Yumed Text
OPEN ACCESS JOURNALS

Journal of Diabetes, Obesity & Metabolism

**Review | Vol 4 Iss 1**

# How Do Minerals along with Trace Elements Influence the Generation of Diabetes Mellitus in Addition to Insulin Resistance: A Systematic Review

**Kulvinder Kochar Kaur[1*], Gautam Allahbadia[2] and Mandeep Singh[3]**

[1]Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction, India

[2]Scientific Director, Ex-Rotunda-A Centre for Human Reproduction, India

[3]Consultant Neurologist, Swami Satyanand Hospital, India

[*]**Corresponding author:** Kaur KK, M.D, Scientific Director, Dr Kulvinder Kaur Centre For Human Reproduction, 721, G.T.B. Nagar, Jalandhar-144001, Punjab, India; Tel: 91-181-9501358180; E-mail: kulvinder.dr@gmail.com

**Received:** May 18, 2021; **Accepted:** June 10 24, 2021; **Published:** June 18, 2021

**Abstract**

**Both minerals along with trace elements are necessary micronutrients needed for the normal working of the body. Nevertheless, they exist only in trace quantities. Yet they carry out significant biochemical responses stabilizing constituents of enzymes along with proteins as well as working as cofactors for a lot of enzymes. With our earlier reviews on etiopathogenesis of both type 1 as well as type 2 Diabetes mellitus (DM) here we decided to conduct a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms likeT2DM; T1DM; Trace elements; Micronutrients; Boron; Copper; Chromium; Cobalt; Iodine; Iron; Magnesium; Selenium; Magnesium; Zinc; Cardiovascular disease (CVD); Anemia; thyroid disorders ; Peroxisome Proliferator Activated Receptorγ (PPAR γ). From 1950 to 2021 till date. We found a total of 450 articles out of which we selected 125 articles for this review. No meta-analysis was done. The amounts of trace elements differ significantly in various populations, based on the dietary constitution. In various Asian countries, a big chunk of population gets implicated by a lot of micronutrient deficiencies. Local variations in Selenium, Zinc, Copper; Chromium, iron along with iodine in the diet are present in developed as well as developing countries, mainly secondary to malnutrition, besides based on indigenous nutritional patterns. These total deficiencies in addition to in occasional subjects, escalated trace elements might result in imbalance of glucose homeostasis, besides insulin resistance (IR). The maximum problem afflicting a minimum of 1 billion people world over have an association with insufficient supply of multiple minerals in addition to trace elements, that include iodine, Selenium, Zinc, Copper, Calcium, Chromium, Cobalt, Iron, Boron as well as Magnesium. In this review a lot of randomized controlled trial (RCT), cohort along with case-controlled studies, observational studies as well as some laboratory dependent studies have been included that represent Asia, Africa along with North America. Alterations of these micronutrients in serum along with urine of subjects might point towards metabolic alterations, Oxidative stress (OS), besides yielding disease specific knowledge.**

**Keywords:** ***Trace elements; Micronutrients; Diabetes; Insulin; Minerals***

**Citation:** Kaur KK, Allahbadia G, Singh M. How Do Minerals along with Trace Elements Influence the Generation of Diabetes Mellitus in Addition to Insulin Resistance: A Systematic Review. J Diab Obes Metab. 2021;4(1):125.

## 1. Introduction

Both minerals along with trace elements are necessary micronutrients needed for the normal working of the body. These have a specific advantageous with regards to the physiological functions [1]. They are necessary for a lot of biochemical responses, existing in the form of stabilizing constituents of enzymes along with proteins as well as working as cofactors for a lot of enzymes. Some trace elements control key biological events by binding to the receptor area of the cell membrane or altering the shape of the receptor to avoid entry of specific molecules into the cell [2]. Micronutrients possess double parts that sustain the stability of cellular structures at their ideal amounts. Nevertheless, once they are not sufficient, that results in alternative pathways getting employed in association with some diseases or disorders [3]. These Micronutrients possess significant physiological involvements in addition to showing a direct correlation with type2 Diabetes mellitus (DM) [4].

Scientific proof along with Clinical results from DM research prove necessary part of these necessary Micronutrients being deficient/or overload evaluation. Nevertheless, the studies that have not been consistent make it tough for the clinician to advocate nutritional recommendations for Diabetic subjects [5]. In view propagation in interventions in addition to research, the life expectancy has escalated with a total enhancement in Diabetic individuals in the geriatric population. Antioxidant enzymes correlated trace elements are changed in Diabetes mellitus [6]. A lot of cohort studies have demonstrated that the homeostasis of trace elements can be changed with Diabetes mellitus [7]. Initial disturbances in particular elements might influence significant part in impairment of insulin metabolism [8,9]. Maximum cohort studies concentrate on single elements or in a few combined elements only. Having reviewed a lot of etiopathogenetic events responsible for both type1(T1DM) in addition to type2 Diabetes mellitus (T2DM)) [10-22], here we further decided to review the role of trace elements in association with Diabetes mellitus generation along with associated comorbidities like CVS side effects in children as well as adults. The studies have been obtained from vast racial groups belonging to Asia, Africa along with North America, with studies included randomized controlled Clinical trial (RCT), cohort along with case-controlled studies, observational studies in addition to laboratory dependent studies.

## 2. Methods

Here we conducted a systematic review utilizing search engine PubMed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like T2DM; T1DM; Trace elements; Micronutrients; Boron; Copper; Chromium; Cobalt; Iodine; Iron; Magnesium; Zinc; cardiovascular disease (CVD); Anemia; thyroid disorders; Peroxisome Proliferator Activated Receptor γ (PPAR γ) from 1950 to 2021 till date.

## 3. Results

We found a total of 450 articles out of which we selected 125 articles for this review. No meta-analysis was done.

## 4. Micronutrients

Micronutrients are isolated as key nutrients that get needed in minute amounts for homeostasis, enzymes control in addition to their working [23]. Macro elements, vitamins, trace elements along with organic acids represent the four main classes of Micronutrients. Primarily are chloride, calcium, P4, Mg, Na, K as well as Fe, while some trace elements like cobalt, copper, sulphur, iodine, zinc and molybdenum escalate insulin effect by stimulation of insulin receptor areas [24]. These trace elements possess particular parts in the etiopathogenesis in addition to propagation type2 Diabetes mellitus [T2DM] as well

as mechanistically a lot of macro as well as trace elements is changed in T2DM [25]. A lot of randomized controlled trial (RCT), cohort along with case-controlled studies, observational studies as well as some laboratory dependent studies (FIG. 1) [rev in 26].

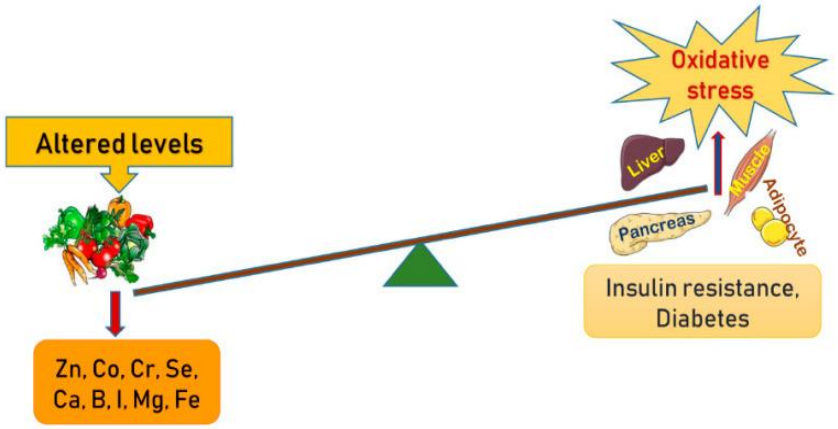


FIG. 1. **Schematic presentation of the altered levels of trace elements and minerals in the manifestation of oxidative stress in amplifying pathways towards insulin resistance and development of diabetes.**

### 4.1 Boron

Boron is a significant nevertheless, less utilized trace micronutrient observed in certain foods, having multiple but significant parts in metabolism [27,28]. In this context the characteristics of boron that possess maximum significance in association with human health are bone generation along with regeneration, wound healing, sex hormone generation, Vitamin D metabolism, besides the calcium in $Ca^{2+}$ addition to magnesium absorption as well as their generation utilization [28]. Studies documented that dietary boron influences plasma insulin amounts. The rats that faced boron deprivation possessed significantly greater plasma insulin amounts was illustrated by Bakken et al. [29], in contrast to rats that had boron delivery. Deficit of boron showed no correlation with equivalent alterations in plasma glucose amounts, besides no dependence on magnesium or Vitamin D status existing in diet [29]. Boric acid hampers $Ca^{2+}$ liberation secondary to ryanodine receptor agonist via binding of $NAD^{+}$ as well as /or cyclic ADP ribose along with hampering the $Ca^{2+}$ liberation, that further influences insulin liberation, besides brain function [30]. In animal studies it was observed that boron is implicated in regulation of triglyceride amounts as well as work in the form of a metabolic controller of the enzyme systems. Nevertheless, a study validated that the maternal boron amounts in normal in addition to Diabetic pregnancies was not associated with lipids in addition to boron amounts. The serum lipids in addition to boron amounts in 15 non gestational Diabetic as well as 19 gestational Diabetic ladies displayed no significant alterations in boron amounts [31].

In another study it was observed that boric acid along with sodium pentaborate pentahydrate (NaB) demonstrated hampering action on adipogenesis in a cell model. Repression of the adipogenesis-associated genes along with proteins by controlling key growth factors, β-catenin, AKT, along with extracellular signal-regulated kinase (ERK) signaling pathway [32]. Boron treatment further documented a reduction in Oxidative stress (OS) in Diabetic animals thus illustrated an antioxidant action with pancreatic-β-cell getting preserved [33].

