***Review Article***

**THE UTILITY OF ZINC AUGMENTATION IN DIABETES- A NARRATIVE REVIEW.**



**ABSTRACT**

Diabetes mellitus has sadly become a pandemic, with chronic and debilitating complications which by far are more pronounced in the developing countries of the world. Despite the availability of a wide array of anti-diabetic drugs (both oral and parenteral medications), micro-vascular and macro-vascular diabetic complications are still common. Owing to this sad reality, the place of micronutrients augmentation in diabetes management has come to the frontline of research in diabetes management. Zinc is one of the well-known micro-elements with diverse functions in various physiologic processes in humans. The authors reviewed the place of zinc augmentation in subjects with diabetes generally, both those with complications of diabetes and those without complications. Emphasis was also laid on the mechanisms of action of zinc in diabetes which includes: anti-oxidant effect, improvement of insulin secretion/sensitivity, increased amylin action, inhibition of gluconeogenesis and atherosclerosis. Impact of zinc supplementation on

fasting plasma glucose, glycated haemoglobin and lipid indices were also detailed while a brief overview of the pharmacology and pharmacokinetics of zinc was also undertaken.

KEYWORDS: zinc augmentation, diabetes mellitus management, diabetes complications, role of zinc in diabetes.



## 1.INTRODUCTION

### 1.1 A BRIEF SYNOPSIS OF DIABETES MELLITUS

Diabetes mellitus (DM) is one of the diseases with significant cardiovascular risk ravaging both developed and developing nations of the world. The condition is characterized by chronic hyperglycemia arising from either total deficiency of the hormoneinsulin as seen in type 1 diabetes or moderate insulin deficiency in type 2 diabetes (T2DM) [1]. Other forms of diabetes include gestational diabetes and diseases affecting the exocrine pancreas and other organs of the body.The most predominant form of DM – T2DM is responsible for over 90- 94% of the DM burden worldwide [2].

The current forecast is that about 642 million individuals would havedeveloped diabetes by the year 2040 and with one in eight persons aged between 20-79 years having their death attributed to diabetes and related complications (3). The increasing prevalence of

DM and its augury - pre-diabetes, even in rural African settlements may be traceable to various factors including sedentary lifestyle consequent upon urbanization, sub-optimal dietary choices and steadily declining physical activity levels. [4, 5]. The aetio-pathophysiology of T2DM is mainly that of insulin hormone resistance, compensatory hyperinsulinemia with progressive beta-cell failure resulting in defective insulin secretion eventually [6]. These and other pathophysiologic events add up to the *ominousoctet* of T2DM. [7]. This comprises: decreased insulin secretion, increased glucagon secretion, decreased glucose uptake in the muscles, increased glucose absorption in the kidneys, the effect from adipose tissues, decreased incretin effect from the gastrointestinal tract, increased hepatic glucose production and effect of brain neurotransmitters[7].Thus, chronic hyperglycemia is the hallmark of diabetes which arises from a combination of the above pathophysiological states.

The hyperglycemic state then results in the glycation of some structural proteins in the body with the resultant effect of advanced glycation end-products (AGEs) formation.In addition, concurrentglucose metabolism going through alternate pathways such as the sorbitol pathway together with the formation of oxidative radicals all act synergystically to drive micro and macro-vascular complications of DM (8,9). Given the rising prevalence of DM and the corresponding increase in its complications, it becomes necessary to understudy the relevance of micro-nutrient supplementation, in this instance, zinc, in diabetes management.

**1.2. OVERVIEW OF ZINC**

The trace element zinc is very vital for life and functions as an important co-factor for many enzymes including those involved in bothribonucleic acid (RNA) and deoxyribonucleic acid (DNA) replication as well as protein synthesis (10). Zinc is found in most cells

throughout the body. It occurs intra-cellularly at pico- to nanomolar concentrations but extra-cellularly in micromolar concentrations. Zinc transporter proteins especially ZIP4 (Zrt-/Irt-like protein) have been implicated in zinc uptake from extracellular milieu or intracellular compartments (11).

Approximately 1.5-2.5 g of zinc is contained in the human body and about 57% of this is present in skeletal muscles (12). The reference ranges for serum and urine zinc levels are 0.7-1.6mg/L and 0.3-0.6mg/24 hours respectively (13).

