OPEN ACCESS ORIGINAL RESEARCH ARTICLE

BLOOD TRACE ELEMENT (ZINC) ESTIMATION IN PATIENTS OF VIRAL HEPATITIS C, LIVER CIRRHOSIS AND HEPATOCELLULAR CARCINOMA IN TERTIARY CARE HOSPITALS OF PESHAWAR.

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ABSTRACT

BACKGROUND: Recent years have shown a significant prevalence of liver ailments in Pakistan, particularly in Khyber Pakhtunkhwa. Therefore, our aim is to investigate the relationship between blood trace elements and cirrhosis, hepatocellular cancer, and the Hepatitis C virus. Primary objective of this study is to explore blood zinc levels in patients with hepatitis C, liver cirrhosis and hepatocellular carcinoma. **METHODS:** The Khyber Teaching Hospital (KTH) and other partners collaborated with Lady Reading Tertiary Hospital to undertake this two-year descriptive cross-sectional study. For this research we selected 90 patients having cirrhosis, hepatocellular carcinoma or chronic hepatitis C. We equally divided our participants into 3 groups. Group I was allocated to patients with hepatitis C virus, group II had cirrhosis patients and group III consisted of hepatocellular carcinoma cases. Results were analyzed by using SPSS version 24. ANOVA test was applied. Significance level was set as $p< 0.05$. **RESULTS:** Comparison of zinc trace element between the three groups reported significant statistical differences. We observed a high ratio of zinc in Hepatitis C patients whereas a low level of zinc was found among the cirrhosis and HCC patients. Regarding age, we only found a significant relationship between the adult age group (41-50 years) with the blood zinc levels. **CONCLUSION:** Zinc plays an anti-cancerous role for cirrhosis, HCC, and HCV. Our study concluded that the reduction in the zinc element triggered many liver complications. Hepatitis C virus becomes more active when the zinc ratio increases.

KEYWORDS: Cirrhosis, Hepatocellular carcinoma, Hepatitis C virus, Zinc element

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How To Cite This Article: Khan M[1], Orakzai SA[2], Khan A[3], Khattak M[4], Khan Y[5], Daud F[6], **Blood Trace Element (Zinc) Estimation In Patients Of Viral Hepatitis C, Liver Cirrhosis And Hepatocellular Carcinoma In Tertiary Care Hospitals of Peshawar.**JPUMHS;2024:14:01,70-76. http://doi.org/10.46536/jpumhs/2024/14.01.497

RECEIVED JAN 05.2024, ACCEPTED ON 15 MARCH 2024, PUBLISHED ON 30 MARCH 2024.

INTRODUCTION

Liver disorders are considered the second crucial cause of death all around the world. In 2013 approximately 29 million people were affected with liver disorders[1]. This morbidity ratio increased in 2017 and around 30 million affected liver cases were identified in developed countries[2]. Following cancer, liver disorder is the second cause of high mortality ratio in England[3]. In 2019, the Indian region reported 10 million new cases of liver disorders[4]. Among liver disorders, the Hepatitis C virus attained researchers' interest because it leads to chronic inflammatory changes in liver eventually causing cirrhosis as well as hepatocellular carcinoma [5,6]. Recent studies explore Hepatitis C infection among 80% of hepatocellular carcinoma cases[7]. This virus is transmitted through infected blood transfusions, dental instruments, sexual contact, and through contaminated syringes[8,9]. Statistical reports revealed that 200 million people in the world are infected by chronic Hepatitis C[6]. Statistically 3.3% world's population is infected by a virus[6]. In Pakistan 8% adult population is affected by the Hepatitis C virus. Among them, 6% population has an

active virus[10]. Approximately 25% cases of HCV were observed in rural and peri-urban populations due to poor dietary patterns and lack of awareness. This virus contains six (6) basic genotypes and in Pakistan 3a genotype of HCV is considered as most prevalent. In the Khyber Pakhtunkhwa and Sindh region of Pakistan, genotype 2a is more effective than other ones[11].

On the other hand, cirrhosis enhances the mortality rate. Cirrhosis is an end stage liver disease in which patients lose their liver tissues and suffering from irreversible liver scarring. About 1% of the world population is at risk of cirrhosis which needs management and treatment[12]. Initially, cirrhosis is asymptomatic at the initial stage which causes hurdles in management and prevention. Cirrhosis also results in hepatorenal syndrome and also causes many other complications including esophageal variceal bleed and hepatocellular carcinoma[13].

Hepatocellular carcinoma is one of the most frequent types of cancer worldwide. It is the sixth most common cancer and the second leading cause of mortality globally. Hepatocellular carcinoma was the cause of 745,000 reported deaths in 2012[14]. The male population of the world is more vulnerable to HCC as compared to females[15]. Almost 85% of cases of HCC were observed in underdeveloped countries which burdened their healthcare sector[16]. Hepatitis B is considered as the root cause of HCC but in our country, HCC is highly associated (60-70%) with the progression of the hepatitis C virus[17]. There are fewer therapeutic options available for the 3.7–16% of Pakistani population that has HCC[18, 19].

