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CARDIOVASCULAR DISEASE RISK FACTORS AND TRACE ELEMENTS: A SYSTEMATIC REVIEW WITH SPECIAL EMPHASIS ON SOUTH ASIAN POPULATION

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ABSTRACT

Background: The neoteric industrialization has deliberately uplifted the exposure of several heavy trace elements leading to multiple ecological and public health burdens like cardiovascular diseases (CVDs). **Aim of the study:** Thus, the present review aims to elucidate the extent of association of trace elements with CVD risk factors. **Methodology:** 78 full-length papers considering only human subject from peer-reviewed journals were reviewed using Google Scholar, PUBMED, Research Gate and by manual searching. **Result:** Findings suggest elevated level of the essential trace elements like zinc, copper, chromium, selenium, iron and manganese as well as the noxious metals like mercury, cadmium and lead alter glucose and insulin homeostasis, lipid metabolism, hypertensive disorders and obesity.

Conclusion: Hence, it seems reasonable to argue that trace elements have significant contribution in developing CVD.

Keywords: trace elements, metal toxicity, CVD risk factors, metabolic syndrome and ethnicity

INTRODUCTION

Cardiovascular disease (CVD) has become a global health burden causing 31% death in the worldwide population.[1] CVD is the congregation of several clinical sequels including atherosclerosis, coronary heart disease (CHD), heart attack, and stroke etc. The pervasiveness of CVD can only be prevented by modifying the lifestyle factors like increasing physical activity, relinquishing unhealthy diet, smoking and alcohol etc. The most common factors for predicting the CVD risk are impaired lipid metabolism, impaired glucose metabolism and hypertension (HT) and obesity which are apparently the consequences of an unhealthy lifestyle.

Further extending the investigation beyond the conventional risk factors in the CVD epidemiology, abundant evidence of underlying role of several trace elements is available from researches since decades. The essential, non-toxic elements like zinc (Zn), copper (Cu), chromium (Cr), selenium (Se), iron (Fe), manganese (Mn) bear vital role in vascular system by catalyzing many enzymatic activities, regulating the metabolic and immune system and preventing the oxidative stress and inflammation in the cellular membranes: the two principal factors of

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cardiac dysfunction. Besides, the non-essential toxic elements broadly mentioned in numerous studies are mercury (Hg), cadmium (Cd), and lead (Pb). These are the oxidative stress inducing metals with fatal effect in the oxidative defense, lipid metabolism, mitochondrial function and immune system.

Since a few decades, an increasing concern regarding the ecological and public health burden due to heavy metals exposure has transpired. Plentiful literatures can be found from different global zones specifically focused on the association of CVD risk with the metal toxicity. Although these trace elements can affect different organs in the body, the present study is an attempt to enlighten the association of CVD risk with the metal toxicity in human.

OBJECTIVE AND HYPOTHESIS OF THE STUDY

The present review aims to elucidate the association of the trace elements with CVD risk factors with the hypothesis that there existed significant association between available trace elements in the body and CVD risk factors.

MATERIALS AND METHODS

We did a literature search using Google Scholar, PUBMED and Research Gate to identify the relevant studies of the selected topic from the year 1965 till date. 78 papers were reviewed out of which 30 papers were collected from Google Scholar, 30 from PUBMED and 11 from Research Gate. Besides, 7 papers were retrieved by manual searching. These papers have been selected from the peer-reviewed journals and studies from all countries across the world were taken into consideration. Local journal were not included in the study. Only full-length papers were considered for the review. The keywords used for the literature search are ‘cardiovascular disease’, ‘cardiovascular risk’, ‘trace elements’, ‘zinc’, ‘copper’, ‘chromium’, ‘selenium’, ‘iron’, ‘manganese’, ‘mercury’, ‘cadmium’, ‘lead’, ‘cobalt’, ‘molybdenum’ ‘diabetes mellitus’, ‘dyslipidaemia’, ‘hypertension’, ‘metabolic syndrome’, ‘obesity’ and ‘metal toxicity’. Researches on only the human subject were selected for the review.

FINDINGS

Zinc:

Zn builds the structure of 10% of proteome in human body which includes nitric oxide synthase that regulates the blood pressure (BP) and several cardiovascular functions. An altered Zn homeostasis is associated with increased lipid oxidation, HT and several cardiovascular complications like myocardial infarction and atherosclerosis.[2] A follow-up study reported low serum Zn level to multiply the odds of CHD and CHD mortality[48] while another study reported high serum Zn level among the atherosclerotic and hypertensive patients.[57] A follow-up study revealed high Zn level among the hypertensive pregnant mothers and baby’s Apgar score increased with maternal Zn level.[60]

Many clinical studies have documented decreased level of serum and/or urinary Zn among the diabetic individuals.[17,24,42,49,50] Serum Zn level showed positive association with the risk of impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM)[23] Again, higher Zn level in maternal blood and umbilical artery was revealed among the obese pregnancies with gestational diabetes (GDM).[47] Although a clinic-based study from Kashmir showed no association between Zn and diabetes.[56]

