



## STUDY OF THE ASSOCIATION OF BLOOD MANGANESE LEVEL WITH DIABETES AND CHRONIC RENAL DISEASE IN INDUSTRIAL AREA OF RAIPUR CHHATTISGARH

**Dr. Swati Hiwale\***

Professor and HOD, Department of Biochemistry, RIMS, Raipur, Chhattisgarh. Pin-492001. \*Corresponding Author

**Dr Brajendra kumar**

Professor and HOD, Department of Medicine, RIMS, Raipur, CG, India-492006.

### ABSTRACT

The purpose of this study was to evaluate the association between blood manganese levels and the prevalence of chronic diseases in the industrial area of RAIPUR, CHHATTISGARH STATE. The study included 400 participants 20 years of age or older whose blood manganese levels had been measured. The participants were also evaluated for the presence of five chronic diseases: diabetes, renal dysfunction, hypertension, ischemic heart disease, and stroke. Blood manganese levels were significantly lower in the diabetes group compared with the non-diabetes group ( $1.26 \pm 0.02$  vs.  $1.35 \pm 0.01$   $\mu\text{g/dL}$ ;  $p = 0.001$ ) and the renal dysfunction group compared with those with normal renal function ( $1.28 \pm 0.03$  vs.  $1.35 \pm 0.01$   $\mu\text{g/dL}$ ;  $p = 0.04$ ). There was no significant association between blood manganese levels and the presence of ischemic heart disease or stroke. A multivariate logistic regression analysis adjusted for age, sex, and body mass index was performed; the odds ratio was 0.652 (95% CI: 0.46–0.92) for diabetes and 0.589 (95% CI: 0.39–0.88) for renal dysfunction when comparing the higher quartiles (Q2-4) with the lowest quartile (Q1) of blood manganese level. The prevalence of diabetes was 7.6% in Q1 and 5.3% in Q2-4 ( $p = 0.02$ ). Similarly, the prevalence of renal dysfunction was 6.8% in Q1, compared with 4.6% in Q2-4 ( $p = 0.02$ ). The prevalence of diabetes and renal dysfunction increased in participants with low blood manganese levels, suggesting that blood manganese may play a role in glucose homeostasis and renal function.

**KEYWORDS :** Serum Manganese , Diabetes, Renal dysfunction.

### INTRODUCTION

Being an essential trace metal with insufficient intake in virtually all diets, Mn is involved in normal immune functions, regulation of blood sugar and cellular energy, and the defense mechanisms against free radicals. Experimentally induced Mn deficiency caused a number of detrimental effects, such as impaired bone formation, abnormal glucose tolerance, low levels of high-density lipoprotein (HDL) cholesterol, and skin abnormalities in both animals and humans. Conversely, excess occupational inhalation of Mn may be neurotoxic to humans, producing effects such as psychosis and Parkinsonism. Mn deficiency and intoxication are both associated with adverse metabolic and neuropsychiatric effects. Nevertheless, little is known about the optimal blood Mn levels for maintaining homeostasis in humans. Oxidative stress and inflammation are the main pathophysiology behind most chronic diseases. Therefore, we hypothesized that blood Mn levels could be related to the prevalence of chronic diseases. We conducted a cross-sectional analysis on the associations of blood Mn level with five chronic diseases (diabetes, renal dysfunction, hypertension, ischemic heart disease, and stroke) in a representative sample of the adult workers of the Industrial area of the city capital Raipur, CHHATTISGARH.

### MATERIAL AND METHOD

About 400 persons were included in this study from Industrial area of RAIPUR, Chhattisgarh for one year (2016-2017) in RIMS, RAIPUR. We analyzed those who were 20 years of age or older and tested for blood Mn. We excluded participants who were pregnant or had missing values and yielded a final sample size of 400 adults. College Ethic committee approved the study protocol, and written informed consent was obtained from all participants before the study began. Blood Mn was measured using whole blood at RIMS, following a standardized protocol. Blood Mn was analyzed. The limit of detection was 0.016  $\mu\text{g/dL}$  for blood Mn. For internal quality assurance and control, standard reference materials were obtained from Bio-Rad (Lyphochek® Whole Blood Metals Control). The inter-assay coefficients of variation ranged from 0.95% to 4.82% for blood Mn samples (reference values were 0.98, 1.18, 2.46, and 3.28  $\mu\text{g/dL}$ ). During the survey, overnight fasting venous blood samples were collected. Diabetes was defined as having one of the following: a fasting blood glucose  $\geq 126$  mg/dL, a self-reported physician's diagnosis, medication use, or insulin administration at the time of interview. Serum creatinine level was measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Japan) and a modified kinetic Jaffe reaction. The level of kidney function was attained using an abbreviated equation developed from the data from the Chronic Kidney Disease-Epidemiologic Collaboration Group (CKD-EPI)

