concentrations of glucose and other secretagogues decrease the islet cell labile Zinc and video fluorescence analysis showed Zinc concentrated in the islet cells was related to the synthesis, storage and secretion of insulin [16]. In vitro data suggests that insulin binds to isolated liver membranes to a greater extent and that there is less degradation when co-administered with Zinc [17].

Zinc is needed for the healthy function of most hormones, including insulin. Adequate zinc plays at least three roles in insulin health. Zinc binds to insulin so that insulin is adequately stored in the pancreas and released when glucose enters the blood stream. Zinc improves cell health, making up a component of the enzymes necessary for insulin to bind to cells so that glucose can enter and be used as fuel. The process of insulin binding to the cell is what is referred to with the term “insulin sensitivity” and means that the cell is receptive to insulin. Once insulin binds to the cell, it “opens the door” so that the glucose can enter. If the cell is resistant to insulin, glucose may stay in the blood stream, cause high blood sugar, and ultimately lead to fat gain. When zinc concentration falls, there is a reduction in insulin secretion and peripheral insulin sensitivity, which if persistent, leads to diabetes. Zinc has anti-inflammatory effects via its role in abolishing inflammatory markers such as C-reactive proteins. Zinc also helps get rid of substances that cause inflammation in cells, helping to preserve cell health and insulin sensitivity [18].

Zinc supplementation resulted in a significant reduction of plasma total cholesterol, LDL-c and TAG, while increasing HDL-c levels in patients with type-2 diabetes [19]. These findings are in contrast to results from controlled trials involving healthy subjects, where no beneficial effects of Zinc supplementation were observed on plasma total cholesterol, LDL-c, HDL-c or TAG

concentrations. Zinc supplementation among healthy individuals was associated with a significant reduction of plasma HDL-c concentrations (7% decreases from baseline) [20]. Hence, Zinc supplementation in healthy individuals may have detrimental health effects.

A recent study indicated that ZC treatment significantly decreased body weight gain in lean G-K rats, and induced body weight reduction in overweight or obese aged S-D rats. In parallel, plasma leptin levels were significantly decreased in both aged S-D and G-K rats but not in lean G-K rats. In contrast to plasma leptin levels, plasma adiponectin levels were significantly increased ($P < 0.001$) in aged overweight S-D rats, but not in lean, diabetic G-K rats. Plasma adiponectin levels exhibited a tendency to be lower in aged overweight S-D rats than in young G-K rats. These data are consistent with the concept that adiponectin metabolism is generally related inversely to the leptin metabolism in animals and human forms of obesity [21, 22].

Zinc supplementation improves fasting insulin level and fasting glucose in mice [23]. Human studies have also shown the beneficial effects of Zinc supplementation in both type-1 [24] and type-2 diabetes [25]. However, results of isolated randomized controlled trials are frequently contradicted by subsequent studies. Especially, in type-1 diabetes studies have reported a negative effect of Zinc supplementation on glucose homeostasis [26].

3. Role of Zinc on Oxidative stresses

Oxidative stress plays an important role in the pathogenesis of diabetes and its' complications. Zinc is a structural part of key anti-oxidant enzymes such as superoxide dismutase (SOD), and Zinc deficiency impairs their synthesis, leading to increased oxidative stress (13). It exerts its antioxidant effects indirectly by maintaining membrane structures, involving in the structure of SOD, increasing the metallothionein concentrations and, competing with redox reactive metals, iron and cuprous for critical binding sites. Diabetes is accompanied by hypozincemia and hyperzincuria [27, 28]. In addition Zinc deficiency is more common in developing countries where diabetes is also showing an exponential increase in prevalence [29].

Diabetic patients have reduced antioxidant capacity, and this may play a role in the development of complications by increasing protein glycosylation, increasing the atherogenic potential of

serum LDL particles and altering endothelial function [30]. The purpose of an antioxidant is to get rid of free radicals that cause damage to cells in the body by bonding with them and neutralizing them. Zinc has been shown to have an antioxidant potential through the non-enzymatic stabilization of biomembrane and biostructures. The protective effects of zinc could be attributed to its ability to reduce collagen accumulation in liver and also it exert critical physiological role in regulating the structure and function of cells. Zinc is particularly good at countering the damaging effect of high iron. Zinc also targets free radicals that cause inflammation and is especially effective at detoxifying heavy metals from the brain. The super antioxidant effects of zinc allow it to efficiently remove toxins from the body and keep them from building up in tissue and causing damage. The progression of neurodegeneration and Alzheimer's disease is accelerated by heavy metal buildup in the brain. Zinc can help get rid of those toxins, and it also helps maintain cellular homeostasis of brain cells [10, 31].