Zn plays vital role in the metabolic process in human body. A Korean survey revealed decreased Zn level to increase the odds of hypoglycemia and hypertriglyceraemia and increased the number of metabolic syndrome (MS) factors and serum Zn level.[30] A decreased level of serum and erythrocytic Zn was found among the obese women in a case-control study and the body mass index (BMI) and waist circumference (WC) showed significant association with the Zn level of both groups.[35,40]

Zn activates the key signaling molecules essential for the glucose homeostasis and lipid metabolism. Zn obliquely regulates the BP by controlling the sodium absorption and excretion in kidney through sodium chloride

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co-transporter pathway. Thus a Zn supplementation can be useful in therapeutic implication for treating diabetes and dyslipidemia.[33,38] Contrarily, statin treatment significantly reduced Zn level among the hyperlipidemic adults.[51]

Zinc-α glycoprotein is an adipokine with the ability to influence obesity, fertilization and lipid regulation. An elevated level of Zinc-α glycoprotein increased the BMI, WC, DBP, TG and CRP and decreased the BG, creatinine, fasting insulin and HDLC which suggests its association with the development of MS.[40,46]

Copper:

Cu plays important role in regulating the functions of Cu-dependent proteins and the immune system. Deficit Cu contributes reduced metabolism and energy supply to the heart which provokes the ischemic heart attack. Cu ions catalyze the lipoprotein oxidation and prevent oxidative modification of superoxide dismutase (SOD). Cu dysregulation increases the susceptibility of lipoprotein oxidation and HbA1C and total cholesterol (TC) level by increasing hydroxymethylglutary-coenzyme.[3] Positive association of Cu level with HbA1C has been revealed by several studies.[17,24,26] Elevated serum Cu increases TC, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC)[11,43] and TG.[27] A lipid-lowering treatment among the hyperlipidaemic patients showed significant reduction in serum Cu, ceruloplasmin and Zn/Cu ratio in a clinical study from England.[51]

Cu ions promote the reactive oxygen species (ROS) through Fenton reaction which develops diabetes. Several studies reported elevated serum Cu among the patients of IGT and T2DM.[17,24,32,39] Higher level of Cu in maternal blood, their umbilical artery and vein was found among the GDM obese mothers.[47] Blood glucose (BG) was positively correlated with Cu level among the schizophrenic patients.[27]

Several clinical studies have revealed elevated Cu level to have proportional relationship with atherosclerosis and CHD[18,57,59]

A Cu deficiency can bring alternation in the arterial pressure. A proportional relationship between diastolic blood pressure (DBP) and the serum Cu level among the European schizophrenic patients substantiate the statement.[27]

Chromium:

Cr is a vital element for normal lipid metabolism. Cr felicitates insulin signaling hence its deficiency leads to prediabetes which enhances T2DM, MS and other cardiovascular abnormalities.[4] Deficiency in serum Cr leads to elevated BG, insulin, lipid molecules. Majority of studies have focused in the association of Cr level with developing diabetic condition and insulin resistance (IR). Significantly low serum Cr level[12,32,49] and higher urinary Cr[12,29,49] among the diabetic patients have been reported by many researchers. Higher urinary Cr was also reported among the high IR group of Saudi Arabia.[34] Furthermore, Lower Cr in scalp hair was reported in diabetic patients in relation to controls.[49]

Cr-induced oxidative stress stimulates a cluster of cellular activities like increased production of superoxide anion and hydroxyl radicals, increased lipid peroxidation, alternation of intercellular oxidized states etc. which elevates risk of CVDs. A proportional association of Cr level with the C-reactive protein (CRP) is evident from a clinical study of US.[39] An inverse association of toe-nail Cr with CVD risk among both the diabetic and non-diabetic individuals was found in another Spanish study.[15]Association of low Cr level with HT, obesity and dyslipidemia[12] further indicates the influence of Cr concentration on the development of MS.

Selenium:

Se restrains lipid peroxidation through glutathione peroxidase(GPx) and selenoprotein and controls cholesterol accrual in the blood vessels. The association of hyperlipidemia with high Se level is evident in studies.[5] Researchers also suggest the association of Se with obesity for its role in adipocyte hypertrophy and adipogenesis.[6]

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Se, for its anti-oxidant properties, is considered as a regulator of BP by reducing ROS. Significantly reduced serum and hair Se and higher urinary Se was observed among hypertensive subjects in a case-control study.[22] Again, reduced serum Se and GP_x concentration in preeclamptic (PE) mothers and their babies was observed in another case-control study. Moreover, significantly reduced placental GP_x activity among PE mothers was found.[19]

The positive association of Se level with the MS factors[43] suggests its association with the development of MS. Higher plasma Se concentration of women with MS and increasing odds of MS with increasing plasma Se were reported in a study.[37] Se is certainly an essential factor for preventing oxidative stress and inflammation; hence, its dysregulation is presumed to intensify the risk for CVD mortality as well.[45]

Iron:

Fe plays vital role in the transportation of oxygen, regulation of enzyme actions and neurotransmitter metabolism. Fe deficiency may lead to dyslipidaemia, deregulation of immune system and development of CVDs. Lack of cardiac hepcidin leads to heavy Fe load in the heart causing several cardiac dysfunctions. The iron-regulatory protein has crucial role in the regulation of BP hence its deficiency may lead to pulmonary HT.[7]

