Original Research Article: full paper

(2023), «EUREKA: Health Sciences»
Number 1

COMPARISON OF SERUM COPPER LEVELS BETWEEN CORONARY ARTERY DISEASE PATIENTS AND NORMAL INDIVIDUALS: A CASE-CONTROL STUDY

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Abstract

Cardiovascular diseases (CVD) are the leading causes of death in technologically developed and developing countries. Copper, an active redox element, is involved in energy production through various mechanisms. Copper and coronary artery disease can be associated directly, through its direct effect on the vascular endothelium, or indirectly through lipoprotein metabolism. Hence an evaluation of copper in the coronary artery disease individual is important.

The aim is to compare the relationship of serum copper levels between coronary artery disease patients and control individuals based on age, sex, hypertension and diabetes mellitus.

Materials and methods: The study design was a case-control study in which proven coronary artery disease patients attending cardiology OPD were selected as cases. Control individuals were mainly selected from the master health check-up. Serum copper levels, plasma glucose, cholesterol, serum triglycerides, and serum HDL & LDL cholesterol were done. Glycated haemoglobin (HbA_1C) was also measured. The data were analyzed using IBM SPSS software version 24.

Result: The correlation of serum copper level with other quantitative parameters is determined by calculating Pearson's correlation coefficient among cases and controls.

Conclusion: The serum copper level is significantly ($p = 0.001$) higher in CAD patients than in age, sex, DM, and HT-matched controls. The serum copper level has a significant ($p = 0.001$) effect on disease, and the adjusted odds ratio is 1.032 (CI 1.011–1.054). In addition, the serum copper level has a significant (0.01) negative correlation with LDL cholesterol and total cholesterol.

Keywords: copper, coronary artery disease, plasma glucose, serum triglycerides, serum HDL, LDL cholesterol, HbA_1C, diabetes, hypertension, trace elements.

DOI: 10.21303/2504-5679.2023.002744

1. Introduction

Cardiovascular diseases (CVD) are the leading causes of death in technologically developed and developing countries [1]. Coronary artery disease (CAD), also known as ischemic heart

disease, accounts for 50 per cent of morbidity and mortality in cardiovascular diseases [2, 3]. Coronary artery disease caused by ischemia to the myocardium occurs by narrowing or blocking coronary arteries by atherosclerotic plaque due to the oxidation of low-density lipoprotein by free radicals, predominantly the reactive oxygen species [4, 5].

The trace elements zinc, copper and iron are micronutrients with the property of antioxidants [6]. Copper, an active redox element, is involved in energy production through various mechanisms. Because copper ions can catalyze the oxidative modification of low-density lipoprotein cholesterol in the arterial wall, they can result in free radical formation [7, 8]. Thus copper and coronary artery disease can be associated directly, through its direct effect on the vascular endothelium, or indirectly through lipoprotein metabolism [1, 9].

Therefore, an evaluation of copper in the coronary artery disease individual is important.

The aim is to compare the relationship of serum copper levels between coronary artery disease patients and control individuals based on age, sex, hypertension and diabetes mellitus.

2. Materials and methods

The study was conducted at a tertiary care hospital attached to a medical college between July 2018 to 2019. Ethical clearance was obtained from the institutional ethics committee, PSG institute of medical science and research, Coimbatore (PSG/IHEC/2018/Appn Exp/155).

The study design was a case-control study in which proven coronary artery disease patients attending cardiology OPD were selected as cases. Control individuals were mainly selected from the master health check-up. For master health check-up patients, clinical data were available in the case sheet. Persons fulfilling the defined inclusion and exclusion criteria for the control group were selected for the study. For master health check-up patients, clinical data were available in the case sheet. Patients satisfying the diagnosis criteria based on defined inclusion criteria and exclusion criteria were included in this study. The samples were analyzed by collecting, processing and storing samples at –20 degree Celsius for analysis. Control individuals were mainly selected from the master health check-up.

Inclusion criteria & exclusion criteria for cases:

Males and females (≥25 years) with Coronary Artery Disease were included, and patients with Malignancy, Genetic malformation, acute illness and Pregnancy were excluded from the study.