### 4.2 Calcium

Calcium homeostasis has a significant part in insulin resistance (IR) along with liberation [34]. Calcium homeostasis is dysfunctional in Diabetes mellitus (DM), along with aid in disturbed cell controlling in erythrocytes, cardiac muscle, platelets as well as skeletal muscles. The dysfunctional homeostasis is bothersome since it can significantly aid in the control of the proper insulin liberation along with function, further influencing different Vascular complications independently [35].

Pittas et al. illustrated in 2007 that alterations in Calcium as well as Vitamin D amounts seem to be implicated in the generation of T2DM. The study documented a moderate correlation among low Vitamin D amounts in addition to Calcium or dietary intake along with Prevalence of T2DM in addition to Metabolic Syndrome (MetS). The serum 25 hydroxy Vitamin D (25-OHD) amounts as well as prevalence of MetS as well as T2DM got evaluated that demonstrated, inverse correlation with incidence of MetS as well as T2DM for the maximum to vis a vis minimum combination of Calcium along with Vitamin D consumption. Hyperglycemia generated worse implications with Calcium along with Vitamin D deficiency, while delivery of the 2 documented advantageous actions on glucose metabolism [36].

Two small studies had just the serum Calcium documented. One was study comprising of 30 subjects in the age range 30-70 revealed an escalated Calcium amounts with considerable reduction in parathyroid hormone amounts [37]. A 2$^{nd}$ study conducted in India, demonstrated significant reduction in serum Calcium amounts in Diabetic patients in contrast to non-diabetic controls. Escalated plasma blood glucose amounts having a negative association with serum Calcium amounts [38]. A cross sectional study got conducted in North Sudan in 40 patients presenting with T2DM as well as healthy controls for analysing serum Calcium amounts along with glycosylated haemoglobin (HbA1c). Their outcome they documented that the Diabetic patients Possessing escalated HbA1c went through a significant reduction in serum Calcium amounts in contrast to healthy controls possessing normal HbA1C. This negative association with serum Calcium amounts as well as HbA1C in Diabetic patients points to uncontrolled Diabetic patients possessing Hyperglycemia are at a risk of hypocalcemic in contrast to controls [39].

Cohort studies conducting evaluation of part of escalated serum Calcium amounts in the form of biomarkers of dysfunctional glucose metabolism have not been conducted. A similar study illustrated escalated risk of DM in subjects with escalated serum Calcium amounts. They concluded that 77 cases of T2DM illustrated a total escalated serum Calcium amounts at follow up. These outcomes are akin to prior cross-sectional studies where patients with type2 Diabetes mellitus (DM), demonstrated greater, serum Calcium amounts as compared to non-diabetic subjects, that persisted to be important following subjects consuming supplemental Calcium or possessing Calcium amounts that were out of range were not included, thus documented the escalated risk of T2DM with escalated serum Calcium amounts [40]. Akin to this another study illustrated an enhanced risk of T2DM with escalated serum Calcium amounts [40]. The Prevalence of MetS as well as DM with escalated serum Calcium amount in 1329 middle aged along with aged Korean individuals ($p<0.001$). This correlation was not dependent on age, sex, body mass index (BMI), serum creatinine, Phosphorus, parathyroid horomone (PTH), 25-OH-D amounts, smoking alcohol intake, exercise, overall energy along with Calcium as well as sodium consumption [41]. A complicated correlation has been illustrated in studies. Reduction in βcells function was associated with aberrant Calcium control [42], that could subsequently link to changed glucose homeostasis [43]. Greater cytosolic Calcium amounts was

demonstrated, in cell culture studies that might be correlated with insulin resistance (IR) [44]. Prior dose-based meta-analysis of cohort studies illustrated that dietary delivery of Calcium avoids the generation of T2DM [45].

### 4.3 Cobalt

A lot of studies have documented that classical serum amounts of Cobalt are <0.5µg /l. It was demonstrated by Saker et al, [46] that Cobalt chloride ($CoCl_2$) reduced gluconeogenesis in Diabetic rats via its glucose reducing actions [46]. Cobalt by itself or with ascorbate decreases lipid peroxidation in visceral organs of Diabetic rats [47]. Serum amounts of Cobalt reduced in T2D in contrast to non-diabetic rats as well as Cobalt therapy also illustrated abrogation of Diabetic Nephropathy along with heart working in a rat model of T2D by Oxidative stress (OS) getting mitigated [48].

Studies that were conducted in humans for evaluation of amounts of Cobalt in Diabetic patients as well as retrospective controls are not enough. A study in Pakistan targeted both Diabetic patients along with non-diabetic men in 5 age groups [49]. On getting the serum multi-element evaluation they documented a greater mean amount of Cobalt Diabetic patients, that contradicts to the earlier studies conducted on streptozocin (STZ), treatment receiving type1 Diabetic rats. As per Flores et al. [50], a significantly greater amounts of Al, Cd, Cu, Mn, Hg as well as Ni, whereas lesser Cr, Co and V in Diabetic patients in contrast to healthy individuals (unpaired t test, $p<0.05$) [50]. The amounts of Trace elements in the serum as well as urine of Diabetic patients along with healthy individuals were evaluated in 76 individuals belonging to age groups of 52 ± 8 yrs. The study validated greater urine amounts of Cr, As, Cu, as well as Zn in contrast to lesser amounts of Cd, Co, Pb, Mn, Mo, Ni as well as Se in Diabetic patients in contrast to healthy individuals. Nevertheless, only the variations in Cd, as well as Zn possessed statistical significance [50]. A prior study had demonstrated that 2 mm of hexamine Cobalt chloride inhibited 22 mm of glucose-stimulated insulin liberation in mouse pancreatic islet cells without interfering with glucose metabolism along with $Ca^{2+}$ influx into the cytoplasm [51].

### 4.4 Chromium

Subsequent to the invention of Chromium (Cr), in the form of a necessary Trace elements in 1955 [52], it has been observed to efficaciously enhance glucose tolerance by decreasing insulin resistance (IR). A study based in China illustrated that Cr delivery escalated the blood glucose, insulin, cholesterol, along with HbA1c amounts in T2D patients in a dose-based approach [53]. Appropriate chromium supplementation in diet aids in enhancing blood lipid profile along with insulin function [54]. Maximum diets can't meet the advocated Chromium of 50 mg. Insufficient Cr results in signs as well as symptoms akin to that of Diabetes along with cardiovascular disease (CVD) [55]. Chromium escalates the glucose, as well as insulin amounts in individuals with hypoglycemia, hyperglycemia, diabetes in addition to hyperlipidemia with no visible actions on control individuals. Chromium further escalates insulin binding, receptor amounts as well as insulin receptor enzymes by escalated insulin sensitivity, β-cells sensitivity in addition to internalization of insulin [56].

Three regulated studies on Cr (III) supplementation in human subjects with dysfunctional glucose tolerance displayed no specific actions [57], while 12 studies on Cr delivery documented escalated lipid profiles in individuals varying from malnourished children [58] to healthy middle-aged subjects [59-61]. Following studies have demonstrated that Dietary chromium works in the form of a physiological escalator of insulin action in addition was known as glucose tolerance factor (GTF) [62-63]. Kazi et al. [64], conducted a study in Pakistani patients, involving 166 healthy in addition to 257 Diabetic

individuals of both sexes got enrolled, with their whole blood, urine along with scalp hair were collected for assessing the amounts of necessary trace elements Copper, Chromium, manganese, iron, nickel and zinc levels in biological samples. Their study demonstrated that the blood along with scalp samples of Diabetic individuals possessed decreased amounts of Chromium, manganese as well as zinc in contrast to the controls ($p<0.001$). Greater amounts of copper as well as iron were visualized in the Diabetic individuals in contrast to the controls although the variation was not significant ($p<0.05$) [64]. The study by Balk et al. [65] on Chromium supplementation on lipid amounts along with glucose metabolism documented that Chromium had no action on lipid or glucose metabolism in diabetic individuals [65]. Chromium takes part in escalated insulin binding; receptor amounts as well as insulin receptor phosphorylation. A study that compared this with a study conducted in China USA, demonstrated, milder glucose in tolerance individuals needed only 200 mg/day Cr delivery while people with greater glucose tolerance as well as Diabetes mellitus needed higher [66]. Rajendran et al. [67] concluded there was an association with serum Cr along with Diabetes mellitus. As per them, a reduction in amounts of Cr took place secondary to metabolic reaction to Oxidative stress in T2DM individuals. In this study 42 individuals with newly T2DM diagnosed individuals got classified into 2 groups: well controlled, (HbA1c $\leq$ 7 .0%) as well as uncontrolled group (HbA1c >7 .0%) along with Cr amounts were measured. T2DM individuals with uncontrolled glucose amounts illustrated lesser serum Cr amounts ($0.065 \pm 0.03\mu g/l$, vs $0.103 \pm 0.04$ $\mu g/l$ $p<0.05$) in contrast to control group. The HbA1c as well as serum Cr amounts had an inverse association, that had statistical significance ($r=-0.6514$, $p<0.0001$). Escalated age aided in the reduction of Cr amounts in both the groups following 40yrs of age ($p<0.05$) [67]. A different study having experimental Diabetic rat model proved that hypoglycemia-induced Oxidative stress (OS) got attenuated by the Chromium picolinate delivery [68].