Zinc plays important role in immune system regulation, cell growth and division, wound repair and healing and metabolism of carbohydrate (14). Furthermore, it is involved in homeostasis, programmed cell death and oxidative stress. Metallothioneins,which are binding proteins for zinc play vital roles in stress, toxic metal exposure and zinc deficiency [15]. More recently, cytosolic zinc ions have been shown to function as a second messenger, involved in the signal transduction system [16].

Zinc supplementation has been proven to be vital in several disease conditions such as diarrhoea, respiratory diseases, malaria, diabetes mellitus, leishmaniasis, Wilson's disease and Alzheimer's disease [17] and recently in coronavirus infection (18). However, this study seeks to evaluate the importance of zinc supplementation in individuals with DM.

Natural sources of zinc include: fish, poultry and red meat [19]. However, fruits and vegetables contain low amounts of zinc[19].

## 2. MODULATORY INFLUENCE OF ZINC IN DIABETES MANAGEMENT

Zinc supplementation improves diabetes control and reduces diabetes complications through the following mechanisms:

### 2.1 Zinc as an anti-oxidant.

Oxidative stress is paramount to the aetio-pathogenesis of macro-and micro-vascular complications. Reactive oxygen species (ROS) derived from oxidative stress are culpable in the stimulus of the main pathways leading to DM complications such as the AGEs [3], with *in-vivo* and *in -vitro* zinc studies showing significant inhibition of AGEs.

Chronic hyperglycemia gives rise to oxidative stress, consequent to the excessive output of ROS together with decreased activity of the antioxidant defence system [20]. Eventually, this results in oxidative cellular injury and lipid peroxidation with dysfunction in lipid protein metabolic processes and structural changes in DNA [20]. Zinc is an essential co-factor of several enzymes and also enhances the breakdown and inactivation of free radicals [21].

The anti-oxidative effect of zinc ameliorates the oxidative stress of diabetes that accountsfor the multi-systemic complications. By this action, in addition to decreasing rate of AGEs formation, zinc augumentation may retard the progress of DM-associatedcomplications [22].

### 2.2 Zinc improves insulin secretion and sensitivity.

Insulin is a hexamer which contains two ions of zinc, produced in the pancreatic islet cells, via a process ofelectrostatic coupling of proinsulin and zinc within acidic granules of the islet cells [23].Insulin is subsequently released into the portal vein during

degranulation of the cells. Video fluorescence has shown that zinc is concentrated in the islet cells during synthesis, storage [23] and is directly involved in insulin signaling, packaging, maturation crystallization, trafficking and eventual secretion [24].

Zinc transporter 8 (ZnT8) plays an important role inn many processes: insulin secretion moderation and intracellular accumulation of zinc in insulin-containing vesicles [25]. The ZnT8 down-regulated cells show reduced insulin content and decreased insulin secretion in response to hyperglycemic stimuli [25]. In beta cells with specific SLC30A8 deficiency, decreasedplasma insulin levels in peripheral plasma were noted and were attributed to increased degradation on passing through the liver [25, 26]. Thus, SLC30A8 genotyping can be used to forcasttresholdlevels of proinsulin independently of insulin levels showing that ZnT8 levels can affect the integrity of insulin. Hence, raising the possibility that abnormal ZnT8 functioning may be linked to the aetio-pathogenesis of T2DM [26]. Interestingly, the carriers of SLC30A8 mutation, especially the common polymorphism rs13266634 were found to have sub-optimalfunction of the beta cells, function coupled with an increased diabetes prevalence [25].

Zinc rich complexes and nanoparticles of zinc oxide have been shown to possess antidiabetic activity (27). Nanoparticles of zinc oxide favour a preponderant decrement in plasma glucose, while elevating levels of insulin and activity of glucokinase. The zinc nanoparticles also stimulate the expression of insulin-glucose-transporter-2 (GLUT-2) and the glucokinase genes in rats with streptozotocin-induced type 1 diabetes (27). Such an effect was also noticed in type 2 diabetes [28]. Thus, zinc apparently improves insulin sensitivity.