Estimation of copper:

Serum copper levels were estimated using atomic absorption spectroscopy. The Aliquot sample was taken from – 20 °C and allowed to thaw. Nitric acid (1 %) was used for the sample and standard preparation. The copper stock standard was 1000 µg/ml. From the stock solution, 1 ppm and 2 ppm standards were prepared. For 1 ppm standard preparation, 100 µl of stock is made up to 100 ml with 1 % nitric acid preparation. For 2 ppm standard preparation, 200 µl of stock is made up to 100 ml with 1 % nitric acid preparation. Serum samples were diluted in a ratio of 1:5 with 1 per cent nitric acid preparation before analysis. Analysis was done using the flame AAS method [10, 11]. Estimation of plasma glucose was done by the Hexokinase method, and cholesterol estimation was done by enzymatic colourimetric test [12, 13]. Estimation of serum triglycerides was done by enzymatic, colourimetric method. Serum HDL & LDL cholesterol was done by Homogenous enzymatic colourimetric assay. Glycated haemoglobin (HbA_1C) was measured BIO-RAD VARIANT II TURBO HbA1c Kit – 2.0.

Statistical analysis:

The data were analyzed using IBM SPSS software version 24. The data distributions were depicted as histograms or frequency bar diagrams. For the comparison of means independent t-test was used. The effect of copper level is estimated by binomial regression analysis. Unadjusted and adjusted odds ratios were determined. The correlations between quantitative parameters were determined using Pearson correlation and were further checked by scatter plot.

3. Results

The BMI is segmented according to WHO BMI cutoff points and compared in **Table 1**. The systolic and diastolic pressures are interpreted according to the guidelines published in the

journal 'Journal of Hypertension 36 (10):1953–2041, October 2018'. The HbA_1C level and fasting plasma glucose levels of the study groups are compared. The comparison of lipid profile – triglycerides, HDL cholesterol, LDL cholesterol and total cholesterol has been made. The comparison of copper level between the case and control is given in **Table 2**. Binomial logistics determines the effect of copper level. The correlation of serum copper level with other quantitative parameters is determined by calculating Pearson's correlation coefficient **Table 3**. Scatter plots further examine these correlations.

Table 1
Comparison of variables among cases and controls

S.NO		Case/Control	N	Mean	SD	Std. Error Mean	t-value	p-value
1	Age	Case	30	61.4	10.87	1.98	0.378	0.706
		Control	30	60.4	10.27	1.88		
2	BMI	Case	30	25.2	3.11	0.57	–2.046	0.045
		Control	30	27.2	4.43	0.81		
3	BP (Systole)	Case	30	130.7	11.77	2.15	0.655	0.515
		Control	30	128.7	11.89	2.17		
4	BP (Diastole)	Case	30	81.8	9.40	1.72	0.042	0.967
		Control	30	81.7	9.12	1.67		
5	HBA1c	Case	30	6.8	1.623	0.30	1.062	0.293
		Control	30	6.5	1.00	0.18		
6	Fasting plasma glucose	Case	30	146.9	63.64	11.62	–0.095	0.924
		Control	30	148.5	66.52	12.15		
7	TGL	Case	30	126.9	71.64	13.08	–1.455	0.151
		Control	30	155.7	81.59	14.90		
8	HDLC	Case	30	40.6	7.92	1.45	0.390	0.698
		Control	30	39.7	9.85	1.80		
9	LDLC	Case	30	77.3	30.3	5.54	–6.642	0.000
		Control	30	132.8	34.20	6.25		
10	Cholesterol	Case	30	128.0	29.94	5.47	–5.758	0.000
		Control	30	176.1	34.52	6.30		

Table 2
Comparison of serum copper level in case and controls

Parameter	Case/Control	N	Mean	Std. Deviation	t	p
Serum copper Level	Case	30	135.667	35.2580	3.563	<0.001
Serum CopperLevel	Control	30	106.667	27.2774		