### 4.5 Iodine

Deficiency of Iodine results in reduction in thyroid horomone (TH) generation, that in turn results in escalated thyroid stimulating hormone (TSH) liberation in addition to enhanced thyroid gland growth [69]. A current study demonstrated that escalated Iodine reduced cell viability in addition to interference with the insulin liberation action in case of islet β-cells which could get modulated via endoplasmic reticulum (ER) stress along with stimulated proapoptotic proteins [70]. Thyroid function is necessary for controlling energy metabolism, with aberrant thyroid function might possess significant actions on blood glucose regulation in diabetes. Diabetes mellitus patients possess an escalated risk of thyroid disease [71]. For evaluation of the clinical involvement of iodine status along with urinary amounts of iodine in T2DM individuals. A study was performed in a Riyadh cohort study. A total number of 266 adults from Saudi Arabia with age range3 18-55yrs (n=109 T2DM individuals, n=157 healthy controls) got selected randomly. These individuals were analysed for fasting glucose, along with lipid variables, serum amounts of TSH, T3, T4 in addition urine creatinine as well as urine Iodine. The study demonstrated that lesser urine Iodine amounts in T2DM in contrast to healthy controls ($84.6 \pm 2.3$vs $119.4 \pm 3.4$, $p<0.001$) [72]. Insulin resistance (IR) is an aetiological cause for the pathogenesis of dysfunctional glucose metabolism, besides being correlated with escalated thyroid volume in addition to nodule being prevalent in patients presenting with metabolic syndrome [73]. A study conducted by Cooppan and Kozac 70 patients with Diabetes mellitus along with hyper thyroidism were examined along with observation that the incidence of diabetes enhanced on the therapy of hyperthyroidism [74]. In a mild to moderate deficiency of iodine area 156 patients with pre-diabetes in addition to 123 patients with diabetes, along with 114 patients with normal glucose metabolism for analyzing thyroid volume in addition to nodule prevalence in patients with pre-diabetes as well as T2DM were studied. In diabetes group, mean TSH amounts was greater in contrast to normal as well

as pre-diabetes group. However, mean thyroid volume was greater in pre-diabetes in addition to T2DM group vs control group, that points that patient with dysfunctional glucose metabolism have significantly escalated thyroid volume along with nodule prevalence [75].

Thyroid abnormalities are commoner in women (30%). In a retrospective chart reviewed for an American in addition to Indian population illustrated a correlation with among Diabetes as well as hypothyroidism. 156 overall Diabetes mellitus patients in addition to 25 cases of hypothyroidism were isolated among American Indian subjects living in the service region from a north-eastern tribe. In women, hypothyroidism as well as diabetes had a greater prevalence (5% as well as 21% respectively), in contrast to men (13% as well as 0.2% respectively), greater prevalence of hypothyroidism in women aged 60 as well as elder (21%) in contrast to younger women with diabetes (8.8%), pointing that American Indian women subjects have a >prevalence of coexistence with diabetes [76].

### 4.6 Iron

Iron Impacts glucose metabolism. The correlation of glucose homeostasis with Ironmetabolism is bidirectional is getting recognized in an escalated manner [77]. Dysfunctional Iron uptake might be aiding factor which impacts glucose metabolism. Serum ferritin amounts in case of type2 Diabetes mellitus patients might influence insulin sensitivity, Vascular resistance, viscosity along with Oxidative injury. Serum ferritin in addition to body mass index (BMI) might work independently as anticipators of glucose tolerance test (GTT) [78].

A study conducted with utilization of oral GTT (OGTT) in pregnant women without anaemia or DM prior to 20 weeks of gestation, that was repeated at 28 ± 3 weeks of gestation for measurement of Serum Iron, ferritin, addition to transferring amounts. Then the data was analysed subsequently after delivery. Of the 401 women 97 got diagnoses as gestational Diabetes mellitus (GDM), which in contrast to control group from the at risk non-diabetic cases. The outcomes demonstrated no alterations in the weight, BMI or haemoglobin amounts in the 3$^{rd}$ trimester, but illustrated significantly greater amounts of Serum ferritin, Iron in addition to transferrin saturation as well as postnatal haemoglobin amounts, that pointed to an association among escalated, Iron stores in addition to glucose tolerance [79].

The escalated risk of anaemia in diabetic patients was evaluated in a survey in which 820 individuals with diabetes were evaluated in a long term follow up. A lot of tests, that were blood, urine tests along with a total blood count were conducted in these patients over a duration of 2 years. About 23% of patients possessed undetectable anaemia, that was 2-3 times greater in patients with renal dysfunction. The escalated risk of anaemia in diabetic patients might be secondary to other nutritional deficiencies [80]. In this cross-sectional study, plasma iron indices were evaluated, that demonstrated, escalated transferrin saturation (>35%) in diabetic patients which was 3-4 folds greater in contrast to non-diabetic controls. Further this study illustrated that escalated transferrin amounts were further correlated with C Reactive Protein (CRP) along with escalated fasting plasma glucose amounts, that was greater in male subjects ($p<0.0001$). No probable correlation was correlated with among the existence of diabetic complications [81]. In a prospective nested case control study, plasma transferrin amounts was surveyed in addition to ferritin to transferrin receptor ratio was assessed in association with the probability of generation of T2DM. During the enrolment in 1989-90, the 32,826 women subjects not possessing diabetes, cardiovascular disease (CVD)or cancer. The blood test outcomes at 10 years in a follow up study illustrated that 698 women generated diabetes,

with 716 BMI, age, fasting status as well as race matched controls evaluated as well as contrasted. escalated ferritin amounts were had an association with an escalated risk of T2DM in healthy women (that was not dependent on known chances of Diabetes), that was more correlated with a lesser ratio of transferrin Receptors to ferritin [82].

Iron is a strong pro-oxidant in addition to correlation of escalated, oxidative stress (OS) with high body iron amounts can escalate the T2DM risk [83]. A lot of epidemiological studies have detailed an association with great Iron stores through circulating ferritin amounts with T2DM along with other insulin resistant states [84]. Insulin sensitivity in human beings got enhanced following phlebotomy via reduction of Iron amounts that pointed that an association with iron overload along with diabetes risk exists [85]. In placenta iron is in plenty as well as aids in the generation of free radicals, that has a part in GDM, influencing around 7%of all pregnancies. For contrasting iron status at 24-28 weeks of pregnancy, 34 women had a diagnosis of GDM whereas 34 non GDM women in the control group were evaluated for ferritin, haemoglobin (Hb), serum iron, mean corpuscular volume (MCV), total iron binding capacity (TIBC), mean corpuscular haemoglobin (MCH). The tests conducted illustrated that TIBC was lesser in the GDM group, while the amounts of serum ferritin, MCV, MCH Iron, transferrin saturation as well as haemoglobin were greater in the GDM group [86]. The incidence in addition to anaemia risk were evaluated as per sex in addition to glycaemic regulation status in 200 individuals with T2DM broken into 3 groups as per sex in addition to glycaemic regulation. A greater incidence as well as risk of anaemia in women (36%) in contrast to men (27%) where Diabetes was regulated, pointing to a poor glycaemic regulation in addition to sex variations are correlated with the anaemia incidence in T2DM [87].

Iron Possesses a main part in the etiopathogenesis of T2DM, with not many markers of iron metabolism are existent other than ferritin. Transferrin, soluble transferrin receptor (sTfR), transferrin saturation (TSAT), sTfR-to log 10 ferritin (sTfR-F) index and iron with dysfunctional glucose metabolism /prediabetes, T2DM along with insulin traits had an evaluation in 2893 individuals in a population-dependent cooperative health research for Augsburg (KORA) area F4 Study in Germany. TSAT as well as iron had an inverse correlation with T2DM, thus points to a link of secondary iron metabolic markers in the propagation of T2DM [88]. The probable implication of Iron on insulin effect along with liberation via alterations in relative abundance was observed to escalating implicate metabolism of glucose at a lot of levels [77]. Obesity is an excessive adipose tissue collection that may have harmful actions on health. Particularly, childhood obesity has become one of the main public health problems in the 21$^{st}$ century, since its prevalence has widely increased in recent years. Childhood obesity is intimately related to the development of several comorbidities like nonalcoholic fatty liver disease (NAFLD), dyslipidemia, T2DM, non-congenital CVD, chronic inflammation and anemia, besides others. Within this complicated interplay between these comorbidities and correlated pathological conditions, obesity has been intricately associated with significantly greater disturbances in iron metabolism. Recently Gonzalez-Dominguez et al. [89], summarized the proof with regards to the part of the detailed constituents of iron metabolism and their alterations in obesity. Iron is the second most abundant metal on Earth, but its bioavailability is inhibited ed by its capacity to generate highly insoluble oxides, with iron deficiency being the commonest nutritional disorder. Although every living organism needs iron, it may also result in toxic oxygen damage by producing oxygen free radicals via the Fenton reaction. Hence, iron homeostasis and metabolism must be tightly regulated in humans at every level (i.e., absorption, storage, transport, recycling). Dysregulation of any step involved in iron metabolism may lead to iron deficiencies and, eventually, to the anemic state related to obesity (FIG. 2) [89].