Positive association of BP with Fe and ferritin was reported by a clinical study. The study also reported decreased LDLC/HDLC ratio and heart rate after Fe reduction from the phlebotomic patients.[31]

Association of Fe with the development of diabetic condition has been confirmed by many studies. A clinical trial revealed decreased BG and HbA1C level with Fe reduction; HOMA IR showed significant association with ferritin reduction.[31] An Iranian study reported positive association of Fe with HbA1C and significantly reduced Fe among the T2DM patients and their first-degree relatives.[17] Lower Fe in maternal serum and higher Fe in umbilical artery and umbilical vein were found in GDM obese pregnancies.[47] High Fe level in both blood and scalp hair in diabetic patients was revealed in another case-control study.[49]

Manganese:

Mn is an essential trace element for its significant role in the synthesis and activation of several enzymes and BG and lipid metabolism.[8] An optimal Mn level is needed to maintain as its elevation exacerbates the production of ROS, induced oxidative stress and inflammation of leading to cardio-vascular abnormalities.

Mn is pre-eminently notified for its neurological toxicities while its role in the cardiovascular dysfunction is less scrutinized till date. Overexposure of Mn depreciates cardiac contraction multiplying the risk of myocardial infarction.[9] An elevated level of serum Mn has been reported among the patient of CHD and congestive heart failure.[71,74]

With the vasodilation activities Mn can potentially control the BP in human body. Multiple literatures have documented elevated level of Mn to have association with hypertension. A doubled concentration of serum Mn can 1.5fold the risk of hypertension among the non-pregnant individual while a case-control study has parallelly reported its strong association with the development of gestation hypertension as well (OR= 47.0 and 5.5 for the 1^{st} and 2^{nd} trimester respectively).[47,38] Reduced serum Mn is also accounted among the preeclamptic women in a case-control study.[39]

A deficiency in Mn level disrupts the activity of MnSOD (a mitochondrial antioxidant enzyme) which prevents the islets cells from increased ROS production. The islet cells regulate the production of insulin and glucagon which control the optimal level of blood sugar in the human body. Multiple studies can be found documenting an elevated level of Mn level to induce the development of IR and T2DM.[59,24,25]

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Although the association of Mn with dyslipidaemia in animals are abundant but information in human is scarce. However, a study has documented inverse association of Mn level with TG.[12] Another cohort study showed higher level of serum Mn among the dyslipidemic smokers.[21]

Obesity is a state of persistent oxidative stress which can be produced by the dysregulation of MnSOD. A positive association of MnSOD polymorphism with obesity (Adjusted OR 1.949) has been denoted in a Brazilian study.[54]. Another Polish clinical study reported higher concentration of serum Mn among both underweight and obese pregnant women.[15]

Although the association of MS factors with the Mn level is evident but no significant association could be found in the existing literatures.[13,9]

Mercury:

Hg squelches the catecholamines including epinephrine, neropinephrine and dopamine which subsequently develop HT. Individuals with higher level of blood Hg are susceptible to dyslipidaemia, HT, CHD, myocardial infarction, atherosclerosis, cardiac arrhythmias etc.[10]

Higher Hg level in blood, urine and hair scalp of hypertensive individuals were reported by a Pakistani case-control study.[22] Another study also reported a strong dose-dependent relationship of high serum Hg with BP.[28] HT proportionally developed with serum Hg in a Korean population.[25] Few studies have also reported influence of Hg on diabetic condition. Higher level of serum Hg was observed among the patients of T2DM compared to the healthy individuals.[32] Highest tertile of blood Hg 11folded the odds of IR in a study.[36]

A population-based study reported increasing Hg concentration double the odds of MS; BMI, WC, DBP, TC and TG significantly increased with the increasing serum Hg level.[25] Another study reported elevated Hg level among the individuals with MS.[30]

Cadmium:

Cd is another carcinogenic, oxidative stress inductive element, the exact mechanism of which is not well-known till date. However, the studies suggest increased Cd level to have positive association with development of T2DM, HT and dyslipidaemia. Cd instigates the oxidative stress in vascular tissues by triggering nicotinamide adenine dinucleotide phosphate oxidases and xanthine oxidase and disjoining the endothelial nitric oxide synthase. Cd obliquely escalates the lipid peroxidation by generating ROS and disrupts glucose homeostasis by reducing glucose transport in the adipose and renal tissues.[11]

Positive association between blood Cd level and T2DM is documented in the case-control studies.[20,32]

Association of Cd level with the dyslipidemia is substantiated from the outcomes of a Korean survey which revealed an inverse association of low HDLC and a proportional relationship of elevated TG/HDLC ratio with the blood Cd concentration.[30]

Serum Cd level was significantly higher among the hypertensive individuals in a South Korean case-control study. The highest tertile of blood Cd level ~1.5folded the odds of HT.[44] Another case-control study

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revealed significantly higher concentration of Cd among the hypertensive mothers.[54] Similar result was obtained from other studies also.[61,62,64] A study reported patients died due to hypertensive causes to have significantly higher renal Cd than the other cases.[65] Higher level of blood Cd decreased the odds of obesity by 0.46 times.[14]

Association of Cd concentration with T2DM, HT and dyslipidaemia suggests its association with the development of MS. It is further confirmed by the outcomes of a Korean survey.[21]

