ORIGINAL ARTICLE

Iron status and total iron-binding capacity in patients with essential hypertension: A case-control study

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Abstract

Background: Essential hypertension is a multifactorial disease with an unknown cause. Despite extensive research, the underlying mechanisms contributing to essential hypertension are not fully understood. Recent studies have explored various physiological factors that may influence blood pressure regulation, including disturbances in mineral metabolism. Iron, a crucial element in various physiological processes, has been implicated in blood pressure regulation. Abnormal iron metabolism, measured by Total Iron-Binding Capacity (TIBC), has also been explored. Emerging evidence suggests that altered iron metabolism could play a role in the pathogenesis of hypertension. *Aim and Objectives:* This case-control investigates the association between iron and TIBC in essential hypertension patients. *Material and Methods:* The study involved 100 participants, 50 individuals with hypertension and 50 healthy controls, selected based on specific inclusion and exclusion criteria. Clinical histories were obtained from each participant using a data collection form. Blood pressure measurement was done as per the Eighth Joint National Committee guidelines followed by anthropometric measurements as per the World Health Organization STEPwise approach to non-communicable risk factor surveillance guidelines. Biochemical parameters such as iron and TIBC were estimated by a semi-auto analyser using a commercially available kit. *Results:* Mean iron levels were significantly increased and TIBC levels were significantly reduced (179.26 ± 53.47 vs 136.90 ± 38.89; $p < 0.001$, 167.09 ± 80.03 vs 261.33 ± 34.41; $p < 0.001$ respectively) in cases compared to controls. A positive association was found between iron and systolic blood pressure in essential hypertension cases and an inverse association was found between iron and TIBC significantly predicting essential hypertension ($p < 0.001$). Conclusion: The study revealed significant differences in iron metabolism between patients with essential hypertension and healthy controls, suggesting a disruption in iron homeostasis. Elevated iron levels may contribute to oxidative stress and endothelial dysfunction, while reduced TIBC may indicate an imbalance in iron homeostasis or an adaptive response to changes in iron availability. Understanding these associations could pave the way for novel approaches to managing and treating essential hypertension.

Keywords: Essential hypertension, total iron binding capacity, systolic blood pressure, diastolic blood pressure

Introduction

Hypertension is a prevalent medical condition characterized by a persistent increase in arterial pressure [1]. It possesses a significant risk for myocardial infarction, heart failure, stroke, and renal failure [2]. Up to 45% of individuals are affected, with over one billion adults affected globally [3]. The prevalence is constant across all socioeconomic and income levels, making up as much as 60% of the population who are 60 or older [3]. According to the latest estimates, there may be 15–20% more individuals with hypertension by 2025, bringing the total number of patients to approximately 1.5 billion [4].

Hypertension, also known as essential hypertension, is primarily idiopathic and increases with increased salt intake [5]. The genetic ability to

respond to salt is a significant factor in developing essential hypertension [6,7]. Around 50-60% of patients are salt-sensitive, leading to hypertension [8]. Obesity and insulin resistance are major risk factors that contributes to cardiovascular complications. Obesity leads to the accumulation of dietary fatty acids in adipose tissue, causing a saturated storage capacity. This results in lipid spillover to lean tissues like the liver and muscles, leading to inflammation and insulin resistance. This combined state of inflammation and ectopic fat deposition is a significant risk factor for cardiovascular complications [9]. Additionally, recent studies have highlighted disruptions in iron homeostasis as a potential factor in the heightened risk of hypertension, though the role of iron in the development of hypertension remains uncertain [10].

Iron is essential for maintaining physiological balance; nonetheless, excessive iron can cause free radical damage, resulting in tissue damage [11]. Iron storage and blood pressure are not completely understood [12, 13]. It was recently found that an increase in iron levels upregulates oxidative stress, which contributes to the development of hypertension. Experimental studies have further demonstrated that iron-catalysed free radicals cause endothelial damage and eventually lead to an increase in blood pressure [14]. Dietary iron restriction can reduce oxidative stress in the aorta, potentially reducing high salt-induced hypertension and cardiovascular remodeling [11]. Iron deficiency and overload can increase reactive oxygen species, oxidative stress, inflammation, and endothelial function, increasing blood pressure [12]. Thus, one of the major independent factors leading to the development of hypertension is the dysregulation of iron metabolism [13]. Despite a considerable amount of research that has focussed on linking iron and the Total Iron Binding Capacity (TIBC) with essential hypertension, the results were inconsistent.