**2.3Effect of Zinc on Amylin or human amyloid polypeptide (HIAPP) activity**

The hormone amylin, which is stored together with the insulin hormone in the beta-cell secretory granules, consists of 37 amino acids. It is also co-secreted with insulin. Studies have revealed that depleted serum zinc levels result in the aggregation of HIAPP into polymorphic amyloid fibres [29]. Amyloid fibres are toxic to beta cells and may impair their secretory and synthetic functions and may eventually result in type 2 diabetes mellitus [30].

**2.4Zinc and Carbohydrate metabolism**

Zinc inhibits gluconeogenesis and has a stimulatory effect on glycolysis [31]. It also has an inhibitory effect on intestinal alpha-glucosidase activity. These processes reduce results in good glycemic control. Adenosine Monophosphate (AMP) activated- protein kinase is also potentiated by Zinc- alpha-2 glycoprotein thus enhancing glucose uptake in the muscles [32]. Zinc stimulated cellular GLUT-4 protein in adipose tissues has been demonstrated [33].

**2.5 Zincas an inhibitor of atherosclerosis.**Endothelial injury promotes the development of atherosclerosis. In T2DM, impaired zinc homeostasis can result in the elaboration of immune mediators likesome interleukins, which exacerbate endothelial injury and apoptosis [20]. The anti-atherosclerosis influence of zinc may be related to its effect on enhancing endothelial cells' structural integrity and attenuation of lipid peroxidation through zinc-regulated redox signaling pathways [34]. The excessive expression of inducible nitric oxide synthase becomes the thrust for endothelial dysfunction and subsequent aetio-pathogenesis of atherosclerosis [35] as corroborated by some studies on zinc supplementationwhich reported reduced atheroma formation and plasma peroxidation [36, 37].

In addition, the activation of PPAR-α and γ and downregulation ofpro-inflammatory cytokines as well as the activation of endothelial cell adhesion molecules, were noted to be zinc-dependent [38]. A summary of the modulatory effects of zinc in diabetes is shown schematically in fig. 1.