Cigarette smoking is one of the major sources of Cd which increases the Cd level in blood. A markedly elevated Cd level among cigarette smokers than non-smokers was documented in several studies.[54,59,61]

Lead:

Pb ions alter the lipid construction of cell membranes which induces the lipid peroxidation, promotes inflammation, and impairs nitric oxide signaling leading to HT. Individuals, occupationally exposed to Pb were found with markedly higher level of TC and LDLC in a Nigerian study. Blood Pb concentration was proportionally related with the TC and LDLC and the LDLC/HDLC ratio was also higher among the Pb-exposed individuals than controls.[52]

Association of Pb with the HT development was revealed in a study from Poland. In the study, malondialdehyde (MDA), GP_x, and SOD activity was significantly higher among the higher-normotensive Pb-exposed group than the normotensive Pb-exposed group. The SBP and DBP increased with increasing blood Pb level, duration of Pb exposure and MDA and decreased with increasing GP_x.[41] Another study from US reported increasing odds of elevated SBP, DBP and HT among the females with highest quartile of blood Pb level. The diastolic HT risk was 8fold among the post-menopausal women with high Pb.[53] Pb exposure increased the risk of HT at the time of delivery in a clinical study among the expected mothers.[58] Association of high blood Pb with the obesity and MS risk is also evident from studies.[14,21]

Other than the above-depicted trace elements, some studies sporadically mentioned the association of cobalt (Co), molybdenum (Mo), barium (Ba), aluminium (Al) and vanadium (V) with the cardio-metabolic anomalies. High serum Co was found to surge the risk of T2DM and obesity.[14,32] High serum Ba ~1.5folded the risk of obesity,[14] high serum Al and V multiplied the risk of T2DM[32] and high serum Mo level was also found among the GDM obese mothers.[47] Elevated Ni in hair scalp may also have some association with the diabetic condition.[49]

DISCUSSION

The neoteric industrialization has contributed to the heavy exposure of several harmful metal wastes rapidly squandered by agriculture, coal power, plants, mines, foundries and smelters etc. which are augmented in the soil and water deranging the bio-chemical cycles and food web.

Hg is one of the most noxious element with no essential role in human metabolism, accumulates in human by methylmercury manifestation through fish and sea-mammals ingestion and dental amalgam. The human body has no mechanism for Hg excretion but Se and omega-3 fatty acid rich fishes can counteract its toxicity. Sustainable use of Hg-substitute materials can also sway the Hg pollution.

The primary anthropogenic resource of atmospheric Cd effusion is the manufacture of quotidian essential non-ferrous metals.[67] Cigarette smoking twice the Cd concentration in human body which passes through the lungs into the body altering several physiological processes.[68] Cd toxicity can be negated by the stabilizing the concentration of Zn and Se. Besides, quitting smoking, restricted use of Cd-containing products and a Zn and Se-rich diet are presumed to be beneficial for intercepting Cd toxicity.

Beside the industrial sources, more than 75% of the gross Pb over the globe is produced from the Pb-acid battery manufacture for motor vehicles. The Pb enters our body through inhalation and consumption of Pb dust,

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water through lead pipes and foods in lead containers. A confined use of Pb-containing products and consumption of calcium, iron and vitamin C rich foods can antagonize its toxicity.

CONCLUSION

From the systematic review of literatures (Table 1 and 2), the Zn, Cu, Cr, Se, Fe and Mn are found with vital role in the glucose and lipid metabolism, oxidative stress and inflammation protection and strengthening of immune system. The predominationg toxic elements were Hg, Cd and Pb which deliberately contributes to the development of CVD by altering its potential risk factors.

Elevated serum Zn increased the susceptibility of CHD, CHD mortality, IGT, T2DM, GDM, MS, obesity, HT, gestational HT. Low urinary Zn had influence of diabetic condition. Serum Cu level maintained a proportional association with lipid molecules, HbA1C, BG, DBP and risk of CVDs.

High serum Cu escalated the risk of IGT, T2DM, GDM, and obesity. Serum Cu was positively associated with CRP and development of MS.

Low serum Cr multiplied the risk of T2DM, HT, obesity, dyslipidemia and altered BG and insulin. High urinary Cr multiplied the risk of T2DM and IR. Withal, the development of T2DM was also influenced by low hair scalp Cr and high toe-nail Cr increased the CVD risk.

Serum Se significantly influenced the development of MS. Low serum Se concentration increased the risk of HT, PE, CVD mortality and reduced placental GPx activity. Low hair Se increased susceptibility of HT.

Increasing serum Fe significantly increased ferritin level and BP. Low serum Fe proliferated the risk of T2DM, GDM, obesity, decreased heart rate, hypoglycemia, and low HbA1C. High Fe in hair also influenced the development of T2DM.

Overexposure of Mn is found to induce cardiac diseases, HT, T2DM and obesity however its mechanism with MS is not clear.

Hg showed a strong dose-dependent relationship with the BP. Increasing serum Hg intensified the menace of obesity, HT, IR, T2DM, MS, hypertriglyceridemia and hypercholesterolemia. High urinary and hair scalp Hg also induced the development of T2DM.