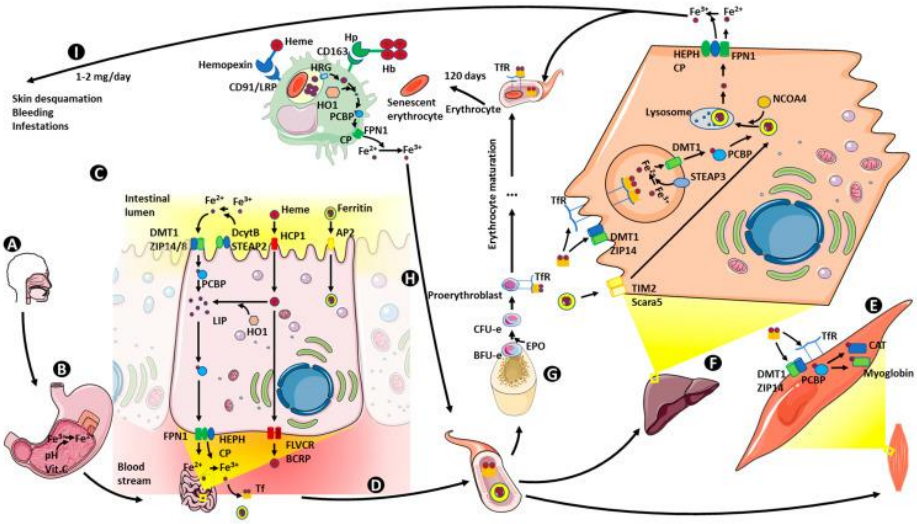


FIG. 2. **Courtesy ref no 89-Physiology of Iron Metabolism. Iron ingested from the diet (A), is reduced from Fe3+ to Fe2+ in the stomach (B). In the duodenum, enterocytes transport Fe2+, heme groups and ferritin across the microvillus membrane (C). Fe2+ is transported by ferroportin across the basolateral membrane into the portal system and must be oxidized to Fe3+ for binding to transferrin and other molecules with high affinity for Fe3+ to be transported to the liver. Transferrin-bound iron is necessary for cells expressing transferrin receptors for uptake of iron, mainly for production of heme proteins (D). Transferrin-bound iron is taken up by myocytes, where Fe3+ is oxidized again to Fe2+ in order to be incorporated into myoglobin (E), hepatocytes being the main ferritin store (F), and by proerythroblasts for synthesis of hemoglobin (G). When mature erythrocytes die, macrophages liberate Fe2+ from hemoglobin, which is oxidized again to recirculate bound to transferrin (H). Finally, 1-2 mg iron is lost per day from the organism by desquamation, bleeding and other mechanisms (I). Vit. C: vitamin C; DMT1: divalent metal transporter 1; ZIP 14/8: Zrt-Irt-like protein 14 and 8; DcytB: duodenal cytochrome B; STEAP 2: six-transmembrane epithelial antigen of the prostate 2; HCP1: heme carrier protein 1; AP2: adaptor-related 2 protein; PCBP: poly (rC) binding protein; LIP: labile iron pool; HO1: heme oxygenase 1; FPN1: ferroportin 1; HEPH: hephaestin; CP: ceruloplasmin; FLVCR: feline leukemia virus subgroup C; BCRP: breast cancer-resistant protein; Tf: transferrin; TfR: transferrin receptor; CAT: catalase; Scara 5: scavenger receptor class A, member 5; TIM2: T-cell immunoglobulin and mucin domain-containing protein 2; STEAP 3: six-transmembrane epithelial antigen of the prostate 3; NCOA4: nuclear receptor coactivator 4; BFU-e: burst forming unit-erythroid; CFU-e: colony forming unit-erythroid; EPO: erythropoietin; Hb: hemoglobin; Hp: haptoglobin; CD163: cluster of differentiation 163; CD91/LRP: cluster of differentiation/ low-density lipoprotein receptor related protein; HRG: heme responsive gene.**

### 4.7 Magnesium

Magnesium represents a co-factor needed for glucose motion into the cell along with carbohydrate metabolism. It is implicated in the cellular action of insulin. Poor Magnesium in diet represents a risk factor for diabetes [90]. Magnesium deficiency hampers the cellular fighting ability against oxidative injury that leads to reduction in resistance to oxidative stress secondary to diabetes, thus accelerating the propagation of diabetes associated complications. Hence hypomagnesemia might exaggerate T2DM, nevertheless, studies illustrated that magnesium intake decreases the risk of T2DM, as well as MetS by amelioration of insulin resistance (IR), [91]. Animal studies illustrated that dietary Mg delivery (50 mg/ml in drinking water)

for 6 weeks reduced blood glucose amounts, enhanced mitochondrial working along with decreased Oxidative stress in Diabetic mice [92].

A lot of studies have demonstrated that hypomagnesemia is a usual presentation in diabetes mellitus as well as takes place with an incidence of 13.5% to 47.7% in subjects with T2DM [93]. In a study the action of insulin resistance on Mg collection in erythrocytes was evaluated. Of the 15 Caucasians© as well as 14 Pima Indian (PI), the PI had >IR in contrast to C's ($p<0.0001$). Baseline Mg amounts in erythrocytes demonstrated that the Mg amounts were akin in both groups. Mg amounts were re-recorded following insulin infusion, as well as its amounts escalation was lower in PI, in contrast to Caucasians ($p<,0.03$). Thus, it was concluded Mg collection in erythrocytes is secondary to the amount of IR [94]. There is a robust correlation of Mg with Diabetes as well as hypertension. Cytosolic free Mg is mostly on lower side in Diabetic patients [95]. IR gets exacerbated by Magnesium deficiency. Hence, Diabetic patients remain at a greater risk of cardiovascular disease (CVD) [96], while the Atherosclerosis risk in communities studies [ARIC) observed that lower dietary Mg consumption did not escalate the risk of diabetes in middle aged population [97].

Magnesium is further a co-factor for the downstream actions of insulin cascade. Reduction in intra cellular Mg injures tyrosine kinase action, blocking actions of insulin within the cell, leading to escalation of insulin tolerance. A lot of clinical trials observed that magnesium administration was advantageous in a Diabetic [98].

During a cross-sectional study the plasma amount of magnesium of Diabetics were evaluated. Eleven T1DM, 25 T2DM, along with 34 control subjects that were matched fore age, sex got recruited. Atomic spectroscopy was utilized to check the magnesium amounts. Plasma magnesium amounts were lesser in both T2DM groups ($p<0.0001$). This aberration could be presumed to be due to escalated glycation of haemoglobin. They concluded the dysfunctional metabolism might be responsible for the diabetic complications occurring [99]. Evaluation of Magnesium amounts along with correlation with fasting blood glucose by Sales et al. [100]. Urine plasma in addition to erythrocytes magnesium amounts were checked by atomic absorption spectroscopy in T2DM pts recruited. Individuals with both T2DM groups had a lesser plasma magnesium amount ($p<0.0001$). Urine magnesium as well as plasma magnesium had an association with fasting blood glucose, while creatinine clearance only was linked with plasma magnesium, thus concluding that magnesium possesses a significant part for sustenance of blood glucose amounts [100].

Malondialdehyde (MDA) as well as trace elements are important factors that work as cofactors with regards to the pathogenesis as well as pathophysiology of DM [101]. For analyzing their aid as markers in glycaemic regulation along with lipid status in diabetic patients, Trace elements Zn, Cu, Mg, Cr, Se, as well as malondialdehyde (MDA) were evaluated in a small group of 50 patients presenting with DM. They further classified pts in controlled diabetic as well as uncontrolled (like neuro/retinopathy) individuals. The mean amounts of Zn, Mg, Se were lesser in diabetic groups, awa demonstrated that there was a significant part of positive association with Hb A1c, cholesterol, total triglycerides (TG), low density lipoprotein (LDL) cholesterol as well as Cu, with a negative association with high density lipoprotein (HDL), Zn, Mg, as well as Se [102]. Spiga et al. [103] evaluated association among serum $Mg^{2+}$ amounts, besides the initiation of T2DM in a large cohort of well-characterized adult white subjects taking part in the CATAMERI study, who had a re-evaluation following a mean follow-up of 5.6 ± 0.9 years. In their evaluation they observed a significant negative association among $Mg^{2+}$ amounts,

fasting glucose, in addition to 2h-post load glucose in subjects who underwent an OGTT. Moreover, $Mg^{2+}$ amounts had a negative association with fasting insulin amounts, while positive with the lipid profile. As for the harmful actions of lower circulating $Mg^{2+}$ amounts, their r data demonstrated a significant decrease of T2DM risk of about 20% for each 1 mg/dL increase of circulating $Mg^{2+}$. The present results corroborated the theory that $Mg^{2+}$ supplementation could mitigate insulin sensitivity, decreasing the risk of T2DM generation [103]. Further Malinowska et al. [104], aimed to evaluate the distribution of serum magnesium amounts in hospitalized patients as per gender, age, and result of hospitalization. The study was conducted from February 2018 to January 2019 at the Central Clinical Hospital in Warsaw. Laboratory test results from 20,438 patients were included in this retrospective analysis. When a lower reference value 0.65 mmol/L was applied, hypermagnesemia occurred in 196 patients (1%), hypomagnesemia in 1505 patients (7%), and normomagnesemia in 18,711 patients (92%). At a lower reference value of 0.75 mmol/L, hypomagnesemia was found in 25% and normomagnesemia in 74% of patients. At a lower reference value of 0.85 mmol/L, hypomagnesemia was observed in 60% and normomagnesemia in 39% of patients. Either hypo- or hyper-magnesemia was correlated with escalated chances of in-hospital mortality. This risk is the highest in patients with hypermagnesemia (40.1% of deaths), but also increases inversely with magnesium concentration below 0.85 mmol/L. Serum magnesium concentration was not gender-dependent, and there was a little positive association with age ($p < 0.0001$, r=0.07). Large fluctuations in serum magnesium amounts were correlated with escalated mortality ($p$=0.0017). The results point that dysmagnesemia is associated with severe diseases and generally severe conditions. To prevent misdiagnosis, an escalation of a lower cut-off for serum magnesium amounts to at least 0.75 mmol/L is advocated [104]. Various studies have demonstrated that a low magnesium (Mg) consumption in the diet is correlated with greater cardiovascular system (CVS) risk, besides a greater chance of diabetes. However, the results are not consistent in all populations. To minimize the biases derived from diet determination, more objective biomarkers of magnesium status have been posited. Despite at present no ideal biomarker for Mg exists, various studies have illustrated that plasma Mg amounts might represent a relatively acceptable biomarker for cardiovascular risk evaluation. Barragan et al. [105], aimed to evaluate the correlation with plasma Mg amounts (detected via inductively coupled plasma mass spectrometry (ICP-MS)) methods, and cardiovascular risk factors in subjects from a general Mediterranean population (aged 18-80 years). The influence of demographic and lifestyle variables, including adherence to the Mediterranean diet, on plasma Mg amounts were evaluated. The mean Mg level of the population studied was 0.77 ± 0.08 mmol/L, the prevalence of hypomagnesemia (<0.70 mmol/L) being 18.6%. They did not observe any statistically significant variations among plasma Mg amounts, with sex, age, tobacco smoking and total adherence to the Mediterranean diet ($p$>0.05). They revealed a statistically significant correlation among plasma Mg amounts and the prevalence of type-2 diabetes (0.77 ± 0.08 mmol/L in non-diabetics versus 0.73 ± 0.13 mmol/L in diabetics; $p$=0.009). Despite the low prevalence of type-2 diabetes in this population (11.24% in subjects with hypomagnesemia versus 3.91%, in normomagnesemia; $p$=0.005), hypomagnesemia was correlated with greater odds of being diabetic in contrast with normomagnesemia (OR=3.36; $p$=0.016, even after adjustment for sex, age, obesity, and medications). Conversely, no statistically significant association of plasma Mg amounts with obesity, hypertension, fasting triglycerides, HDL-cholesterol or uric acid was found. However, in contrast to what was initially expected, a statistically significant correlation was detected among plasma Mg amounts (basically in the highest quartile) and greater total cholesterol ($p < 0.05$) and LDL-cholesterol concentrations ($p$<0.05). In conclusion, their results aid in escalation of proof collected via a lot of studies on the inverse association between hypomagnesemia and type-2 diabetes, as well as to the observation, previously reported in some studies, of a direct association with hypercholesterolemia. This paradoxical link should be deeply investigated in further studies [105].