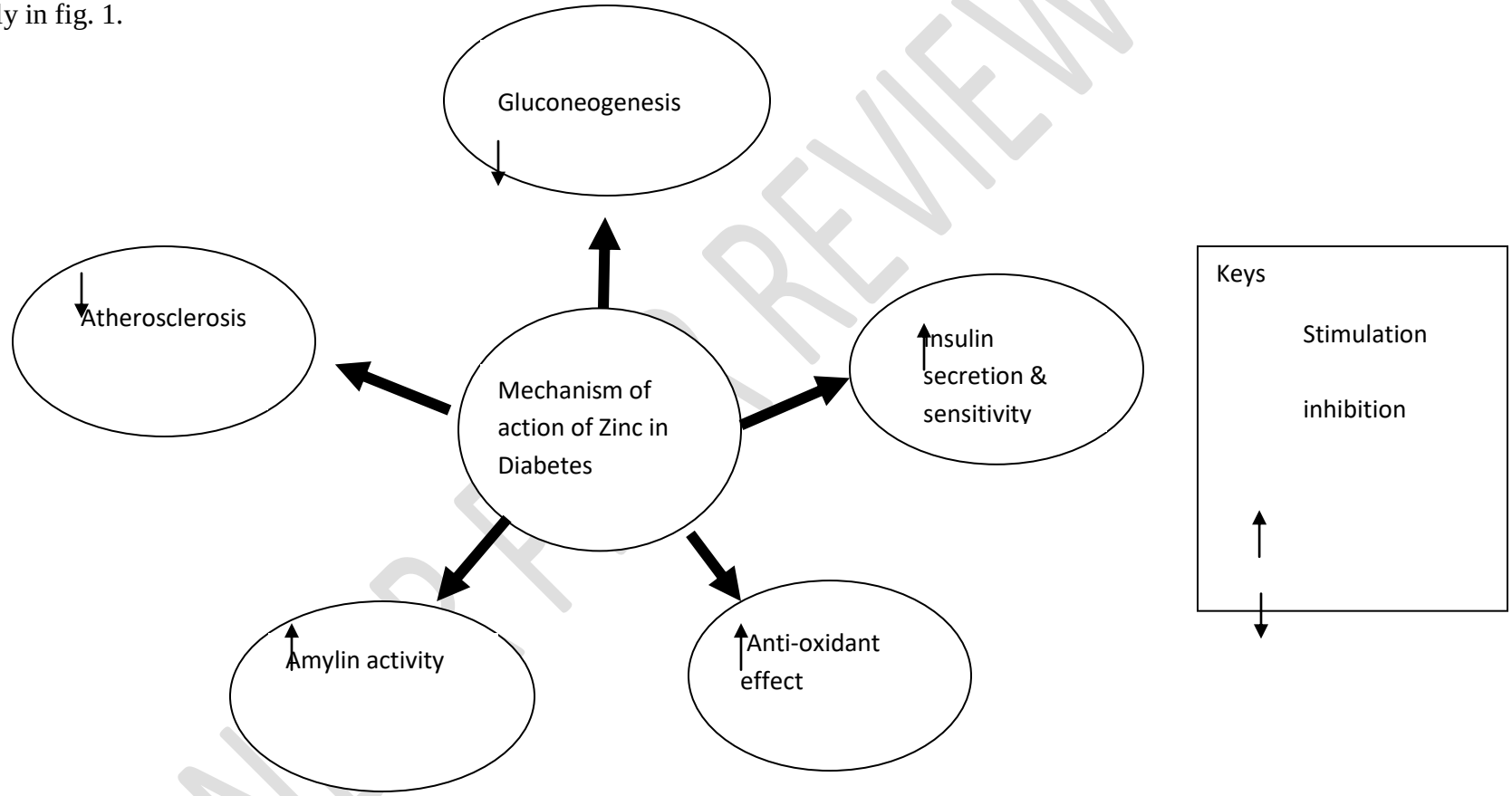


Fig. 1. DIAGRAMATIC REPRESENTATION OF THE MODULATORY EFFECTS OF ZINC IN DIABETES

## 3. COMPARISON OF ZINC LEVELS IN SUBJECTS WITH DM AND SUBJECTS WITHOUT DM

Individuals with diabetes generally, whether those with or without complications have consistently recordedlower serum zinc levels than persons without diabetes. Farooq *et al*, [39] reported in a cohort of 252 with diabetes and 188 controls, the prevalence of zinc deficiency was 67.9% and 6.4% respectively. Similarly, Al- Sharbatti& Al- Maroof[40] reported a mean serum zinc level of 68.9 ± 11.9microg/dl in T2DM patients, a value far lower than healthy controls at 83.4± 12.5 microg/dl. In yet another study, the mean zinc concentration of 79.85 ± 13.4µg/dl in 50 newly diagnosed T2DM patients was remarkably lower than that of the control group at 109.74 ± 9.72µg/dl ($p < 0.001$ , $r = -0.84$) [41]. The consistently lower serum zinc levels between healthy and diabetic cohorts have also been supported by the findings of Fernadez- Cao *et al.*, [42] and Chu *et al.*, [43].

The low serum zinc levels among subjects with DM becomes even more pronounced in the presence of DM-related vascular complications and several attempts have been made to explain the reason why this is so. One of the suggested mechanisms is hyperzincuria which has been noted to accompany hyperglycemia in individuals with diabetes [44]. Another suggested mechanism involves decreased absorption of zinc in the gastrointestinal tract of subjects with diabetes [45].

## 4. INFLUENCE OF ZINC AUGMENTATION ON FASTING PLASA GLUCOSE (FPG), GLYCOSYLATED HAEMOGLOBIN (HBA1C) AND LIPID PROFILE OF DM PATIENTS

Zinc supplementation in subjects with DM has been shown to improve glycemic indices, as reported by various researchers. A study by Kahn *et al*, [46] showed that fastig plasma glucose (FPG), postprandial plasma glucose and HbA1C decreased significantly from baseline, in the DM sub-group whom they placed on oral anti-diabetic drugs plus zinc unlike the group which took anti-diabetic drugs only ($p<0.0001$). In their review of 12 different studies that compared the effects of zinc augmentation among subjects with DM, Jayawardena et al. [47] found that the pooled mean difference in FPG was 18.13mg/dl (95% CI: 33.85, 2.41; $p< 0.05$). They noted also, a decline in HbA1c by 0.54% in the zinc treated group. Appreciable glycemic control ascribed to zinc supplementation has also been substantiated by de Carvalho*et al.*, in their study [48].