4. Other Roles of Zinc on Human Health

4.1 Role in Reproduction

Zinc is a critical mineral for robust testosterone levels, and the cells of the male prostate require a very high concentration of zinc to work optimally. Low zinc in men impairs testosterone production, puts them at risk for developing prostate cancer, and causes infertility. Inadequate zinc has also been linked to low libido [31, 32].

One recent study of 88 men aged 40 to 60 years showed that those with normal testosterone levels had significantly higher zinc compared to those with low testosterone levels. Low zinc was directly correlated with low testosterone levels, which put the men at greater risk of symptoms of male menopause [33, 34].

Importantly zinc is used to produce enzymes that initiate cell division, but the male prostate tissue requires ten times more zinc than other cells in the body to stay healthy. Adequate zinc level in the prostate protects the cells from damage, inflammation, and cancer development. Also, once the prostate cells are damaged and become cancerous, they lack the ability to

accumulate zinc, leading to greater propagation of cancer cells that produce to tumors. Giving a large dose of therapeutic zinc to rats with prostate cancer halted cancer cell proliferation and helped the rats maintain body weight, which is an indicator of better overall health and homeostasis. There was reduced evidence of biomarkers that indicate oxidative stress and inflammation in the prostate from the zinc supplement. Overall enzyme levels were better. In contrast, a placebo group had a rapid increase in cancer cell growth and decrease in body weight. There was also a 50 percent increase in DNA damage and inflammation during the study period, indicating a progressively diseased prostate cancer state [34, 35].

In women, zinc is involved in the growth process of the oocyte or egg. In women zinc deficiency causes immaturity of the egg and impeding of ovulation as result causes infertility. Adequate zinc allows women to use estrogen and progesterone efficiently, supporting reproductivity and ensuring that estrogen does what it's supposed to do in the body. When estrogen levels become too high, or are inefficiently metabolized they can cause poor reproductive health and breast cancer [36].

4.2 Role in Prevention of Cancer and on Immune Function

Zinc is so important because it is found in every tissue in the body and is directly involved in cell division. It is a powerful antioxidant, helping to prevent cancer, but zinc also is directly involved in proper endocrine function and the maintenance of ideal hormone levels [37].

Zinc is promising in anti-cancer treatment and that regular supplementation when men are healthy with no evidence of cancer is the best prevention. It was also suggested that zinc can prevent related cancers such as ovarian, breast, and colorectal [33, 35].

It was noted that simply ensuring adequate zinc levels can help cure a number of the most severe health problems, especially cancer and poor immune function. Along with prostate cancer, low zinc plays a role in the development of most cancers since it is instrumental in healthy cell proliferation. Recent evidence links zinc deficiency to cancers of the breast, colon, ovaries, lungs, skin, and leukemia [36, 37].

Zinc deficiency profoundly affects the immune system because low zinc produces a direct and rapid decline in T cell function. T cells elevate the body's immune system when viruses, bacteria, or challenges to health arise. Older people are at greater risk of zinc deficiency, which is not thought to be solely due to poor dietary intake. There's evidence that a need for more zinc may increase with age to counter inflammation, support the immune system, and ensure healthy cell function [38].

4.3 Role in Cardiovascular Function

Zinc is vital to maintain the health of cardiovascular cells and the endothelium. The endothelium is the thin layer of cells that lines the blood vessels and plays a major role in circulation. Low zinc can cause a deficiency in the endothelial barrier, which leads to high cholesterol buildup and inflammation. Cholesterol and inflammation increase risk of heart disease [38, 39].

Studies show that poor zinc status can amplify the negative cardiovascular effects of a high-fat, high-cholesterol diet, whereas an adequate zinc intake may have a protective effect and inhibit the progression of heart disease. The elderly population is especially susceptible to the buildup of inflammatory markers including C-reactive proteins and cytokines, which have been called "slow, silent killers." [40, 41].