Table 3
Pearson's correlation coefficient

Serum CuLevel		Age	Height (cm)	Weight (kg)	BMI	BP (Systole)	BP (Diastole)	HBA1c	GlcFasting	TGL	HDL	LDL	Cholesterol
Serum Cu Level	R	1.0	–0.1	–0.1	–0.1	–0.1	0.1	–0.1	0.2	0.1	–0.2	–0.2	–.326	–.344
	P		0.3	0.7	0.3	0.3	0.6	0.7	0.2	0.3	0.2	0.2	0.0	0.0
Age	R	–0.1	1.0	–.405	–.389	–0.2	.275	0.0	0.1	0.1	0.0	0.1	–0.2	–0.2
	P	0.3		0.0	0.0	0.1	0.0	0.8	0.7	0.6	0.9	0.5	0.2	0.2
Height (cm)	R	–0.1	–.405	1.0	.499	0.0	–0.1	0.1	–0.1	–0.2	0.1	–0.1	0.2	0.2
	P	0.7	0.0		0.0	0.9	0.3	0.7	0.3	0.2	0.7	0.4	0.1	0.1
Weight (kg)	R	–0.1	–.389	.499	1.0	.853	–0.1	0.0	0.0	0.1	0.1	–0.2	.430	.416
	P	0.3	0.0	0.0		0.0	0.3	0.9	0.7	0.7	0.4	0.1	0.0	0.0
BMI	R	–0.1	–0.2	0.0	.853	1.0	–0.1	0.0	0.1	0.2	0.1	–0.2	.362	.342
	P	0.3	0.1	0.9	0.0		0.5	0.9	0.3	0.2	0.5	0.2	0.0	0.0
BP (Systole)	R	0.1	.275	–0.1	–0.1	–0.1	1.0	.604	0.0	0.1	–0.1	0.2	–0.1	0.0
	P	0.6	0.0	0.3	0.3	0.5		0.0	0.8	0.6	0.5	0.1	0.7	0.9
BP (Diastole)	R	–0.1	0.0	0.1	0.0	0.0	.604	1.0	–0.2	0.0	0.0	.338	0.2	.257
	P	0.7	0.8	0.7	0.9	0.9	0.0		0.1	0.9	0.9	0.0	0.2	0.0
HBA1c	R	0.2	0.1	–0.1	0.0	0.1	0.0	–0.2	1.0	.678	0.2	–0.2	–0.2	–0.2
	P	0.2	0.7	0.3	0.7	0.3	0.8	0.1		0.0	0.1	0.2	0.1	0.2
Glucose Fasting	R	0.1	0.1	–0.2	0.1	0.2	0.1	0.0	.678	1.0	0.2	0.0	–0.1	0.0
	P	0.3	0.6	0.2	0.7	0.2	0.6	0.9	0.0		0.2	1.0	0.5	0.9
TGL	R	–0.2	0.0	0.1	0.1	0.1	–0.1	0.0	0.2	0.2	1.0	–.446	0.2	.344
	P	0.2	0.9	0.7	0.4	0.5	0.5	0.9	0.1	0.2		0.0	0.1	0.0
HDLc	R	–0.2	0.1	–0.1	–0.2	–0.2	0.2	.338	–0.2	0.0	–.446	1.0	0.1	0.1
	P	0.2	0.5	0.4	0.1	0.2	0.1	0.0	0.2	1.0	0.0		0.7	0.3
LDLc	R	–.326	–0.2	0.2	.430	.362	–0.1	0.2	–0.2	–0.1	0.2	0.1	1.0	.929
	P	0.0	0.2	0.1	0.0	0.0	0.7	0.2	0.1	0.5	0.1	0.7		0.0
Cholesterol	R	–.344	–0.2	0.2	.416	.342	0.0	.257	–0.2	0.0	.344	0.1	.929	1.0
	P	0.0	0.2	0.1	0.0	0.0	0.9	0.0	0.2	0.9	0.0	0.3	0.0	