Zinc has been shown to disrupt glucose absorption by inhibiting the activity of alpha-glucosidase in the small intestinal mucosa. [49]. In experimental mice, it was shown that low zinc intake is characterized by increased glucose absorption and utilization [50]. Zinc promotes the activities of phosphofructokinase and pyruvate kinase enzymes thus, enhances glycolysis [51]. Zinc improves lipogenesis and supports the expression of PPARγ thus, effective in insulin sensitization [20].

The influence of zinc on thevarious plasma lipid constituents of DM patients has been reported. Triglycerides (TG) were remarkably reduced in the sub-group on oral anti-diabetic drug plus zinc when contrasted with those on oral glucose-lowering drugs only ($p=0.002$), as demonstrated by Kahn *et al.* [46]. No remarkable differences from baseline values were however observed in the low-density lipoprotein (LDL) andtotal cholesterol (TC) levels, after zinc augmentation. Jayawarden*et al.*, [47] showed some significant

reduction in TC and LDL by 32.37mg/dl and 11.19mg/dl respectively in zinc-treated diabetic patients compared to the cohort who was placed on placebo.

A meta-analysis of 13 pooled clinical trials by Jafarnejad*et al.*, [52] showed an appreciable decline in serum TC levels among those who received anti-diabetic drugs plus zinc compared with the control group who received only anti-diabetic drugs by 18.51mg/dl (p for heterogeneity p <0.00001, 95% C.I:-21.36, -15.66). The same study demonstrated a significant decrease in the level of hs-CRP from the initial value of 10.51± 1.68mg/L to 7.75±1.56mg/L after 12 weeks of zinc augmentation.

In a meta-analysis of 9 studies, zinc augmentation was shown to have an outstanding lowering effect of on plasma TG and TC levelsof DM patients with weighted mean difference and p values of -17.08 & 0.01 and -26.16 & 0.02 respectively [53].

## 5. ZINC AND MICROVASCULAR COMPLICATIONS-

### 5.1 ZINC AND DIABETIC NEPHROPATHY

Reduced plasma zinc levels have been linked with diabetic nephropathy. The study by Kahn and co-researchers [46] showed that zinc supplementation significantly reduced urine microalbumin level ($p< 0.0001$) among the sbjects who received it versus those that did not. In a separate study, serum zinc level was shown to be inversely correlated with serum microalbuminuria ($r = -0.587$, $p< 0.001$ and creatinine ( $r= -0.331$, $p< 0.001$) but correlated positively with values of the estimated glomerular filtration rate ($r = 0.194$, $p< 0.01$)

[54]. Microalbuminuria is one of the earlier changes noticed in DM nephropathy and if properly managed can avert further deterioration in kidney function. The above may imply that zinc augmentation may retard the progression of DM nephropathy. Furthermore, zinc supplementation lowers blood sugar [46] and may, therefore, prevent further deterioration of DM nephropathy.

Zinc supplementation has appreciable benefit in overt diabetic nephropathy. This was demonstrated by Barman *et al.*, (55) after six-week zinc supplementation in diabetic rats. Diabetes-indced experimental rats who received zinc supplementation elaborated marked reversal of increased kidney mass and improved creatinine clearance. Likewise, a modulation in the elaboration of lipid oxidative marker and expression of markers of inflammation; fibrosis factors; cytokines and regulatory proteins involved in apoptosis have been reported [55].

### 5.2 ZINC AND DIABETIC RETINOPATHY

In a study among 412 patients with DM, the zinc level in 78 of the subjects with retinopathy was markedly lower, compared to subjects with no evidence of retinopathy ($p<0.001$) [56]. The study also showed that long duration of DM, significantly elevatedHBA1c values and sub-optimal C-peptide levels were found in those with retinopathy compared to those without retinopathy. Zinc acts as a protective factor in the retina, by helping in membrane stabilization, metallothionein activation, inhibition of lipid peroxidation and neovascularization [57]. Rostamkhani*et al,* [58] have also shown that hypozincemia and hypovitaminosis A are predominant in DM subjects who have proliferative retinopathy compared to healthy controls with normoglycaemia ($p=0.03$, $p=0.008$) respectively.