4.4 Role in Central Nervous System Functions

Zinc plays an essential role in neurotransmitter function and helps maintain brain structure and health. It is necessary in the metabolism of melatonin, which regulates dopamine. Also, zinc is part of an enzyme that is necessary for the anabolism of fatty acids in the brain membrane. This is very important because a key part of supporting brain health and function is to ensure the membrane gets the nutrients it needs [40].

A study on rats tested the effect of giving supplemental zinc to pregnant females during gestation and lactation and found better spatial memory and overall cognitive development in the

offspring. A large zinc dose produced the best results. Human studies are limited, but data on how zinc treats attention deficit hyperactivity disorder (ADHD) indicate its importance [36, 40].

Zinc is a commonly ignored mineral for treating ADHD. Studies show children with ADHD tend to have lower zinc than healthy children. Even more promising, one study of 400 children with diagnosed ADHD found that taking 150 mg/d of zinc sulfate improved impaired social behavior and made subjects less hyperactive and impulsive than a placebo. Subjects that had higher body mass index and lower fatty acid level had more dramatic improvements in socialization and hyperactivity measures from taking zinc [40].

The exact relationship between zinc deficiency and depression is unknown; however it surely has to do with the role of zinc in neurotransmitter and hormone production. Dopamine production, which is partly regulated by zinc status, is a chemical that boosts energy, mood, and reward-driven learning. Poor insulin health or low testosterone levels can lead to health problems that increase rates of depression and low energy. Throw in the antioxidant power of zinc and its ability to get rid of inflammatory biomarkers such as C-reactive protein and tumor necrosis factor (causes cell damage), and it is reasonable to ensure zinc intake is adequate when treating depression [41].

A recent study showed that zinc deficiency may affect depression in women more than men. Women in that study who were already using antidepressants and had low zinc levels had a five times greater risk of ongoing depression. It's thought that the gender-based relationship between low zinc and depression is related to how zinc influences energy levels and production of the hormone estrogen [42].

In women, estrogen is involved in serotonin production—the neurotransmitter that makes people feel good—and zinc supplementation can increase the density of serotonin receptors in the brain [43].

4.5 Role in Development of Muscular systems

Adequate zinc directly affects athletic performance and strength development from training because it plays a primary role in anabolic hormone production. Research shows having ample zinc available in the body allows for a more robust release of the three most important anabolic hormones, testosterone, growth hormone and insulin-like growth factor-1 (IGF-1) [37, 44]. Hence, Zinc is highly required to muscle strengthening during exercise.

It was found that giving trained athletes a zinc supplement for four weeks prior to an exhaustive exercise test resulted in a greater post-workout testosterone response than a placebo. Taking zinc produced higher testosterone levels in the athletes than taking a selenium supplement (a powerful antioxidant that minimizes oxidative stress in the testis). It was noted that zinc enhances the conversion rate of androstenedione to testosterone, and that paired with high-intensity exercise, it allows the body to produce testosterone at an even higher rate. Male and female athletes may benefit from adequate zinc since this mineral ensures healthy release of growth hormone and IGF-1, which are essential for performance and muscle development in both sexes. Ensuring enough zinc provides more energy and improve metabolism [39, 44].

5. Future Directions

The relationship between diabetes, insulin and Zinc is complex with no clear cause and effect relationship. Therefore further study is required to establish clear correlation between diabetes mellitus, insulin and Zinc levels for initiation of Zinc supplementation in diabetic patients as well as insulin abnormality disorders.

Although the measurement of serum and or plasma Zinc level in diabetic patients may not be cost effective, it will be interesting to see if supplemental Zinc would result in a better glycemic control in management of diabetes mellitus.

Moreover, prospective studies in high risk individuals like with a positive family history of diabetes mellitus and obesity are needed to see whether normalization with supplemental Zn intake will prevent or delay the onset of diabetes mellitus.

6. Conclusions

Zinc plays multiple roles in human health, affecting numerous chemical messengers that play complex, essential, interconnected biological activities in human beings thereby zinc has significant on prevention of cancer, cardiovascular disorder, infertility, central neurodegerative disorders and boosting effect on immune function and muscles. Zinc is involved in synthesis, secretion and storage of insulin and has antioxidant activity which makes zinc vital trace element in management of blood glucose level and its associated complication's.

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