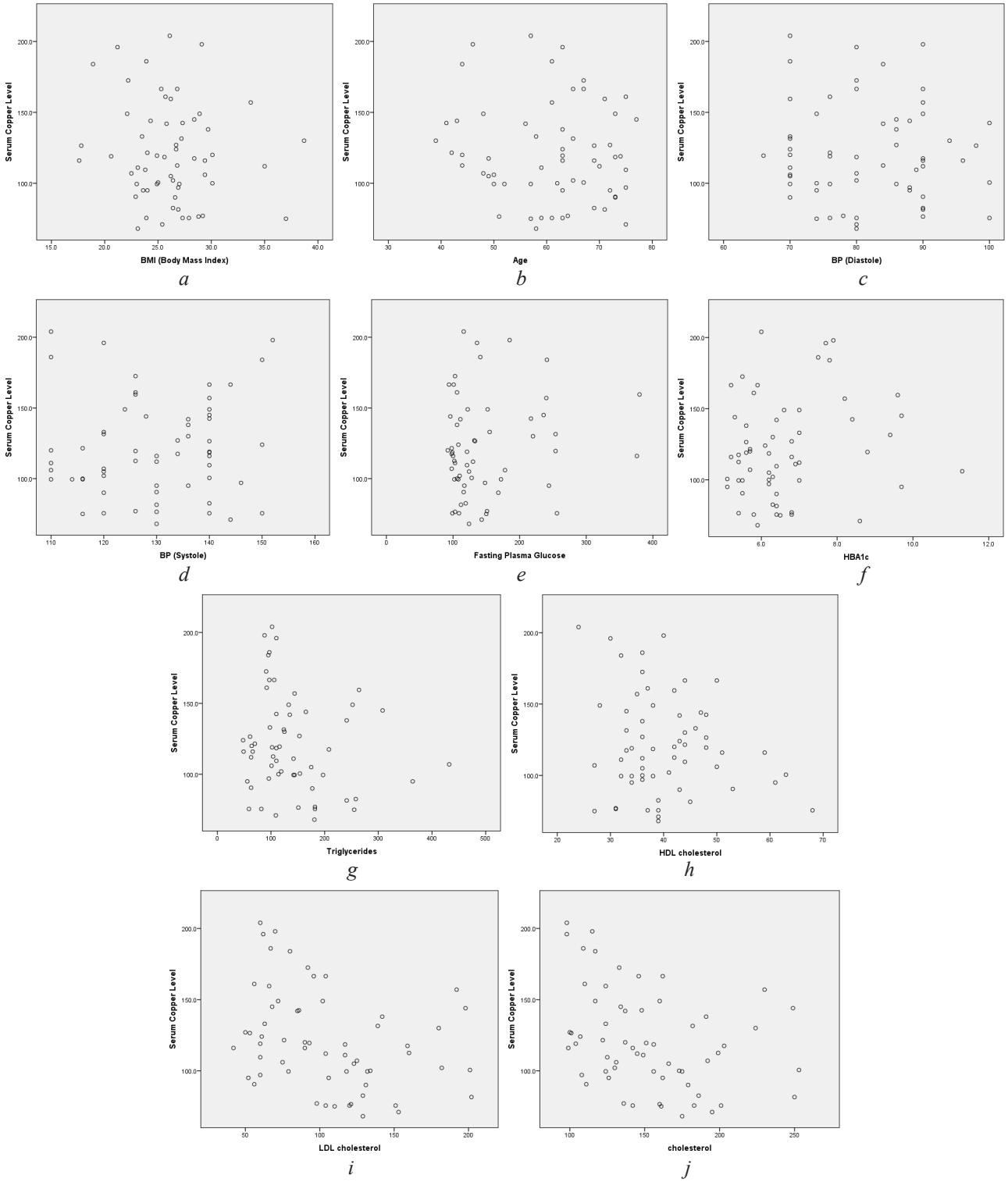

Fig. 1. Scatter plots of copper with various parameters: *a* – BMI; *b* – Age; *c* – BP Diastole; *d* – BP Systole; *e* – Fasting Plasma Glucose; *f* – HbA1c; *g* – Triglycerides; *h* – HDL Cholesterol; *i* – LDL Cholesterol; *j* – Cholesterol

4. Discussion

The study was done to compare the serum levels of copper in coronary artery disease patients and control individuals matched for age, sex, diabetes mellitus and hypertension. Coronary artery disease patients (n = 30) and control individuals (n = 30) were recruited for the study.