High adenosine triphosphate (ATP) consumption in the retina coupled with chronic hyperglycemia in diabetic patients predisposes the retinal cells to develop high levels of reactive oxygen species. Zinc supplementation improves insulin sensitivity and also has an antioxidant effect through its enhancing effects of some major anti-oxidant enzymes such as superoxide dismutase, gluthatione peroxidase and catalase [59]. Thus, it counteracts the central mechanisms responsible for T2DM and diabetic retinopathy respectively.

### 5.3 ZINC AND DIABETIC NEUROPATHY

Diabetic neuropathy, a common microvascular complication in individuals with T2DM correlates positively with prolonged disease duration and poor control of plasma glucose. Different manifestations of DM neuropathy include: distal symmetrical polyneuropathy, diabetic amyotrophy, autonomic neuropathy, and mononeuropathy [60]. However, distal symmetrical polyneuropathy occurs most commonly and has a predilection for long nerves.

The accepted gold standard for diagnosis of DM peripheral neuropathy is nerve conduction studies (NCS) [61] andJayawarden*et al.*, [47] demonstrated that zinc supplementation can improve both diabetic neuropathy (DN) and glycemic control. In their study, Gupta *et al* [62] revealed that among 25 cases with DN and 20 controls without DN, there was significant improvement ($p>0.05$) in NCS parameters with a 12-week zinc supplementation. However, the HBA1c was not significantly improved after the supplementation.

The plasma levels of zinc in 90 subjects with DN among 412 with diabetes was significantly lower than the non-neuropathic counterparts [56]. Further logistic regression analysis showed that low zinc levels correlated negatively with diabetic neuropathy and

this correlation remained so even after adjustments were made for duration of DM, age, HbA1c levels, body mass index and eGFR [56].

## 6. ZINC AND MACROVASCULAR COMPLICATIONS

### 6.1 ZINC AND MYOCARDIAL INFARCTION

Diabetes is notoriously associated with atherogenesis. Endothelial injury and oxidation of lipids are important in the pathogenesis of atheromas. Zinc has shown promise both as an antioxidant and as an anti-inflammatory agent (3). Soinio*et al.*, [63] demonstrated(in an 8- year prospective study among 1,059 T2M patients) an increased risk of death as a result of coronary heart disease in participants who have serum zinc levels ≤ 14.1µmol/l compared to their counterparts with zinc levels> 14.1µmol/l(20.8% versus 12.8%, p=0.001).

Studies have proposed that plasma zinc levels may be a helpful diagnostic pointer for acute myocardial infarction (MI). In a meta-analysis involving 2886 subjects, it was shown in 41 case-control studies, that those with MI had significantly lower plasma levels of zinc in addition to having significantly lower zinc levels in their hair strands, compared to controls [64]. Significant inverse correlations were also found between plasma zinc levels and important markers of myocardial infaction/ischemia [65].

### 6.2ZINC AND DIABETIC FOOT ULCERS

Zinc is a co-factor fora variety ofenzymes that are involved in the biochemical processes of wound healing, enhancing re-epithelialization and granulation thus, it is considered important in diabetic foot ulcer (DFU) management. It has also been shown that

topical zinc hyaluronate improves healing in DFU [66]. Mitsgumin, whichis made up of two zinc-binding domains in the ring-finger and B-box motifs (MG53) and Tripartite motif (TRIM) family proteins are involved in cell membrane repair mechanisms [67]. Zinc therefore functions as a molecular control switch, facilitatingoxidative stress and membrane-sealing properties of MG53 [68].

Momen-Heravi*et al.*, [69] showed that administration of 50 mg of elemental zinc for 12 weeks yielded a significant reduction in length of ulcer (-1.5± 0.7 versus -0.9± 1.2 cm, p=0.002) and breadth (-1.4± 0.8 versus -0.8± 1.0). In the study, fasting plasma glucose reduction and HbA1c levels were markedly reduced among the cohort who received zinc augmentation versus the placebo group.

In a prospective study to assess the micronutrient deficiencies in diabetic patients with DFU, Pena *et al.*, [70] demonstrated zinc deficiency in 26.9% of 131 participants. Other micronutrient deficiencies in the study cohort included Vitamin D (55.7%), Vitamin C (50.8%), Vitamin A (10.9%) and ferritin (5.9%). Based on these micronutrient deficiencies, clinicians advise nutritional supplementation of Vitamins A and C, magnesium, copper and zinc most especially when their deficiencies are established [71].