High serum Cd also escalated the susceptibility of T2DM, HT, altered level of lipid molecules and MS. However, it showed a negative association with obesity.

Individuals with prolonged Pb exposure were found with altered lipid level and lipid ratio. High serum Pb also contributed to the developing HT, and obesity. It deliberately reduced the GPx and MDA activities.

A balanced diet with the essential trace elements is beneficial to obligate the metal toxicity.

LIMITATIONS

The trace elements are the sources of the essential micro-nutrients important for optimal growth and development of the human body. The consumption of these micro-elements according to the age-specific reference values has lucrative health effect among the children and adolescents. Among the geriatric population, the absorption of the essential trace elements reduces eventually leading to the phenotypic expression of several lifestyle diseases.

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The noxious effect of pollutant metals depends on several factors i.e. age, gender, genetics and nutritional status of individuals. Majority of literatures in this review are clinical and cross-sectional in nature specifically focused on the patients. Hence, age and sex specific, population-based, longitudinal studies are much needed for the early prediction of many lifestyle diseases.

Foods are the major source of many essential trace elements which greatly differ in several ecological zones and diet pattern is highly influenced by many socio-economic factors (for example, cultural taboos, religion, ethnicity etc.) as well. No such probable solution could be found in any studies to negate the ecological and cultural influence in the prevalence of micro-element deficit cardiac disorders.

Higher prevalence of CVDs with the growing industrialization obliquely suggests the effect of metal toxicity on the regulatory mechanism of certain genes triggering CVDs. However, information in this domain is markedly scarce. Therefore, future studies are expected to emphasize in this area.

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1 Table 1: Trace elements and CVD risk in the global population beyond South India.

Authors	Year	Area	Nature of the Study	Studied Population	Findings
Yang et al.[12]	2020	China	Cross-sectional Cohort	2017 Mn-exposed workers	Time-weighted Mn-level was inversely associated with the TG level (OR 0.51).
Chen et al.[13]	2020	China	Cohort	3272 adults	No significant association between Mn level and MS.
Li et al.[14]	2020	China	Case-control	4134 adults; 2095 with MS and 2039 controls	No significant association between Mn level and MS.
Suliburska et al.[15]	2019	Poland	Case-control	225 singleton pregnancies; 26 underweight, 148 normal and 51 overweight/obese	Higher concentration of serum Mn among both underweight and obese pregnant women.
Leite-Lais et al.[16]	2018	Brazil	Cross-sectional	53 individuals; 27 patients with amyotrophic lateral sclerosis and 26 healthy controls	Cu level of patients was lower and was positively correlated with HDLC in patients. Copper level of control group was positively correlated with TC, HDLC and LDLC.
Ngala et al.[17]	2018	Bolgatanga, Ghana	Case-control	331 adults; 163 patients with T2DM and 168 controls	Patients with T2DM had significantly low Cr level. Low Cr level was associated with HT, obesity and dyslipidemia.
Kyong et al.[18]	2018	Yuengnam, South Korea	Cross-sectional	500 adult individuals	Very mild relation between toe-nail Cr level and development of dyslipidemia.
Jiang et al.[19]	2017	United States	Cross-sectional survey	6602 children (6-19 years aged)	Ba exposure increased the odds of obesity by 1.43 times. Higher level of blood Cd, Co and Pb decreased the odds of obesity by 0.46, 0.56 and 0.57 times,

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					respectively.
Gutiérrez-Bedmar et al.[20]	2017	Spain	Nested case-control	418 adults; 147 patients with CVD and 271 controls	Toe-nail Cr level showed mild association with the CVD risk among both the diabetic patients and controls however; the risk was lower in control group (adjusted OR 1.37 and 0.25, respectively).
Vallejo et al.[21]	2017	Mexico	Cross-sectional Cohort	63 adults	Higher level of serum Mn among the dyslipidemic smokers was found.
Kim et al.[22]	2016	Korea	Cross-sectional Case-control	9880 adults; 4882 males and 4998 females	Higher Pb and Cd level was found in individuals with MS was found. Hg level was higher in females and lower in males with MS. Blood Cd level showed significant difference between MS and controls.
Kheradmand et al.[23]	2016	Iran	Cross-sectional	142 adult patients; 46 with T2DM, 46 non-diabetic 1st degree relatives of the patients and 50 controls	Significantly decreased level of Zn and increased level of Cu and Fe in patients and their 1st relatives in relation to the controls. HbA1C was positively correlated with Cu and Fe level and negatively correlated with Zn in patients and their 1st degree relatives.
Liu et al.[24]	2016	China	Case-control	3228 patients; 1614 diabetic and 1614 controls	Linear association between plasma Mn level and development of T2DM. Compared to the middle tertile of plasma Mn, the lower and higher tertile 1.89 and 1.56folded the risk of T2DM.
Huang et al.[25]	2016	China	Cross-sectional	2042 adults; 964 men and 1438 women	Mild association was observed between the Serum Mn level and prediabetes and diabetes.
Mokhberi et al.[26]	2015	Iran	Cross-sectional	337 patients with chronic	Serum Cu level was significantly higher in the