Angio-graphically proven cases of coronary artery diseases were taken as cases. Among 30 such cases taken serially, 16 had single vessel disease, 2 had double vessel disease, and 12 had triple vessel disease. The controls were matched for age, sex, DM and HT.

When comparing the age distribution of cases and controls, there is no significant difference in the distribution pattern except for a 2–3y shift to the right in the case. The comparison of the mean by T-test also showed no significant difference. The frequency of males and females shows that the sex is well matched.

The BMI of cases and control did not have much difference in less than 30 ranges. And actually, controls were only in the above 30 ranges. Three controls were in the obesity class 1 range, and 3 more were in the obesity class 2 range, while none of the cases was there in this range. Two of the cases were in the under-weight category. There was a significant difference in the mean. The control group had a higher mean (27.2, CI 25.5–28.9), and the case group had a lower mean (25.2, CI 24.0–26.4) (**Table 1**).

The distribution of Systolic BP and Diastolic BP was quite matching, and there was no significant difference in means. The frequencies of HT among case and control were exactly the same as this was a matched control group. Similarly, the frequency of DM and the frequency of both DM & HT were the same as they were matched (**Table 1**).

When looking into the frequencies of 'smoking' and 'alcoholism', surprisingly, smoking was less among the cases, but alcoholism was more. The HbA_1C distribution was compared between cases and controls, as was the Fasting Plasma Glucose distribution. This shows that the matching control is perfect; as expected, there is no significant difference in the mean. In cases, the distribution of Triglycerides and HDL cholesterol was also akin to the corresponding distributions in the control. There was no significant difference in the t-test (**Table 1**).

The LDL and Total cholesterol levels were significantly ($p < 0.001$) higher in controls than in cases. In the control group, LDL levels were borderline (100–129 mg/dL) for 12 persons and high (130 mg/dL and above) for 14 persons. The control group's LDL cholesterol mean was 132.8 mg/dL (CI 119.8–145.4), while that of the case was 77.3 mg/dL (CI 66–88.6). Similarly, the mean total cholesterol concentration of control was 176.1 mg/dL (CI 163.2–189.0) and, of cases, was 128 mg/dL (CI 116.8–139.2) (**Table 1**). This could be due to drug therapy with statins.

When analyzing the group statistics, there is no significant difference in age, sex, BP (Systole), BP (Diastole), HBA_1C, fasting plasma glucose, TGL and HDL cholesterol. This shows the age, sex, DM and HT matching of controls with cases. Unexpectedly, the BMI, LDL cholesterol and total cholesterol were significantly higher in the control group. The control group was selected from the master health check-up. The controls should be from economically affluent families.

The controls might have been concerned about their health, which might have brought them to master health check-ups. Student's test compared the copper level of cases and control. The mean copper level of cases is significantly ($p = 0.001$) higher than the mean copper level of control (Copper level mean – cases 135.7 μg/dL CI 122.6–148.8 & copper level mean – control 106.7 μg/dL CI 96.5–116.9) (**Table 2**).

The effect of the copper level was determined on the disease by binomial regression. The unadjusted odds ratio was 1.030 (CI 1.010–1.051). The adjusted odds ratio was 1.032 (CI 1.011–1.054). Both odds ratios were statistically significant ($p = 0.001$) (**Table 2**).

In a study done by Bandmann et al., 2015 and Babak Bagheri et al., 2015 [14, 15], they found that there was no significant difference in tobacco smoking, the occurrence of diabetes mellitus and hypertension, serum total cholesterol/High-Density Lipoprotein and blood glucose levels between the groups. They found that the copper level was significantly higher in atherosclerotic groups (p-value = 0.001). In the study done by Młyniec et al., 2015 [16], they found that the mean Copper levels of ischemic cardiomyopathy patients (1.54 +/–0.52 mg/L) were significantly higher than the normal groups (1.31+/–0.24 mg/L; $p = 0.048$).