Material and Methods

Study design

The case-control study was conducted in the Department of Biochemistry at Integral Institute of Medical Sciences and Research (IIMS&R), Lucknow, India. The Institutional Ethics Committee of IIMS&R, Lucknow, Uttar Pradesh, approved human participant enrolment and blood sample collection (IEC No.: IEC/IIMS&R; R/2023 /66) following the ethical standards of the 1964 Helsinki Declaration and its amendments. Clinical histories were obtained from each participant using a data collection form. A written informed consent was obtained from each participant in the study.

Sample size estimation and sampling method

The sample size was calculated using the formula

$$\frac{r+1}{r}\frac{(SD2)Z\beta+2\alpha/2)2}{\alpha 2}$$

where r = ratio of control to cases, 1 for an equal number of cases and control, Z_{β} = standard normal variate for power = for 80% power it is 0.84. $Z_{\alpha/2}$ = standard normal variate for a level of significance as mentioned in the previous section, d^2 = expected mean difference between case and control may be based on previously published studies. Non-probability purposive sampling method was used to identify the study population. A total of 100 participants, 50 hypertension cases, and 50 healthy controls were selected based on specific inclusion and exclusion criteria.

Inclusion and exclusion criteria for study subjects

The study included individuals aged 30-60 years with essential hypertension as per the Eighth Joint

National Committee (JNC 8) guidelines [15], and healthy individuals aged 30-60 as controls. Individuals having a history of iron-deficient anemia, pregnant or lactating women, and those suffering from acute or chronic diseases were excluded from both cases and controls.

Blood pressure measurement

Blood pressure measurement was done as per JNC 8 guidelines. Patients were asked to sit quietly for a few moments ensuring that the patient was relaxed before taking the measurements. Three readings were recorded and an average of the two readings was considered for the final blood pressure readings [16].

Anthropometric measurements

Body Mass Index (BMI) was determined using the formula: body weight (kg) / height (m^2). Measurements of weight and height for BMI estimation followed the World Health Organization STEPwise approach to noncommunicable disease risk factor surveillance (STEPS) guidelines [17].

Laboratory investigations

Sample collection and serum separation

Each participant in the study had 2 mL of venous blood drawn, which was then centrifuged at 3000 rpm for 5 minutes to separate the serum, which was then used to measure iron and TIBC levels.

Estimation of iron and TIBC

Iron, as well as TIBC levels, were estimated using a commercial kit and ERBA CHEM 7 semiauto-analyzer machine, using the ferrozine/magnesium carbonate method.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 20.0 (IBM, USA) and GraphPad Prism 2023 (GraphPad Software, Boston, MA, USA). The findings were reported as mean ± Standard Deviation (SD). An unpaired student's t-test was performed to compare research parameters in the case and control groups. Pearson's correlation coefficient and regression analysis were used to determine the relationship between variables. A value of $p < 0.05$ indicated statistical significance.

Results

Table 1 shows a significant increase in mean levels of Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and iron in essential hypertension cases compared to healthy controls. TIBC levels were significantly reduced in these cases compared to controls (179.26 ± 53.47 vs 136.90 ± 38.89; $p < 0.001$, 167.09 ± 80.03 vs 261.33 ± 34.41; $p < 0.001$ respectively). Age and BMI were also increased in cases, although not statistically significant. A significant positive association between iron and SBP and an inverse association between iron and TIBC in essential hypertension cases is shown in Table 2; Figures 1 and 2. Regression analysis indicated that iron and TIBC were associated with essential hypertension. Model 1 shows the regression analysis of TIBC ($F(5,44) = 6.426$, $p < 0.001$). $r^2 = 0.422$ depicts that model 1 explains 42.2% of the variation in hypertension whereas model 2 shows the regression analysis of iron ($F(5,44) = 11.132$, $p < 0.001$). $r^2 = 0.558$ depicts that model 2 explains 55.8 % of the variation in hypertension illustrated in Table 3.