## 7.EFFECT OF ZINC ON PREDIABETES

Prediabetes, which prevalence continues to increase globally, particularly in low-and-middle-income countries, continues to fuel the global diabetes scourge [72].Ranasinghe*et al.*, [73] showed that using 20mg of zinc in individuals with pre-diabetes over 12 months,

resulted in lower glycemic and lipid parameters. In addition, beta-cell function, estimated througha standard surrogate measure – the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), was found to be significantly improved. A prospective, double-blind study on the influence of zinc augmentation on pre-diabetes is also being carried out in Australia by Peel *et al.*, [74] for a period of 12 months among 410 pre-diabetic participants aged 40-70 years. The outcome of the study will generate new evidence to further substantiate the capacity of zinc augmentation in halting the progression of pre-diabetes to diabetes.

Similarly, a study by Eshak*et al.*, [75] among 16,160 healthy middle-aged Japanese adults, demonstrated a reduced risk of developing T2DM with zinc supplementation though the reverse was the case with iron and copper supplementation.

## 8. SUMMARY OF STUDIES ON ZINC SUPPLEMENTATION IN DIABETIC PATIENTS

Table 1 showcases various desirable effects arising from zinc augmentation, as reported from different experimental studies.

**Table 1: Studies on zinc supplementation in diabetes/prediabetes.**

| s/n | Study title | Authors | Intervention/Review | Effect |
|---|---|---|---|---|
| 1 | Zinc supplementation in 60 calcium fed male Wistar rats | Derouiche&Kechrid [76] | Zinc after calcium feed | Calcium increased blood glucose and cholesterol while Zinc lowered the parameters. |
| 2. | Zinc supplementation improves glycemic control for diabetes | Wang *et al.*, [77] | Meta-analysis Registered as CRD42018111838 at PROSPERO | Statistically significant reduction in FBG, 2HrPP, HbA1C with zinc supplementation. |
| 3 | A medley correlation of | Naik*et al.*, [78] | Prospective cross-sectional | There was a negative correlation |

| | | | | |
|---|---|---|---|---|
| | serum zinc with glycemic parameters in T2DM patients | | study. Group A (n=20 T2DM patients on metformin. Group B (n=13 T2DM patients on metformin and glimepiride. | between zinc and FBG, Postprandial blood glucose (PPBG) but a positive correlation with HbA1C at ≥ 9.5% ( but p values >0.05 ) |
| 4 | ZIPPeD study-Zinc in Preventing the Progression of pre-Diabetes | Peel *et al.*, [74] | Randomised double-blind trial with trial number: ACTRN12618001120268 for a period of 12 months among 410 participants with pre-diabetes aged 40-70 years | Outcome: HbA1C, Fasting cholesterol, FBS, Insulin sensitivity.Samples collected at baseline, 1, 6,12 months. The results are yet to be published. |
| 5 | Effects of zinc supplementation on DM | Jayawardena *et al.*, [47] | A systematic review and meta-analysis | The pooled mean difference in FBG was 18.13mg/dl ($p<0.05$). 2hpp was reduced by 34.87mg/dl, HbA1c reduction by 0.54% |
| 6 | Zinc and glycemic control: A meta-analysis of randomized placebo-controlled supplementation trials in humans | Capdor*etal.*, [79] | Meta-analysis of 14 studies with study population of 3978 | FBG reduction by 0.19±0.08mmol/l ($p=0.013$), HbA1C reduction of 0.64±0.36%($p=0.072$). FBG reduction in those with type 1 diabetes (TIDM), T2DM and Obesity was 0.49±0.11mmol/l ($p=0.001$) |
| 7 | Effects of zinc supplementation alone or with multi-nutrient on glucose control/lipid levels in Type 2 DM patients | Jafarnejad*et al.*, [52] | Meta-analysis of 20 studies based on inclusion and exclusion criteria. | FBG and HbA1c reductions were 19.66ng/dl and 0.43mg/dl respectively. |