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				stable angina	atheroscrelotic patients than the normal coronary group. Serum Cu level significantly increased with the severity of atherosclerosis.
Pipkin et al.[27]	2015	Nottingham, England	Case-control	74 women; 27 normotensive pregnancies, 25 preeclamptic pregnancies and 22 non-pregnant women	Significantly reduced serum Se and GP_x concentration in pregnant women than the non-pregnant women. Furthermore, the serum Se and GP_x concentration was more reduced in PE mothers and their babies than the normotensive pregnancies and non-pregnant women. Placental GP_x activity was significantly reduced in PE mothers.
Jin et al.[5]	2015	China	Cross-sectional	1859 individuals of ≥65 years age	Higher Se level was significantly associated with higher TC, HDLC and LDLC.
Barregard et al.[28]	2014	Gothenburg, Sweden	Cohort Case-control	590 geriatric women; 205 with T2DM, 199 with IGT and 186 control	Significant association was found between Cd level in blood and T2DM.
Kim et al.[29]	2014	Korea	Cross-sectional survey	1926 individuals; 939 males and 987 females	With the increasing serum Zn level in males, FBG decreased and TG increased (adjusted OR 0.58 and 1.47, respectively). In females with MS, the serum Zn level decreased with the presence of increasing number of MS components.
Liu et al.[31]	2014	China	Case-control	1796 participants; 218 patients with impaired glucose regulation, 785 patients with T2DM and 793 controls	The risk of impaired glucose regulation and T2DM increased with each 10μg/dL increment of serum Zn level (adjusted odds ratio 0.87 for both). Furthermore, the risk of developing any of the

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					two events was found to increase with each 10μg/dL increment of serum Zn level (adjusted OR 0.88).
Zhou et al.[32]	2013	North-east China	Case-control Cross-sectional	239 adults; 25 with T1DM, 137 with T2DM, 12 with impaired fasting glucose, 15 with IGT and 50 controls	Lower serum Zn and higher urinary Zn level among diabetic patients. Zn/Cu ratio was significantly lower in both prediabetic and diabetic patients. Serum Cu level was significantly higher in prediabetic and T2DM patients than T1DM and control group. Positive association between HbA1C and serum Cu level in T2DM patients.
Park et al.[33]	2013	Korea	Population-based Cross-sectional	2114 healthy adult individuals; 920 men and 1194 women	BMI, WC, DBP, TC and TG significantly increased with the increasing serum Hg level. High Hg level increased the risk of HT and high TG. Odds of MS also increased with increasing Hg concentration (OR 1.56 and 1.99 for middle and highest tertiles, respectively).
Vedović et al.[35]	2013	Serbia, Europe	Case-control	120 individuals; 60 with Schizophrenia and 60 control	BG and DBP were positively correlated with the serum Cu level in schizophrenic patients. Serum TG level was positively correlated with the serum Cu level in healthy controls.
Shah et al.[36]	2013	Hawaii, Ohio and Washington	Multicentre Population-based Observational	193 youths	Hg level and BP were significantly correlated (r=0.94).
Robertson et al.[37]	2013	United Kingdom	Case-control	40 adults; 20 Caucasian males with well-controlled T2DM and 20	Significantly increased urinary recovery of ^{51}Cr-EDTA of diabetic patients compared to the controls. ^{51}Cr-EDTA significantly correlated

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				controls	with their serum CRP level.
Vigeh et al.[38]	2013	Tehran, Iran	Case-control	224 pregnancies; 16 hypertensive and 174 normotensive	Strong association of increased level Mn level in first and second trimester with gestational hypertension (OR= 47.0 and 5.5, respectively).
Kim K[40]	2012	Korea	Cross-sectional	3903 adults	High blood Cd level with the risk of low HDLC. Higher quartile of blood Cd level increased the odds of TG/HDLC ratio (OR 1.36 for 4th quartile and 1.41 for 5th quartile of blood Cd).
Michalsen et al.[41]	2012	Germany	Randomized, controlled, single-blind clinical trial	64 patients of MS; 33 assigned for Fe reduction by phlebotomy and 31 controls	SBP reduced significantly after Fe reduction in the phlebotomy group than the control group. BG, HbA1C, LDLC/HDLC ratio and heart rate significantly decreased after Fe reduction. HOMA IR and BP showed significant association with ferritin reduction.
Wrobel et al.[42]	2011	Mexico	Cross-sectional	76 patients with T2DM	Higher level of serum Al, Cd, copper,Hg and lower level of Cr, Co and V was observed among the patients of T2DM compared to the healthy individuals.
Alissa et al.[44]	2011	Jeddah, Saudi Arabia	Multi-centre Cross-sectional	209 adults; 76 males and 133 females	High urinary Cr level was found in the high IR group.
Marreiro et al.[45]	2011	Brazil	Transectional Case-control	73 pre-menopausal women; 37 obese and 36 non-obese controls	Significant association was found between BMI and WC with Zn in erythrocytes. Zinc level in serum and erythrocytes was lower in obese women than the non-obese women.
Lee et al.[46]	2011	China	Cross-sectional	1449 non-diabetic individuals; 758 males and 691 females	IR increased with higher level of blood Hg level. Highest tertile of blood Hg increased the odds of IR by 11 times (OR 11.0).