### 4.8 Selenium (Se)

Selenium **(**Se) in diet represents a micronutrient that is necessary for the generation of Selenoproteins for performance of biological functions. Selenoproteins has been acknowledged for possessing antioxidant along with cytoprotective characteristics, along with along with supplementation is thought to avoid in view of its counteracting oxidative characteristics for the initiation of Metabolic diseases; like T2DM [106].

During a cross-sectional evaluation studies conducted in US adults, serum Se was assessed via atomic absorption spectroscopy in a diabetic population with a fasting plasma glucose amounts of 126 mg/ml, diabetic receiving insulin therapy in addition to a control group. Subsequently accommodating for age, sex, race along with, body mass index (BMI), the mean variation in serum Se among diabetic along with controls was 2.1 ng/ml (95% CI 0.4 -0.8. p=0.02). Thus, concluding that greater serum Se had a positive association with prevalence of diabetes. Nevertheless, no recommendation was advocated with regard to Se supplementation or restrainment regarding Diabetes avoidance [107]. On the other hand, Se treatment of 0.2 μmol/μl in drinking water of non-obese diabetic mice for 3 weeks demonstrated low serum glucose amounts in addition to enhanced lipid metabolism [108].

One more cross-sectional study that enrolled 5423 middle aged along with elderly Chinese adults was conducted for evaluation of the association among diabetes in addition to dietary Se. In the study population the prevalence was 9.7% [106]. A significant positive association among dietary Se intake along with diabetes was pointed by the results of the study that was in acceptance with the conclusions from akin studies. Another cross-sectional evaluation including 8876 adults spanning 20 years of age in US under the National Health and Nutrition Examination Survey illustrated a significant positive association of greater Se amounts along with the prevalence of diabetes [107,109].

Selenium is necessary for glutathione peroxidase (GSH-Px) enzyme action. Diabetes results in escalated oxidative burden secondary to ROS generation. GSH-Px is a significant cellular method for protection from free radicals. In a cross-sectional evaluation, GSH-Px action along with Se amounts in the blood were assessed, in a study population of 50 diabetics from India along with China, with age matched control population of 50 healthy college students. A significant reduction was seen in both GSH-Px action along with Se amounts in diabetic patients. The reduction of GSH-Px action was explained by fall in Se amounts. Thus, the pathogenesis of diabetes may thus be secondary to oxidative stress (OS) dysfunction [110].

For evaluation of the long-time exposure in addition to the risk of initiation of diabetes mellitus in healthy individuals, Mozaffaran et al., evaluated the correlation among toenail Se along with incidence of T2DM.Slightly greater than 7000 women as well as men took part in a follow up study that was along greater than 2 decades, with the study observed that individuals with the maximum amounts of toenail Se possessed 24% lesser risk of generation of diabetes in contrast to those possess lower Se amounts [111]. On the other hand, in Northern Taiwan, a hospital dependent case control study implicating 847 adults (Diabetes: non-diabetes=1:2) who were greater than 40 years of age illustrated that greater Se amounts were positively correlated with escalated chances of diabetes [112]. The advocated daily need of Se amounts is 55 mg for adults, that can be met just with diet. Subsequently it is tough to decide if a correlation exists with Se amounts along with chances of Diabetes since this might differ among geographical areas in addition to the source of minerals. Thus, Se supplementation is only needed in regions where high Se soil is scanty.

### 4.9 Zinc

Zinc (Zn) represents a necessary micronutrient which controls greater than 100 enzymes required for protein folding in addition to gene expression along with generation in addition to neutralization of ROS. Zn possesses a significant part in cell signaling like cell multiplication along with apoptosis, besides aberration in Zn homeostasis are correlated with diabetes in addition to insulin resistance (IR). It reduces cytokine generation, with its deficit resulting in dysfunctional immunological working [113]. Partially Zn acts as an antioxidant with its administration causing a decrease in ROS generation, that is of advantage in ageing addition to diabetes mellitus [114]. It is key for the proper processing, storing, liberation as well as action of insulin in mammalian pancreatic cells [115], in addition to that Zn deficiency escalates the cytokines stimulated injury in the autoimmune attack [115]. It might aid in T2DM propagation via genetic polymorphism in the zinc-transporter 8 gene (ZnT8), besides in metallothionen (MT)-encoding genes which are correlated with T2DM [116]. Diabetes, insulin in addition to Zinc possess a complicated association. Diabetes impacts Zinc homeostasis besides resulting in escalated urinary loss along with reduction in total body Zinc [117]. Comparison of Zinc amounts in addition to Hb A1c amounts among children with T1DM along with healthy controls was done in 2003. The Zinc amounts were associated significantly lesser in diabetic children as compared to healthy controls. The serum Zinc amounts were associated negatively with HbA1c.Thus concluding that children with T1DM had a deficiency of Zn, with Zn therapy being a probable treatment [118]. Prior animal studies who received Zn delivery (5 mg/kg) × 1mth in diabetic rats demonstrated changed serum glucose amounts in addition to oxidative injury markers [119].

For evaluation of the correlation serum Zinc amounts among non-insulin dependent diabetes mellitus (NIDDM) along with, insulin dependent diabetes mellitus (IDDM) individuals. Zinc amounts were checked by spectrophotometry, that was significantly reduced in diabetic patients in contrast to control populations. This action was more obvious in NIDDM patients in contrast to IDDM patients ($p<0.001$). Hence conclusions derived were that oxidative stress was greater in diabetes mellitus with more so in NIDDM patients [120]. In an exploratory evaluation, the association of serum Zinc amounts with diseases like diabetes along with hypertension was analysed. The study did not find any association of Zinc amounts as well as glucose amounts. The serum Zinc amounts were greater in patients with hypertension alone or hypertension with diabetes mellitus. Thus, El Zabda arrived at the conclusions that with the different Zinc amounts in both diseases, it points to a separate etiopathological mode for the two [121]. Another cross-sectional study evaluated the association among serum Zinc amounts in addition to T1DM correlation in children. Thirty T1DM children with age varying from 6 to 18 years got matched with 30 healthy control children by age along with sex. Serum zinc amounts were statistically not significant ($p=0,4$) among these two groups. No association was observed among these two groups. No link was seen among serum Zinc amounts, fasting blood sugar (FBS), degree of robustness of disease (HbA1c) in addition to time period of disease. Estakhry et al. [122]. Thus, interpreted that the serum Zinc amounts are not dependent on the glycaemic regulation [122].

In a different study both serum along with urine Zinc amounts were determined in pre diabetic in addition to diabetics belonging to North east China. Twenty-five T1DM, 137 T2DM in addition to 50 age along with sex matched controls got recruited. The serum Zinc amounts were diminished in both T1DM in addition to T2DM, whereas urinary Zinc amounts were escalated in both T1DM as well as T2DM. Therapy with simvastatin was not observed to be efficacious on determination of serum along with urine Zinc amounts. Thus, conclusions were drawn by Xu et al, [123], that further exploration is required to find the influence of Zinc amounts on diabetes mellitus [123].

There is a tendency for T2DM patients for generation of microangiopathic complications like diabetic nephropathy along with diabetic retinopathy. Evaluation of microangiopathic complications on serum Zinc amounts in T2DM patients was conducted by Meenakshi as well as Nayyar in 2013 [124]. They recruited 50 T2DM patients with under 2 microangiopathic complications in addition to a minimum of 2 microangiopathic complications. A significantly lower serum Zinc amounts were observed in patients with a minimum of 2 microangiopathic complications ($p<0.05$). They posited that these observations were secondary to side effects of greater glucose amounts resulting in a diminished Zinc reabsorption from the kidneys [124]. The action of T2DM on serum Zinc amounts was contrasted in a comparative study by recruiting 50 T2DM patients in addition to 50 healthy controls. Those subjects with renal disease along with obesity got excluded. It was found that T2DM patients possessed significantly lesser serum Zinc amounts in contrast to control subjects ($p<0.0001$). Thus, it was assumed that diabetes impairs Zinc metabolism [125]. Another study contrasted the serum Zinc amounts among T2DM patients along with healthy controls, by recruiting 50 T2DM patients in addition to 25 healthy controls, in the study. Gagandeep et al. [126] observed that serum Zinc amounts were significantly lesser in diabetic patients ($p<0.05$). No association was seen among trace elements like Zinc amounts in addition to lipid profiles. Thus, concluding that dysfunctional metabolism of elements like Zinc might have an etiopathogenetic part in diabetes mellitus [126]. Hasanto RM [127] tried evaluation of serum amounts of copper (Cu), zinc (Zn) and selenium (Se) in T2DM patients with adequate and poor glycemic control. Their study got conducted at King Khalid University Hospital, Riyadh. A total of 100 consenting T2DM patients comprising of 50 patients with glycated hemoglobin (HbA1c) less than 6.5% and 50 patients with HbA1c ≥ 6.5% along with a group of 50 normal healthy individuals were recruited in the study. Serum amounts of Cu, Zn and Se were detected by inductively coupled plasma-mass spectrometry (ICP-MS) instrument. Of the T2DM patients with HbA1c<6.5%, mean serum Cu levels (13.4+4.3 µmol/L) were not separate from the controls (14.5+1.92 µmol/L) whereas Zn (9.9+2.7 µmol/Lvs 15+3.2 µmol/L; $p<0.0001$) and Se levels (1+0.2 µmol/Lvs1.62+0.2 µmol/L; $p<0.0004$) were lower than the controls. Among T2DM patients with HbA1c>6.5% mean serum Cu (18.1+4.1 µmol/Lvs1 4.5+1.9 µmol/L; $p<0.0001$), Zn (15+3.2 µmol/Lvs13.5+1.9 µmol/L; $p<0.009$) and Se (1.62+0.2 µmol/Lvs1.17+0.16µmol/L;$p<0.0001$) were significantly higher than the controls. HbA1c% negatively correlated with HbA1c>6.5% ($r=-0.302$; $p<0.03$). Thus, drawing conclusions that Cu, Zn and Se homeostasis was altered in T2DM patients and differed with glycemic control.