## 10. PHARMACOLOGY OF ZINC

Zinc has a wide array of formulations available for use and each has its peculiar characteristics:

i. zinc gluconate- The most common form of zinc formulation over the counter. It is found in cold remedies and lozenges. It is available in 50mg or 100mg which contains 7mg or 14 mg of elemental zinc respectively [80].

ii. zinc acetate: Similar to zinc gluconate and also found in cold remedies and speeds recovery.

iii. zinc sulphate: It is used specifically to prevent zinc deficiency and effective in acne. It is available in 110mg or 220mg per tablet which contains 25mg or 50mg of elemental zinc respectively [80].

iv. zinc picolinate: Better absorbed than other forms of zinc

v. zinc orotate: It is bound to orotic acid and the most common zinc supplements available

vi. zinc citrate: Has less bitter taste but well absorbed like zinc gluconate.

Overall, zinc sulphate, gluconate or acetate are more widely used because of the increased rate of absorption [81].

**i. ABSORPTION**: Absorption of zinc with food is about 26-33% while the fasting state increases the absorption to 60-70% [82]. Absorption occurs mostly in the small intestine. The bioavailability of zinc glycine complex was significantly superior to zinc sulphate (49% versus 42%) due to the greater absorptive tendency of the former while phytates reduce the rate of absorption in the intestines. Factors affecting the bioavailability of zinc include: the quantity of elemental zinc contained in a meal, the matrix into which

elemental zinc is incorporated, the host's zinc status, genetic factors of the host, presence of effectors of absorption [83].Generally, the more soluble the zinc salt, the greater its bioavailability, and vice-versa.

Zinc absorption occurs predominantly in the small intestine especially in the duodenum. Absorption involves both passive diffusion and a zinc carrier-mediated process and passive diffusion across cells. The former apparently being the preferred modewith low plasma zinc levels, requiring a saturable cysteine-rich intestinal protein (CRIP) [84].

Zinc can also be taken via inhalational route but is unsafe as it is associated with anosmia [85].

**ii. DISTRIBUTION:** In humans, coparatively higherconcentrations of zinc are found in muscle, bone, liver and prostate [86]. Approximately, 98% of zinc is bound, 85% bound to albumin and 12% to α-macroglobulin and the rest to amino acids [87].

**iii. METABOLISM:** Zinc does not undergo metabolism being found as a divalent cation in the body. It however, undergoes electrostatic interaction with anions-carbonate, hydroxide and oxalate [88].

**iv. EXCRETION**: Seventy to eighty percent of zinc is excreted through the gastrointestinal tract in faeces [88] while about 14% is excreted in the urine. However, with increased zinc intake the urinary excretion may rise to 25%. Age can also affect the rate of excretion of zinc as highfaecal excretion is noticed in adult mice compared to young ones [89].

**11. SIDE EFFECTS OF ZINC/ DOSAGE**

Zinc is most likely safe when taken orally at a dose of 40mg daily [80]. The following may however, be noticed: nausea, vomiting, diarrhoea, metallic taste and flu-like symptoms [85]. Higher doses of more than 100mg daily for years may increase prostate cancer risk and necessarily the doses of zinc used in supplementation are usually below 100mg daily. Of note is the fact that zinc-induced copper deficiency and decreased high-density lipoprotein (HDL) has been reported by some researchers [31].

Zinc is safe in pregnant and breastfeeding mothers when the dose used is within the recommended daily amounts (RDA). The maximum limit of intake of elemental zinc in pregnancy and lactation is 40 mg [80].

In mild zinc deficiency, correction with 2-3 times the RDA over 6 months is adequate while moderate to severe zinc deficiency requires correction using 4-5 times the RDA, for a 6-month period [90] and the RDA for zinc in adults is 11mg/day for males and 8mg/day for females [91].

## 12. CONCLUSION

Evidence from several studies above suggest that individuals with T2DM have lower plasma zinc levels,compared to normoglycaemic controls. Hypozincaemia is even more pronounced when complications of DM have developed, necessitating the need for zinc supplementation.

Zinc improves insulin sensitivity; inhibits gluconeogenesis; suppresses atherosclerosis and retards the development of macro-vascular and micro-vascular complications of DM. Zinc compounds however, produce the most-optimal desirable effects when used in

combination with standard anti-diabetic medications. The element zinc is generally well tolerated with minimal,mostly, gastro-intestinal side effects.

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