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Kim et al.[47]	2011	Korea	Population-based	1991 adults; 99 males and 992 females	Doubled concentration of serum Mn ~1.5 folded the risk of hypertension.
Arnaud et al.[48]	2010	Italy, Belgium and England	Cross-sectional	1902 non-diabetic participants; 942 men and 960 women	Higher plasma Se concentration of women with MS than without MS. 1SD increase in plasma Se concentration was likely to increase the risk of MS in women (OR 1.09). Zn and Cu concentration had no significant association with MS.
Kelishadi et al.[49]	2010	Iran	Triple-masked, randomized, case-control, crossover trial	97 obese children of 6-10 years	Significant decrease in apolipoprotein B/ Apolipoprotein A-I ratio, oxidized LDL, leptin, MDA, TC, LDLC, high-sensitivity CRP, FBG, and fasting insulin was observed after receiving Zn supplementation. Mean weight, BMI and BMI Z-score also decreased significantly after receiving Zn supplementation.
Yeung et al.[51]	2009	China	Population-based Epidemiological	258 adults in accord with BMI; 130 lean, 100 overweight and 28 obese	A progressive elevation of zinc-α2-glycoprotein was observed with the presence of increasing number of MS components. Zinc-α2-glycoprotein was positively associated with WC, BMI, fasting insulin, Homa-IR, TG, adipocyte -fatty acid-binding protein, CRP, DBP and negatively associated with HDLC.
Kaspersczyk et al.[52]	2009	Poland	Cross-sectional Case-control	122 adults; 92 metal workers exposed to lead and 30 office workers	Malondialdialdehyde, GP_x, and superoxide dismutase activity was significantly higher among the higher-normotensive Pb exposed group than the normotensive Pb exposed group. SBP and DBP increased with increasing blood Pb level, duration of Pb exposure and

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					malondialdialdehyde and decreased with increasing GP_x.
Cruz et al.[54]	2009	Brazil	Case-control	815 adults; 198 males and 617 females	Positive association of MnSOD polymorphism with obesity (Adjusted OR 1.949).
Obeid et al.[55]	2008	Lebanon, Arab	Multi-centre cross-sectional	398 adult male and female	Plasma Se level was positively correlated with all MS factors while Cu level correlated with TC, HDLC and LDLC. Plasma Zn had no significant relation with any MS factors.
Paek et al.[56]	2008	South Korea	Population-based Cross-sectional survey	1902 adults; 499 hypertensive and 1403 normotensive	The blood Cd level was significantly higher among the hypertensive individuals compared to the normotensive individuals. The highest tertile of blood Cd level increased the odds of HT by 1.52 times and a dose-response relationship was observed.
Guallar et al.[57]	2008	United States	Follow-up	13887 adult participants	High Se level was responsible for cardiovascular mortality (hazard ratio 0.94; 95% CI).
Stejskal et al.[58]	2008	Czech republic, Europe	Case-control	228 adults; 92 with metabolic syndrome and 136 non-obese controls	Difference in the level of serum zinc-α glycoprotein was not significant between case and control groups however; its association with glucose, creatinine and uric acid were significant.
Al-Saleh et al.[60]	2007	Kuwait, Middle-east	Case-control	21 pregnant women; 10 gestational diabetic obese women and 11 control obese women	Significantly higher blood Mo level was found in GDM obese pregnant mothers compared to the control group. Higher Cu and Zn level and lower Fe level was found in GDM obese pregnant mothers but the difference was not significant.

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					Higher level of Cu, Mo and Fe and lower Zn level in umbilical artery was found in GDM obese pregnancies; only Mo showed significant difference. Higher level of Cu, Mo, Fe and Zn in umbilical vein was found in GDM obese pregnancies; the difference was not significant.
Soinio et al.[61]	2007	Finland	Follow-up	1050 adult patients with T2DM	Lower level of serum Zn was significantly associated with the development and mortality due to CHD (relative risk 1.37 and 1.70, respectively).
Al-Sharbatti et al.[63]	2006	Babil Governorate, Iraq	Hospital-based Follow-up Case-control	266 adults; 133 patients with T1 and T2DM and 133 non-diabetic controls	Lower serum Zn level was observed in both type of diabetic patients and highest reduction was observed in T1DM patients compared to the controls.
Ferns et al.[64]	2005	Guildford, England	Hospital-based Follow-up Case-control	34 adult patients; 20 patients not under statin treatment and 14 controls	After statin treatment, the Cu and Zn level, Zn/Cu ratio and ceruloplasmin reduced significantly among the cases compared to the controls. No significant change in Se and GP_x was found in either group.
Ademuyiwa et al.[65]	2005	Nigeria	Cross-sectional Case-control	110 males; 99 Pb exposed and 11 controls	TC was 1.5-2.0 times higher and LDLC was 1.6-2.4 times higher among the Pb exposed individuals than controls. Significant correlation of blood Pb with TC and LDLC was observed (r=0.372 and 0.283, respectively). LDLC/HDLC ratio was higher among the Pb exposed individuals than controls.