## 5. Conclusions

Thus, diabetes mellitus can change the amounts of trace elements, that might lead to alterations in the nutritional status of a person. Despite certain micronutrient which are believed to be implicated in the etiopathogenesis in addition to propagation of diabetes mellitus, rest might be secondary to depleted or changed carbohydrates tolerance along with insulin resistance. There are usually conflicting statements as per reports revealed by studies. The serum or tissue amounts of some elements, like Copper, Chromium, Manganese, Iron in addition to Selenium might be greater in diabetics patients in contrast to non-diabetic controls. Despite most of diabetics patients do not possess micronutrient deficits, zinc, magnesium along with chromium deficiencies got noticed in a subgroup of patients. Greater cohort of studies are essential for isolation of the micronutrient deficiencies in diabetes mellitus. Thus, trace elements deficiencies directly or indirectly have a correlation with oxidative stress (OS) that ultimately ends in insulin resistance (IR), or diabetes. Further Tabassum et al. [128], in animal studies aimed to evaluate the insulin sensitizing actions of Peroxisome Proliferator Activated Receptorγ (PPAR γ) agonists on trace elements in obesity stimulated T2DM, besides correlation with serum visfatin. Wistar rats were divided into 5 groups. Group I acted as control. Group II received high fat diet (HFD)**,** Group III, besides receiving HFD got therapy with

rosiglitazone (3 mg/kg) × 7d. Group IV represented type2 diabetes mellitus rats induced via HFD in addition to low dose streptozocin (STZ), (i.p. 35 mg/kg; Group V were rats receiving rosiglitazone (3 mg/kg) × 7d. Serum as well as tissue electrolytes amts in addition to renal, hepatic along with cardiac tissue trace elements by flame photometer in addition to atomic absorption spectroscopy. For evaluation of Serum visfatin ELISA was utilized. Pearson correlations were evaluated among FBG, Serum visfatin as well as tissue trace element. This study illustrated that hyponatraemia, hypokalaemia, hypomagnesimia in addition to hypercalcemia in HFD as well as T2DM further demonstrated escalated copper and iron amounts, nevertheless zinc along with Selenium amounts got diminished. Rosiglitazone treatment escalated insulin sensititizing actions, besides changing these observations. A strong correlation was seen in FBS, serum visfatin along with trace element in HFD as well as T2DM. Thus, these findings might be utilized in avoidance of diabetic complications [128].

## REFERENCES


1. Calabrese EJ, Canada AT, Sacco C. Trace elements and public health. Annu Rev Public Health. 1985;6:131-46.
2. Young VR. Trace element biology: the knowledge base and its application for the nutrition of individuals and populations. J Nutr. 2003;133(Suppl 1):1581S-7S.
3. Nordberg M, Nordberg GF. Trace element research-historical and future aspects. J Trace elements Med Biol. 2016;38:46-52.
4. Zhang Q, Sun X, Xiao X, et al. Alterations of serum Trace elements in patients with type2 Diabetes. J Trace elements Med Biol. 2017;40:91-6.
5. Siddiqui K, Bawazeer N, Joy SS. Variation in Macro and Trace elements in progression of type2 Diabetes. Sci World J. 2014;2014:1-9.
6. Badran M, Morsy R, Solimon H, et al. Assessment of Trace elements levels in patients with type2 Diabetes using multivariate statistical analysis. J Trace elements Med Biol. 2016;33:114-9.
7. Wolide AD, Zawdie B, Alemayehu T, et al. Association of Trace metal elements with lipid profiles in type2 Diabetes mellitus patients: a cross-sectional study. BMC Endocr Disord. 2017;17:64.
8. SunY, Yang J, Wang W, et al. The beneficial effects of Zn on Akt –mediated insulin and cell survival signaling pathways in Diabetes. J Trace elements Med Biol. 2018;46:117-27.
9. Zhang Q, Sun X, Xiao X, et al. Dietary chromium restriction in pregnant mice changes the methylation status of hepatic changes involved with insulin signaling in adult male offspring. PLoSONE. 2017;12:e0169889.
10. Kaur KK, Allahbadia GN, Singh M. An Update on Etiopathogenesis and Management of Type 1 Diabetes Mellitus. Open Access J Endocrinol. 2017;1(2):1-23.
11. Kaur KK, Allahbadia GN, Singh M. An update on the Immunotherapy Strategies for the treatment of Type 1 Diabetes (TID)-How far have we reached in reaching insulin independency in TID therapy.-A Systematic Review. An Update on the Immunotherapy Strategies for the Treatment of Type 1 Diabetes (TID)-How Farhave we Reached in Reaching Insulin Independency in TID therapy-A Systematic Review. J Endocrinol. 2020;4(1);1-15.
12. Kaur KK, Allahbadia GN, Singh M. Path Directed towards a Stage when we almost Cure Type1 Diabetes Mellitus (T1dm) aftera Century of Insulin Advent". EC Diabetes Metab Res. 2020;4.6:37-46.
13. Kaur KK, Allahbadia GN, Singh M. How to classify type 2 diabetes mellitus and approach its treatment in view of associated diabetes and complications-a short communication. Series Endo Diab Met. 2019;1(2):29-34.

14. Kaur KK, Allahbadia GN, Singh M. An Update on Management of Diabetic Neuropathy with Diabetic Foot Syndrome-Optimization of Therapy Cost Effectively with Avoidance of Gangrene and Amputation-A Systematic Review. J Endocrinol 2020, 4(1):000145.
15. Kaur KK, Allahbadia GN, Singh M. Advantage of Cardiovascular Outcome Trials (CVOT's) for SGLT2 (Sodium Glucose Transporter 2) Inhibitors in Type 2 Diabetes Mellitus (T2 DM)". EC Endocrinol Metab Res. 2019;4.9:38-44.
16. Kaur KK, Allahbadia GN, Singh M. How can we use Empagliflozin as an adjuvant in reducing required need of insulin in type1 diabetes along with lowered HbA1c,weight without fear of DKA.-A Minireview. J Clin Cases Rep. 2020;4(2):30-08.
17. Kaur KK, Allahbadia GN, Singh M. Utilization of Extracellular Vesicles for Treatment of Type 1 Diabetes Mellitus (T1DM) Along with Type 2 Diabetes Mellitus (T2DM) besides Complications Associated with Diabetes- A Systematic Review. J Clin Diabetes Obes. 2020;1:001-013.
18. Kaur KK, Allahbadia GN, Singh M. Are we any close to unraveling the mechanisms of interactions among Susceptibility genes towards type 1 Diabetes, Gut Microbiota along with Environmental factors -Specifically Early Diet patterns - A Systematic Review? Endocrinol Surg Endocrinol. 2021;2(1):1-20.
19. Kaur KK, Allahbadia GN, Singh M. Potential role of Epigenetic Modulation in prevention or therapy for Diabetic Kidney Disease-still a dream or a reality - A Systematic Review. J Diab Nephrop Diabetes Manage. 2021;1(1):1-26.
20. Kaur KK, Allahbadia GN, Singh M. Can Vitamin D Supplementation prevent / delay/ halt the progression of Diabetic nephropathy; A Systematic Review on mechanism of Vitamin D Crosstalk with Vitamin D Receptor, with others like Megalin-Cubilin and Amnioless Complex along with FGF23-Klotho Complex.''2021-under review.
21. Kaur KK, Allahbadia GN, Singh M. Would it be advantageous utilizing beta cell therapies over immunotherapies for avoidance of Type 1 Diabetes-A Systematic Review on the role of beta cells in etiopathogenesis of Type 1 Diabetes along with treatments targeting beta cells or combination therapy would be better. Aditum J Clin Biomed Res. 2021;1(2):1-13.
22. Kaur KK, Allahbadia GN, Singh M. Importance of simultaneous treatment of obesity and diabetes mellitus: A sequelae to the understanding of diabesity-A review. Obes Res Open J. 2019;6(1):1-10.
23. Kashiv Y, Austin JR, Lai B, et al. Imaging Trace elements distribution in single organelles and subcellular features. Sci Rep. 2016;6:21437.
24. Derakhshanian H, Javanbakht M, Zarei M, et al. Vitamin D increases IGF1 and insulin levels in experimental Diabetic rats. Growth Horom IGF Res. 2017;36:57-59.
25. Sujatha P. Trace elements in Diabetes mellitus. J Clin Diagn Res. 2013;7:1863-5.
26. Uluisic I, Karakaya HC, Koc A. The importance of boron in biological systems. J Trace Elements Med Biol. 2018;45:156-62.
27. Khaliq H, Juming Z, Ke-Mei P. The physiological role of boron in health. Biol Trace Elements Res. 2018;186:31-51.
28. Bakken NA, Hunt CD. Dietary boron decreases peak pancreatic in situ insulin release in chicks and plasma insulin concentrations in rats regardless of Vitamin D or magnesium status. J Nutr. 2003;133:3577-83.
29. Dubey P, Thakur V, Chattopadhyay M. Role of minerals and Trace elements in Diabetes mellitus and insulin resistance. Nutrients. 2020;12:1864.