Table 1: Characteristics of subjects

Anthropometric and biochemical parameters	Cases (N=50) Mean ± S. D	Controls (N=50) Mean ± S. D	*p*
Age (Years)	46.88 ± 9.21	43.88 ± 9.46	0.111
BMI (Kg/m^2)	24.68 ± 3.53	23.70 ± 3.17	0.147
SBP (mmHg)	157.64 ± 17.21	120.3 ± 4.77	<0.001
DBP (mmHg)	93.08 ± 8.02	80.84 ± 4.73	<0.001
Iron (µg/dl)	179.26 ± 53.47	136.90 ± 38.89	0.001
TIBC (µg/dl)	167.09 ± 80.03	261.33 ± 34.41	<0.001

***Statistically significant at 0.01 level (2-tailed), p<0.01, ∗Statistically significant at 0.05 level (2-tailed), p<0.05, BMI is body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure: TIBC: total iron binding capacity*

Table 2: Correlation between variables in cases

Parameters	BMI	Age	SBP	DBP	Iron	TIBC
BMI (Kg/m^2)	1	0.156	**0.535****	271	276	0.030
Age (Years)	-	1	0.124	0.052	0.251	-0.021
SBP (mmHg)	-	-	1	0.301	**0.500****	-0.204
DBP (mmHg)	-	-	-	1	0.203	-0.022
Iron (µg/dl)	-	-	-	-	1	**-0.603****
TIBC (µg/dl)	-	-	-	-	-	1

***Statistically significant at 0.01 level (2-tailed), p<0.01, ∗Statistically significant at 0.05 level (2-tailed), p<0.05, BMI is body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure: TIBC: total iron binding capacity*

Table 3: Regression analysis model

Model	r	r^2	Adjusted r^2	Std. Error of the Estimate	Change Statistics				
					r^2 Change	F Change	df1	df2	Sig. F Change
1	0.650[a]	0.422	0.356	64.20847	0.422	6.426	5	44	0.001
2	0.747[a]	0.558	0.508	37.49153	0.558	11.132	5	44	0.001

1. Predictors: (Constant), iron, diastolic blood pressure, body mass index, age, systolic blood pressure; Dependent variable- total iron binding capacity

2. Predictors: (Constant), total iron binding capacity, body mass index, age, systolic blood pressure, diastolic blood pressure; Dependent Variable- Iron