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Nash et al.[66]	2003	United States	Cross-sectional	2165 adult females	Highest quartile of blood Pb level increased the odds of diastolic HT, systolic HT and general HT (adjusted OR 3.4, 1.5 and 1.4, respectively). Among the post-menopausal women, the highest quartile of blood Pb level increased the odds of diastolic HT by 8.1 times.
Kosanovic et al.[67]	2002	Belgrade, Yugoslovia	Cross-sectional	60 pregnant mothers of 3rd trimester;37 normotensive and 23 hypertensive	Significantly higher concentration of Cd was found among the hypertensive mothers and their amniotic fluid compared to the normotensive mothers. Furthermore, significantly higher concentration of Cd was found among the smoking mothers than the non-smoking mothers.
AKYÜZ et al.[69]	1993	Turkey	Cross-sectional Case-control	230 individuals; 60 with atherosclerotic heart disease, 60 with HT, 60 with the both, and 80 healthy controls	Significantly higher Cu level among the cases in relation to controls. Zn level was higher in patients than the healthy controls however; the difference was not statistically significant.
Rabinowitz et al.[70]	1987	Boston, United States	Cross-sectional	3851 pregnant women	Pb exposure increased the risk of HT at the time of delivery and no association with PE was found.
Manthey et al.[71]	1981	Heidelberg, Germany	Case-control	106 male patients; 34 with moderate CHD, 41 with severe CHD and 31 controls	Significantly lower serum Cu and Mn level among the patients with severe CHD compared to the controls. Such difference was not significant in case of moderate CHD compared to the controls. Markedly elevated Cd level among cigarette smokers than non-smokers (r=0.725).

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Cherry et al.[72]	1981	Orleans, France	Follow-up	272 adolescent pregnant mothers	Mothers with HT/toxemia had significantly lower plasma Zn level. Plasma Zn level of mother showed statistically significant association with Apgar score at both 5 min and 1 min of the baby.
Revis et al.[73]	1981	Rome	Case-control	60 adults; 30 hypertensive and 30 normotensive individuals	Blood Cd level among the smokers was significantly higher than the non-smokers and further among the hypertensive individuals than the normotensive individuals.
Burch et al.[74]	1979	United States	Clinical Cross-sectional	185 adult male patients	Patients with congestive heart failure had elevated level of Mn.
Dally et al.[75]	1978	Paris	Hospital-based Cross-sectional Case-control	58 adult males; 29 with untreated hypertension and 29 controls	Blood Cd level was higher in hypertensive males compared to the control group but the difference was not statistically significant.
Glauser et al.[76]	1976	United States	Case-control Cross-sectional	27 adults; 17 with untreated HT and 10 normotensive	Blood Cd level was significantly higher among the hypertensive individuals compared to the normotensive individuals.
Schroeder et al.[77]	1965	United States, Far east, Middle east and Africa	Cross-sectional	358 death cases of adults	Patients who died due to hypertensive causes had significantly higher level of renal cadmium than the other cases.

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4 Table 2: Trace elements and CVD risk in the South Indian population.

Authors	Year	Area	Nature of the Study	Studied Population	Findings
Afridi et al.[30]	2014	Hyderabad, Pakistan	Epidemiological Cross-sectional Case-control	423 adults; 257 hypertensive individuals and 166 normotensive controls	Cd and Hg level of hypertensive individuals in blood, urine and hair scalp were higher than the controls. Zn and Se level in scalp hair and blood was lower and higher in urine in hypertensive subjects than the controls.
Mohanty et al.[34]	2013	Bangalore, India	Case-control Cross-sectional	200 individuals; 100 with T2DM and 100 non-diabetic control	Positive correlation of serum Cu with HbA1C. Higher Cu level was found among the diabetic patients.
Islam et al.[39]	2013	Bangladesh	Case-control	108 pregnancies; 50 preeclamptic and 58 controls	Lower level of serum Zn, Cu, Mn and Fe among the preeclamptic pregnant women than the normotensive pregnancies.
Hettiarachchi et al.[43]	2011	Sri Lanka	Follow-up	96 adults	FBG and serum lipid level significantly decreased after Zn and multivitamin/mineral supplementation. HbA1C also decreased but the change was not significant.
Muttigi et al.[50]	2010	Manipal, India	Case-control	201 adults; 123 T2DM patients and 78 non-diabetic individuals	Significantly increased Cu level among T2DM patients compared to the pre- and non-diabetic individuals.
Memon et al.[53]	2009	Hyderabad, India	Case-control	84 adults; 42 patients with T2DM and 42 non-diabetic individuals	Significantly lower serum Zn level among the diabetic patients in relation to the controls.
Kazi et al.[59]	2008	Pakistan	Case-control	225 adult patients; 135 diabetic and 90 controls	Significantly reduced Mn level in blood and scalp-hair of the diabetic individuals.

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Kazi et al.[62]	2007	Pakistan	Cross-sectional case-control	423 adults; 257 with T2DM and 166 non-diabetic controls	Lower mean values of Zn, and Cr in blood and scalp hair and higher mean values of these elements in urine were found in diabetic patients in relation to controls. Mean values of Cu and Fe in blood and scalp hair were higher in diabetic patients in relation to controls. Elevated level of Ni was found in scalp hair of diabetic patients in relation to controls.
Zarger et al.[68]	1998	Kashmir, India	Clinic-based Cross-sectional	83 T2DM adult patients; 40 males and 43 females	T2DM did not influence Zn level.

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