30. Ablikim M, Achasov MN, Albayrak O, et al. Observation of a charged ($DD^{*}$) ± Mass Peak ine +e-→π($DD^{*}$)ats=4.26.GeV. Phys Rev Lett. 2014;112:022001.
31. Caglar GS, Cakal GO, Yuce E, et al. Evaluation of serum boron levels and with lipid profiles in pregnancies with or without gestational Diabetes. J Perinatal Med. 2012;40(2):137-40.
32. Dogan A, Demirci S, Apdik H, et al. A new hope for obesity management: boron inhibits adipogenesis in progenitor cells through the Wnt/ β-cateninpathway. Metabolism. 2017;69:130-42.
33. Coban FK, Ince S, Kuckukkurt I, et al. Boron attenuates malathion -induced Oxidative stress and acetyl cholinesterase inhibition in rats. Drug Chem Toxicol. 2014;38:391-9.
34. Ozcan L, Tabas I. Calcium signaling and ER Stress in insulin resistance and Atherosclerosis. J Int Med. 2016;280:457-64.
35. Chen C, Jiang W, Zhong N, et al. Impaired processing speed and attention in first -episide drug -naïve schizophrenia with deficit syndrome. Schizophr Res. 2014;159:478-84.
36. Pittas AG, Lau J, Hu FB, et al. The role of Vitamin D and Calcium in type2 Diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab. 2007;92:2017-29.
37. Abbas WA, Al-Zubaidi MA, Al-Khazraji SK. Estimation of serum Calcium and parathyroid hormone (Phh) levels in Diabetic patients in correlation with age and duration of disease. J Community Med. 2012;25(2):161-4.
38. Kanchana N, Saikumar P. Serum Calcium Levels in type2 Diabetes mellitus. IOSR J Dent Med Sci. 2014;13:1-3.
39. Hassin SAE. Serum Calcium Levels in correlation with glycated haemoglobin in type2 Diabetes Sudanese patients. Adv Diabetes Metab. 2016;4:59-64.
40. Chen S, Itoh Y, Masuda T, et al. Subnanoscale hydrophic modulation of salt bridges in aqueous media. Science. 2015;348:555-9.
41. Kim MK, Kim G, Jang EH, et al. Altered Calcium homeostasis is correlated with the presence of metabolic syndrome and Diabetes in middle aged and elderly Korean subjects: The Chungju Metabolic Disease Cohort study(CMC study). Atherosclerosis. 2010;212:674-81.
42. Sun G, Vasdev S, Martin G, et al. Altered Calcium homeostasis is correlated with abnormalities of fasting serum glucose, insulin resistance and cell function in the new founded population. Diabetes 2005;54:3336-9.
43. Ly LD, Xu S, Choi SK, et al. Oxidative stress and Calcium dysregulation by palmate in type2 Diabetes. Exp Mol Med. 2017;49:e291.
44. Henquin JC. The dual control of insulin secretion by glucose involves triggering and amplifying pathways in β-cells. Diabetes Res Clin Pract. 2011;93:S27-S31.
45. Gijsbers L, Ding EL, Malik VS, et al. Consumption of dairy foods and Diabetes incidence: A dose - response meta-analysis of Cohort studies. Am J Clin Nutr. 2016;103:1111-24.
46. Saker F, Ybarra J, Leahy P, et al. Glycaemia - lowering effect of Cobalt chloride in the Diabetic rat: role of decreased gluconeogenesis. Am J Physiol Content. 1998;274:E984-91.
47. Yildrim O, Buyukbingol Z. Effect of Cobalt on the Oxidative status in heart and aorta of streptozocin-induced Diabetic rats. Cell Biochem Funct. 2002;21:27-33.
48. Cao J, Vecoli C, Neglia D, et al. Cobalt-Protoporphyrin improves heart function by blunting Oxidative stress and restoring NO-Synthase equilibrium in an animal model of experimental diabetes. Front Physiol. 2012;3:160.

49. Anjum A. Comparative study on Calcium, magnesium and Cobalt in Diabetic and nondiabetic patients (males) in Punjab, Pakistan. Afr J Biotechnol. 2012;11:7258-62.
50. Flores CR, Puga MP, Wrobel K, et al. Trace elements status in Diabetes mellitus type2: possible role of interaction between molybdenum and copper in the progress of typical complications. Diabetes Res Clin Pract. 2011;91:333-41.
51. Tsubamoto Y, Eto K, Noda M, et al. Hexammine Cobalt (III) chloride inhibits glucose induced insulin secretion at the exocytic process. J Boil Chem. 2000;276:2979-85.
52. Mertz W, Schwartz K. Impaired intravenous glucose tolerance as an early sign of Dietary necrotic liver degeneration. Arch Biochem Biophys. 1955;58:504-06.
53. Andersen RA, Polansky MM, Bryden NA, et al. Chromium supplementation of human subjects: effects of glucose, insulin, and lipid variables. Metabolism. 1983;32:894-9.
54. Chen ZC, Ma JF. Improving nitrogen use efficiency in rice through enhancing root nitrate uptake mediated by a nitrate transporter NRT1.1B. J Genet Genom. 2015;42:463-5.
55. Cheng Y, Ma W, LiX, et al. Polyamines -stimulated hyphal branching and infection in the early stage of Giomus etunicatum colonization. World J Microbiol Biotechnol. 2011;28:1615-21.
56. Andersen RA. Nutritional factors influencing the glucose /insulin system: Chromium. J Am Coll Nutr. 1997;16:404-10.
57. Offenbacher EG, Rincko CJ, Pi-Sunyer FX. The effects of inorganic Chromium and brewer's yeast on glucose tolerance, plasma lipids and plasma Chromium in elderly subjects. Am J Clin Nutr. 1985;42:454-61.
58. Cefalu WT, Rood J, Pionsonat QP, et al. Characterization of the Metabolic and physiological response to Chromium supplementation in subjects with and without non insulin-dependent Diabetes. Metab Clin Exp. 2009;59:755-62.
59. Vrtovec M, Vrtovec B, Brisky A, et al. Chromium supplementation shortens QTc interval duration in patients with type2 Diabetes mellitus. Am Heart J. 2005;149:632-66.
60. Wang ZQ, Qin J, Martin J, et al. Phenotype of subjects with type2 Diabetes mellitus may determine clinical response to Chromium supplementation. Metab Clin Exp. 2007;56:1652-5.
61. Wells JC, Classen JP, Andersen RA. A test for adequacy of Chromium Nutrition in human-relation to type2 Diabetes mellitus. Biochem Biophys Res Commun. 2003;303:825-7.
62. Mertz W. Chromium in human Nutrition: A review. J Nutr. 1993;123:626-33.
63. Vincent JB. Elucidating a biological role for Chromium at a molecular level. Acc Chem Res. 2000;33:503-10.
64. Kazi TG, Afridi HL, Kazi N, et al. Copper, Chromium, manganese, iron, nickel and zinc levels in biological samples in Diabetes mellitus patients. Biol Trace elements Res. 2008;122:1-18.
65. Balk E, Tatesioni A, Lichtenstein AH, et al. Effect of Chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled Clinical trials. Diabetes Care. 2007;30:2154-63.
66. Andersen RA. Chromium, glucose intolerance and Diabetes. J Am Coll Nutr. 1998;17:548-55.
67. Rajendran K, Manikandan S, Nair L, et al. Serum Chromium levels in type2 Diabetic patients and its association with glycaemic control. J Clin Diagn Res. 2015;9:OC05-8.
68. Sundaram B, Aggarwal A, Sandhir R. Chromium picolinate attenuates hyperglycemia-induced Oxidative stress in streptozocin- induced Diabetic rats. J Trace elements Med Biol. 2013;27:117-21.
69. Markou K, GeorgopoulousN, KyriazapoulouV, et al. Iodine -induced hyperthyroidism. Thyroid. 2001;11:501-10.

70. Sun Z, Wang X, Chen J, et al. Effects of Iodine excess on islet beta cells(beta-TC-6) function and mechanism. J Hyg Res. 2017;46:610-14.
71. Sabekti I, Pramono LA, DewiastyE, et al.Thyroid dys function in Diabetes mellitus type2 Diabetes mellitus patients. Acta Med Indones. 2017;49:314-23.
72. Al-Attas OS, Al-DaghriN, Alkharfy KM, et al. Urinary Iodine is associated with insulin resistance in subjects with Trace elements Diabetes mellitus type2. Exp Clin Endocrinol Diabetes. 2012;120:618-22.
73. Rogowicz-Front czak A, Pilacinski S, Chwialkowska AT, et al. Insulin resistance is associated with larger thyroid volume in adults with type1 Diabetes independently from presence of thyroid autoimmunity. Scand J Clin Lab Invest. 2018;78:287-92.
74. Coopan R, Kozac JP. Hyper thyroidism and Diabetes mellitus. An analysis of 70 patients. Arch Int Med. 1980;140:370-03.
75. Anil C, Akkurt A, Ayturk S, et al. Impaired glucose metabolism is a risk factor for increased thyroid volume and nodule Prevalence in a mild-moderate Iodine-deficient area. Metab Clin Exp. 2013;62:970-05.
76. Michaelek AM, Mahoney MC, Calebaugh D. Hypothyroidism and Diabetes mellitusin an American Indian population. J Farm Pract. 2000;49:638.
77. Fernandez Real JM, McClain D, Manco M. Mechanisms linking glucose homeostasis and Ironmetabolism towards the onset and progression of type2 Diabetes. Diabetes Care. 2015;38:2169-76.
78. Fernandez Real JM, Lopez-Bermejo A, Ricart Engel W. Crosstalk between Ironmetabolism and Diabetes. Diabetes. 2002;51:2348-54.
79. Lao TT, Chan PL, Tam KF. Gestational Diabetes mellitus in the last trimester - a feature of maternal excess? Diabetic Med J Br Diabet Assoc. 2001;18:218-23.
80. Thomas M, Mac Isaac RJ, Tsalamandris C, et al. Unrecognized anaemia in patients with Diabetes: a cross-sectional survey. Diabetes Care. 2003;26:1164-9.
81. Thomas M, Mac Isaac RJ, Tsalamandris C, et al. Elevated Iron indices in patients with Diabetes. Diabetes Med. 2004;21:798-802.
82. Jiang R, Manson JE, Meigs JB, et al. Body Iron stores in relation to risk of type2 Diabetes in apparently healthy women. JAMA. 2004;291:711-7.
83. Dongiovanni P, Ruscica M, Rametta R, et al. Dietary Iron overload induces visceral adipose tissue insulin resistance. Am J Pathol. 2013;182:2254-63.
84. Krisai P, Leib S, Aeschbaker S, et al. Relationship of Iron metabolism with insulin resistance and glucose levels in young and healthy adults. Eur J Int Med. 2016;32:31-7.
85. Rajpathak SN, Crandall JP, Wylie Rosett J, et al. The role of Iron in type2 Diabetes in humans. Biochem Biophys Acta (BBA)Gen Subj. 2009;1790:671-81.
86. Afkhami-Ardekani M, Rashidi M. Iron status in women with and without Gestational Diabetes mellitus. J Diabetes complicat. 2009;23:194-8.
87. Sharif A, Younus S, Baig K, et al. Prevalence and risk of anaemia in type2 Diabetic patients. Health. 2014;6:1415-9.
88. Huth C, Buerle S, Zierer A, et al. Biomarkers of Ironmetabolism are independently associated with impaired glucose metabolism and type2 Diabetes: The KORA F4 Study. Eur J Endocrinology. 2015;173:2643-53.