study to estimate the glomerular filtration rate (GFR). We defined renal dysfunction as an estimated GFR (eGFR) of  $< 65$  mL/min/1.73 m<sup>2</sup> [9]. Hypertension was defined as having one of the following: a mean systolic blood pressure of  $\geq 140$  mmHg, a mean diastolic blood pressure of  $\geq 90$  mmHg, a self-reported physician's diagnosis, or antihypertensive medication use at the time of interview. Ischemic heart disease and stroke were based on a self-reported physician's diagnosis. Information on age, sex, residential area, educational status, smoking exposure and alcohol consumption, occupation, body mass index (BMI), and nutritional intake were based on a health questionnaire. Residential area was categorized as either urban or rural. Educational status was divided into  $\geq$  college or  $\leq$  high school. Alcohol consumption was indicated as positive for participants who had consumed at least 30 g per day over the last year. The participants' occupations were categorized as services (which included students, housewives, and the unemployed), agriculture, fishery, or industry. BMI was calculated as weight in kilograms divided by height in meters squared. All statistical analyses and calculations were performed using SAS V9.2 (SAS Institute). The baseline characteristics were presented as mean  $\pm$  standard error (SE), median and range, or frequency and proportions. Comparisons of each variable between the two groups were performed using Student's t-test or modified Rao-Scott chi-square test. Demographic characteristics were analyzed according to eGFR ( $< 65$  or  $\geq 65$  mL/min/1.73 m<sup>2</sup>), the presence of chronic diseases (diabetes, hypertension, ischemic heart disease, or stroke), and quartiles of blood Mn levels (first lowest quartile vs. other quartiles). The odds ratios (OR) and 95% confidence intervals (95% CI) of the associated factors for reduced eGFR and blood Mn quartiles were estimated using logistic regression. A p-value of  $< 0.05$  was considered statistically significant.

### DISCUSSION

We examined the effects of blood Mn on chronic diseases in the general population and determine that blood Mn levels affected the morbidity of chronic diseases. It was found that low blood Mn levels increased the risk and prevalence of diabetes and renal dysfunction, suggesting that blood Mn deficiency might be involved in the pathophysiological processes of diabetes and renal dysfunction. Mn is stored primarily in skeletal bones and tissues rich in mitochondria. However, no existing biomarker can reliably determine the exact level of Mn accumulated in the body. Because there is a discrepancy in the half-life of Mn in the tissues and blood, Mn levels in red blood cells or whole blood are believed to be more reliable than plasma Mn for measuring Mn accumulation in the body. For practical reasons, whole blood samples have been used as an exposure biomarker of Mn inhalation in most epidemiological studies and were used accordingly

in the present study to measure blood Mn. In the present study, we found a statistically significant relationship between blood Mn levels and diabetes. Blood Mn levels were lower in participants with diabetes but not in participants with ischemic heart disease or stroke. Furthermore, the prevalence of diabetes significantly increased in participants with blood Mn levels in the lowest quartile. Many studies have focused on environmental Mn toxicity rather than on its deficiency and metabolism. Mn toxicity in humans primarily occurs as a consequence of chronic inhalation of high concentrations of airborne Mn-containing particles, linking symptoms of Mn toxicity mainly to miners as well as ferroalloy and battery manufacturing workers. Mn may be exposed occupationally or environmentally. Typical toxicity symptoms resemble those of idiopathic Parkinson's disease and include tremor, rigidity, bradykinesia, and posture instability. Patients may also display neuropsychological difficulties that include apathy and even psychosis as Mn affects the dopaminergic systems with a neuropathology that closely resembles Parkinson's disease. Most studies have examined outcomes following relatively high-level acute or chronic exposure to Mn. Less is known about the effects of chronic exposure to lower levels of Mn or the threshold levels sufficient for altering cognitive and motor function. Oxidative stress and inflammation play a major role in the progression of renal damage in chronic kidney disease (CKD). Mn is a potent antioxidant and cofactor of the enzyme MnSOD, which is the main antioxidant enzyme in the mitochondria responsible for protecting the cell from reactive oxygen species (ROS) by scavenging mitochondrial superoxides. The results in this study showed a significant association of blood Mn level with the prevalence and risk of renal dysfunction after adjusting for diabetes and hypertension in logistic regression analysis, although not in linear regression. High blood Mn levels were found, in this study, to be consistently associated with high systolic, diastolic, and mean arterial blood pressures after adjustment, although no differences in the prevalence of hypertension were found between the lower and higher blood Mn quartile subgroups.

## RESULT

The total number of participants was 400. The mean participant age was  $45 \pm 0.2$  years. The mean blood Mn level in adult population was  $1.34 \pm 0.01$   $\mu\text{g/dL}$ , and the mean eGFR as calculated by the CKD-EPI equation was  $95.1$   $\text{ml/min/1.73 m}^2$ . The mean systolic blood, diastolic blood, and arterial pressures were  $116.9 \pm 0.4$   $\text{mmHg}$ ,  $76.7 \pm 0.3$   $\text{mmHg}$  and  $88.7 \pm 0.2$   $\text{mmHg}$ , respectively. Blood Mn levels were significantly different in the baseline characteristics of the following variables: sex, smoking exposure, the history of alcohol drinking, and residential area (data not shown). Mn levels were also different according to the presence of chronic disease. Participants with diabetes had significantly lower blood Mn levels than those without diabetes ( $p < 0.05$ ). Renal dysfunction and hypertension presented similarly ( $p < 0.05$ ). There was no significant difference in the blood Mn levels of participants with or without ischemic heart disease or stroke. We also evaluated the association of blood Mn level with eGFR and blood pressure. In a linear regression analysis adjusted for age, sex, and BMI, there was no statistically significant association between blood Mn levels and eGFR. However, blood Mn levels were positively associated with systolic blood ( $\beta$  coefficient =  $1.52$ ,  $p = 0.01$ ), diastolic ( $\beta$  coefficient =  $1.01$ ,  $p = 0.02$ ), and mean arterial blood pressures ( $\beta$  coefficient =  $1.26$ ,  $p = 0.004$ ) after adjusting for age, sex, BMI, and presence of diabetes.

## CONCLUSION

In our study prevalence of diabetes and renal dysfunction decreased in participants with high blood Mn levels, suggesting that blood Mn may have some role in glucose homeostasis and renal function. Further studies are needed to determine any protective effects of Mn on diabetes and renal dysfunction.

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