In a study by Grubman A&White AR 2014 [17], they found that the demographic and baseline clinical characteristics were not statistically significant between the groups regarding age and sex. Serum copper (171.27±28.87vs.121.33±28.52μg/dl, $p = 0.0001$) was significantly higher in CAD patients.

From this study, they found out that the subgroups of CAD patients according to Diabetes Mellitus and Hypertension had a significant (p-value < 0.05) higher level of copper in diabetic and hypertensive patients than in non-diabetic and normotensive individuals, respectively (p-value < 0.05). There was a statistically significant difference in smoking behaviour (p-value < 0.05), with CAD patients being more smokers than the other group.

They also found that by logistic regression analysis, serum copper was significantly associated with CAD (OR = 0.743, 95 % CI = 0.6480.838, p = 0.0001) after adjusting for risk factors in the study population. In contrast, no such association was found with the other factors. They also found that there was a statistically significant difference in the serum Copper level (p-value < 0.05) between diabetic and diabetic-free CAD patients in which copper was high in diabetic than non-diabetic patients.

In a study done by Jamal A. Al-Dohanet al., 2015 [18], they found out that in Cox-multivariate survival models adjusted for age, ischemic electrocardiogram in exercise, maximal oxygen uptake, family history of CAD, cigarette smoking years, diabetes mellitus, mean systolic blood pressure, HDL cholesterol subfraction HDL_2 and low LDL cholesterol concentrations and blood leukocyte count, examination year, serum copper concentration in the two highest tertiles (1.02–1.16 mg/litre and 1.17 mg/litre or more) are associated with 3.5-fold (95 % confidence interval (CI) 1.3–9.4, p < 0.05) and 4.0-fold (95 per cent CI 1.5–10.8, p < 0.01) risk for acute myocardial infarction.

Scheiber et al., 2014 [19] study found that total mean copper levels were notably higher in patients with acute coronary artery disease (141.0 ± 15.2) compared to controls (97.0 ± 10.8) with p-value = 0.004 and this difference was seen in both males and females (p < 0.01 and p < 0.001 respectively). Their study revealed that triglycerides, total cholesterol and low-density lipoprotein-cholesterol were elevated in patients, and high-density lipoprotein-cholesterol was lower in our patients but not significantly (p>0.05).

In this study, the copper level had a significant negative correlation with LDL cholesterol (R = –0.326, p = 0.011) and total cholesterol (R = –0.344, p = 0.007). The scatter plot was also consistent with a negative correlation (**Fig. 1**). Regression analysis was not done since the R-value was not higher than 0.6.

Limitations of the study

– Limited sample size

– Lack of association between other trace elements and coronary artery disease, which could act as a better prognostic tool.

Prospects for further research

Our future studies will be aimed at larger prospective cohort studies to confirm our observations and further experimental data to rule out the pathophysiology behind the association between copper and coronary artery disease.

5. Conclusion

The serum copper level is significantly (p = 0.001) higher in CAD patients than in Age, Sex, DM, and HT-matched controls. The serum copper level has a significant (p = 0.001) effect on disease, and the adjusted odds ratio is 1.032 (CI 1.011–1.054). In addition, the serum copper level has a significant (0.01) negative correlation with LDL cholesterol and total cholesterol.

Conflict of interest

The authors declare that there is no conflict of interest concerning this paper, the published research results, the financial aspects of conducting the research, obtaining and using its results, and any non-financial personal relationships.

Financing

The study was performed with no additional financial support.

Data availability

Data will be made available on reasonable request.

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Received date 15.12.2022
Accepted date 24.01.2023
Published date 31.01.2023

Rajan, Z. S., Jaganathan, S., Arokiasamy, S., Kandhi, S., Sasikala, P. M. (2023). Comparison of serum copper levels between coronary artery disease patients and normal individuals: a case-control study. EUREKA: Health Sciences, 1, 43–50. doi: http://doi.org/10.21303/2504-5679.2023.002744