**p<0.05 is considered significant.*

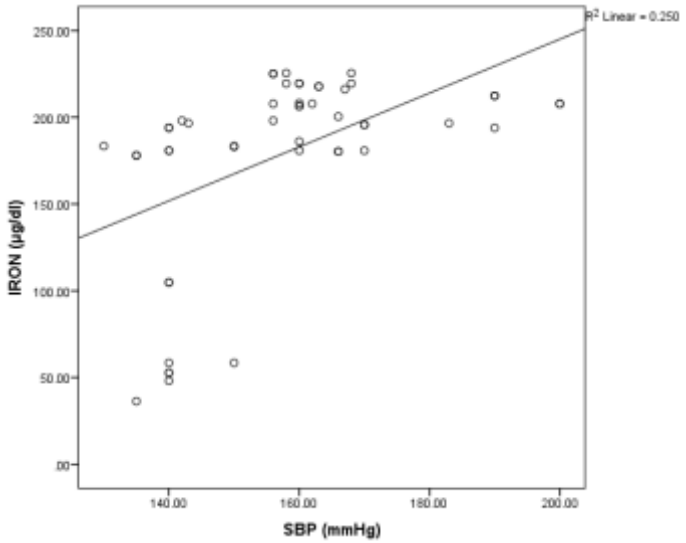

Figure 1: Relationship between systolic blood pressure and iron in cases

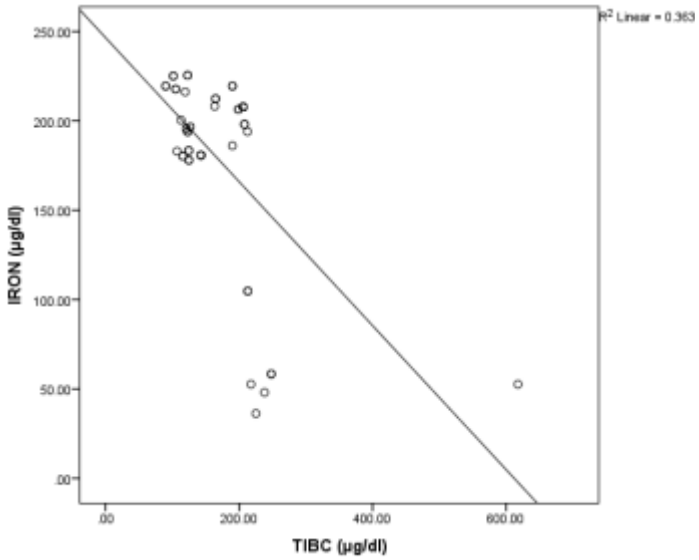

Figure 2: Relationship between iron and TIBC in cases

Discussion

Hypertension remains a significant global public health issue. Increased serum iron levels and reduced TIBC can lead to the production of free radicals and the process of lipid peroxidation, both of which are linked to a higher risk of cardiovascular disease, a leading cause of illness and death worldwide [18]. The study observed that patients with essential hypertension had higher serum iron levels and lower TIBC than controls. Iron was found to have a positive relationship with SBP and an inverse relationship with TIBC in cases with essential hypertension. According to regression analysis, the iron profile, including iron and TIBC, may predict essential hypertension and its compli-

cations. Numerous studies have shown that changes in levels of iron and TIBC in the blood have negative effects [18]. The generation of reactive oxygen compounds, which leads to inflammation as well as oxidative stress has negative effects on the functioning of mitochondria and results in hypertension, which may be influenced by iron overload [19].

Elevated body iron levels can lead to stress from oxidation that may transform less reactive free radicals into more reactive forms such as hydroxyl radicals (OH), hydroxide radicals (OH), & (O_2^-) superoxide anions, which may contribute to the development of hypertension and cardiovascular diseases [20]. The formation of Reactive Oxygen Species (ROS), which increases inflammation and oxidative stress and may lead to an increase in arterial blood pressure, may be influenced by excess iron and inadequate iron levels [21]. The combination of Low-Density Lipoprotein (LDL) and isoprostane oxidation, which act as indicators for oxidative stress, can cause endothelial damage from excessive amounts of iron, which can lead to the development and progression of atherosclerosis. Following is the atherosclerosis process, which could raise the possibility of hypertension [22]. Early work by Kiechl *et al*. 2007) found that cardiovascular disease and body iron levels were positively associated [23]. Another study on the topic by Sempos *et al*. (2004) asserts no association between stored iron and high blood pressure [24]. Similarly, Rauramaa et al. (1994) also reported an insignificant correlation between iron reserves and heart disease [25]. A recent work conducted by Ruiter *et al*. (2011) found that TIBC levels were increased and iron levels were decreased in patients with hypertension and may also show a positive correlation [26]. Likewise, Kim *et al*. (2012) in their study found that the emergence of hypertension was positively correlated with increased iron and decreased TIBC [27].

Previous studies have certain limitations, such as the fact that the inclusion and exclusion criteria differed in these studies, with varying age and ethnicity groups. This study does not yield consistent findings regarding the essential hypertension risk and the link between an iron profile and essential hypertension. To confirm the findings, more longitudinal and clinical studies with larger sample sizes controlled for confounding factors are recommended, including removing smoking and alcohol.

Conclusion

This study found that patients with essential hypertension had significantly higher iron levels and lower TIBC compared to healthy controls. This suggests that iron metabolism may be disrupted in essential hypertension. The positive association between iron levels and SBP in hypertensive patients, along with the inverse relationship between iron and TIBC, suggests iron dysregulation may play a role in the pathophysiology of essential hypertension. Iron and TIBC are valuable biomarkers or therapeutic targets in hypertension management, but further research is needed to understand the mechanisms and therapeutic implications.

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