89. Gonzalez-Dominguez A, Visiedo Garcia FM, Dominguez-Riseart J, et al. Iron metabolism in obesity and metabolic syndrome. Int J Mol Sci. 2020;21:5529.
90. Lopez-Ridaura R,Willett WC, Rimm EB, et al. Magnesium intake and risk of type2 Diabetes in men and women. Diabetes Care. 2004;27:134-40.
91. Dibaba DT, Xun P, Fly AD, et al. Dietary Magnesium intake and risk of Metabolic Syndrome: A meta-analysis. Diabet Med. 2014;31:1301-09.
92. Liu M, Jeong EM, Liu H, et al. Magnesium supplementation improves Diabetic mitochondrial and cardiac diastolic function. JCI Insight. 2019;4(1):e123182.
93. Pham PCT, Pham SV, Miller JM. Hypomagnesmia in patients with type2 Diabetes mellitus. Clin J Am Soc Nephrol. 2007;2:366-73.
94. Paoliso G, Ravussin E. Intracellular Magnesium and insulin resistance: results of Pima Indians and Caucasians. J Clin Endocrinol Metab. 1995;80:1382-5.
95. Djurhuus M, Klitgaard N, Pedersen K, et al. Magnesium reduces insulin-stimulated glucose uptake and serum lipid concentrations in type1 Diabetes. Metab Clin Exp. 2001;50:1409-017.
96. Rosique-Esteban N, Guasch-Ferre M, Hernandez-Alonso P, et al. Dietary Magnesium and cardiovascular disease: a review with emphasis on epidemiological studies. Nutrients. 2018;10:168.
97. Esaris N, Mervaala E, Karpapanen H, et al. Magnesium: An update on physiological, clinical and analytical aspacts. Clin Chim Acta. 2000;294:1-26.
98. Barbagallo M, Dominguez LJ. Magnesium metabolism in type2 Diabetes mellitus. Arch Biochim Biophys. 2007;458:40-07.
99. Victorinova A, Toserova E, Krizko M, et al. Altered metabolism of copper, zinc and Magnesium is associated with increased level of glycated haemoglobin in patients with Diabetes mellitus. Metab Clin Exp. 2009;58:1477-82.
100. Sales CH, Pedrosa LFC, Lima J, et al. Influence of Magnesium status and Serum Magnesium intake on the blood glucose control in patients with type2 Diabetes. Clin Nutr. 2011;30:359-64.
101. Shah G, Pinaas JL, Lung CC, et al. Tissue specific distribution of malondialdehyde modified proteins in Diabetes mellitus. Life Sci. 1994;55:1343-9.
102. Manal Kamal MS, Naglaa K, Khadega A. Evaluation of trace elements and malondialdehyde levels in typeII Diabetes mellitus. Diabetes Metab Syndr Clin Res Rev. 2009;3:214-8.
103. Spiga R, Chiara Mannino G, Mancuso E, et al. Are circulating $Mg^{2+}$ associated with glucose tolerance profiles and incident type2 Diabetes. Nutrients. 2018;11(10):2460.
104. Malinowska J, Malecka M, Ciepela O. Variations in Magnesium concentrations are associated with increased mortality: Study in an unselected population in hospitalized patients. Nutrients. 2020;12(6):1836.
105. Barragan R, Llopis J, Portoles O, et al. Influence of Demographic and lifestyle variables on plasma Magnesium concentrations and their association with cardiovascular risk factors in a Mediterranean population. Nutrients. 2020;12(4):1018.
106. Wei J, Zeng C, Gong QY, et al. The association between Dietary Selenium intake and Diabetes: a cross-sectional study among middle aged and older adults. Nutr J. 2015;14:18.
107. Bleys J, Navas-Acien A, Guallar E. Serum Selenium and Diabetes in US adults. Diabetes Care. 2007;30:829-34.

108. Hwang DY, Seo S, Kim Y, et al. Selenium acts as an insulin like molecule for the down regulation via endoplasmic reticulum stress and insulin signaling proteins in Diabetes induced non-obese diabetic mice. J Biosci. 2007;32:723-35.
109. Stranges S, Sieri S, Vinceti M, et al. A prospective study of Dietary Selenium intake and risk of type2 Diabetes. BMC Public Health. 2010;10:564.
110. De Vega RG, Fernandez- Sanchez ML, Fernandez JC, et al. Selenium levels and glutathione peroxidase activity in the plasma of patients with type II Diabetes mellitus. Int J Pharma Biosci. 2016;37:44-9.
111. Park K, Rimm EB, Siscovick DS, et al.Toenail Selenium and incidence of type2 Diabetes in US men and women. Diabetic Care. 2012;35:1544-51.
112. Lu CW, Chang HH, Yang KC, et al. High Serum Selenium levels are associated with increased risk of type2 Diabetes mellitus independent of central obesity and insulin resistance. BMJ Open Diabetic Res Care. 2016;4(1): e000253.
113. Foster M, Samman S. Zinc and regulation of inflammatory cytokines: implications for cardiometabolism disease. Nutrients. 2012;4:676-94.
114. Kloubert V, Rink L. Zinc as a micronutrient and its preventive role of Oxidative damage in cells. Food Funct. 2015;6:3195-204.
115. Li YY. Zinc and insulin in pancreatic beta cells. Endocr. 2013;45:178-89.
116. El Dib R, Gameiro OLF, Ogata MSP, et al. Zinc supplementation for the Prevalence of type2 Diabetes mellitus in adults with insulin resistance. Cochrane Database Syst Rev. 2015:CD005525.
117. Bandeira VDS, Pires LV, Hasimoto LL, et al. Association of reduced Zinc status with poor glycaemic control in individuals type2 Diabetes mellitus. J Trace elements Med Biol. 2017;44:132-6.
118. Maher M, Ahmed SRH. A Study of Serum Magnesium, copper, zinc and status and glycohaemoglobin in children with type1 Diabetes mellitus. Alex J Pediatrics. 2002;16:285-9.
119. Aly HF, Mantawy MM. Comparative effects of Zinc, Selenium and Vitamin E or their combination on carbohydrate Metabolising enzymes and Oxidative stress in streptozocin-induced Diabetic rats. Eur Rev Med Pharmacol Sci. 2012;16:66-78.
120. Abu Seif MA, Youssef AA. Evaluation of some biochemical changes in Diabetic patients. Clin Chim Acta. 2004;346:161-70.
121. El Zabda GA. Significance of Serum levels of copper and in zinc in type II Diabetic, hypertensive and Diabetic hypertensive patients in Gaza City. Available online: http//library.jugaza .edu.ps/thesis/220pdf(accessed june 22, 2020).
122. Estakhry M, DjaazayeryA, Eshraghian MR, et al. Serum zinc in levels in children and adolescents with type1 Diabetes mellitus. Iran J Public Health. 2011;40:83-8.
123. Xu J, Zhou Q, Liu G, et al. Analysis of Serum and urinal copper and zinc in Chinese North east population with pre Diabetic or Diabetics with and without complications. Oxid Med Cell Longev. 2013;2013:1-11.
124. Meenakshi PUG, Nayyar SB. Comparative study of Serum Zinc, Magnesium and copper levels among patients with type2 Diabetes mellitus with and without microangiopathic complications. Innovat J Med Health Sci. 2013;3:274-8.
125. Anil Kumar VSPD, Jaiprabhu J, Krishnan R. Serum copper and in zinc levels Significance in type 2 Diabetic patients. J Med Sci Tech. 2014;3:79-81.

126. Gagandeep DSJ, Shailaza S, Rahul R. Evaluation of trace elements and glycated haemoglobin in type2 Diabetes mellitus. World J Pharm Pharm Sci. 2015;14:940-07.
127. Hasanto RM. Trace elements in type2Diabetes mellitus and their association with glycation control. Afr Health Sci. 2020;20(1):287-93.
128. Tabassum A, Zaidi SNF, Yasmeen K, et al. Potential role of Peroxisome Proliferator Activated Receptor gamma activation on Serum visfatin and Trace elements in high fat diet inducedtype2Diabetes mellitus. Life Sci. 2018;205:164-75.