These all liver disorders occur due to deficiency or toxicity of trace elements. The term "trace elements" refers to those components of the human body that are extremely small (0.02%) in quantity but have a significant impact on the body's development. These trace elements include zinc, copper, manganese, and iron[20]. In recent years many studies have explored the correlation of low trace elements with the development of carcinogenesis. Results show that these trace elements help to activate enzymatic reactions which affect the permeability of the cell membrane. In chronic hepatitis, researchers observed alterations in elements of transportation and build malignancies[21].

In recent years, Pakistan has seen a rise in the frequency of liver ailments, particularly in Khyber Pakhtunkhwa. So, we want to look at the link between blood trace elements and Hepatitis C virus, cirrhosis, and hepatocellular cancer. The purpose of this study was to determine zinc trace element levels in individuals with cirrhosis, Hepatitis C, and hepatocellular cancer.

MATERIAL AND METHOD

This two-year descriptive cross-sectional study was undertaken at Lady Reading Tertiary Care Hospital in cooperation with Hayatabad Medical Complex, Khyber Teaching Hospital (KTH), North West General Hospital, and the Institute of Radiotherapy and Nuclear Medicine (IRNUM) in Peshawar.

For this research we selected 90 patients having cirrhosis, hepatocellular carcinoma, and chronic hepatitis C. We equally divided our participants into 3 groups. In group I, we had patients with hepatitis C virus, group II included cirrhosis patients, and group III consisted of hepatocellular carcinoma cases. All the patients were selected using a nonprobability convenient sampling technique. This research follows all Helniski principles and is approved by the ethical committee of Khyber Medical University. We included Hepatitis C patients with positive Elisa. Only those patients were included who already had a biopsy and radiological evaluation of new cancer with positive alpha-fetoprotein. There was no age limitation for this research. All the patients have Wilson disease, Menkes disease was not part of this research. We further exclude Hepatitis C patients who were on interferon therapy and all patients who already consume mineral supplements before 4 months of the study period. All the patients with a history of chemotherapy and radiotherapy were not part of this research.

After taking the patients' comprehensive histories, we ensured the availability of aseptic solutions, clean syringes, and blood collection tubes. Because the patient's comfort was our primary concern, we investigated arm exposure in the supine position, as well as typical healthcare safety precautions. Venous blood samples were collected from all patients in the morning using a sterile syringe. A 3ml blood sample was collected in heparinized tubes. All samples were kept refrigerated until sample analysis was completed. The samples were subsequently processed using an atomic absorption spectrometer located at the Nuclear Institute for Food and Agriculture (NIFA)

department. Ten milliliters (10 ml) of nitric acid and perchloric acid were mixed with blood samples in a 4:1 ratio and stored overnight. Furthermore, blood samples were heated until white vapors appeared and then cooled to room temperature. The chilling procedure was carried out with fifty milliliters (50 ml) of distilled water. An atomic absorption spectrometer with 213 wavelengths was installed at the NIFA Institute. We also changed the fuel gas flow rate per minute to 2.0, the slit width to 0.5, and the Hallow cathode (HC) lamp current to 4.0. The acquired data was analyzed using ANOVA. Nominal variables are given as percentages, whereas continuous variables are provided as means and standard deviations.Non-normally distributed variables were evaluated using the Mann-Whitney U test, whereas regularly distributed and nominal variables were studied using the student t-test and Chi-square, respectively. A p-value < 0.05 is deemed significant in all analyses.

RESULTS

Out of 90 patients, 27 patients (i.e. 30%) belonged to the older age group (above 60 years). Whereas the patients between the middle and old age groups (40 to 60 years of age) had a high exposure to liver disorders. In early adult age, people were less prone to liver disorders. While comparing the gender majority of the patients were from a male population with a mean age range of 42.4 - 61.5 years. The male Population of the study had high exposure to cirrhosis whereas the female population was most vulnerable to hepatocellular carcinoma tumors. (Table 1, 2, 3).

Table 1: Association of age group and liver disorders.

Age group	Cirrhosis	HCC	HCV	Total	Percentage
>60 years	7	17	3	27	30%
51-60 years	12	7	2	21	23.3%
41-50 years	7	5	9	21	23.3%
31-40 years	4	0	7	11	12.2%
20-30 years	0	1	9	10	11.1%
Total	30	30	30	90	100%

Table 2: Mean age of affected groups

Variables	Cirrhosis	HCC	HCV	P-value
Age	54.8 ±11.99	61.5 ± 11.66	42.4 ± 14.74	0.005

Table 3: Gender association with liver disorders

Variables	Cirrhosis	HCC	HCV	Total	Percentage
Female	12	14	13	39	43.3%
Male	18	16	17	51	56.7%
Total	30	30	30	90	100%

Comparison of zinc element between the three groups reported significant statistical differences. We observed a high ratio of zinc in Hepatitis C patients whereas a low level of zinc was found among the cirrhosis and HCC patients. Regarding age, we only found a significant relationship between the adult age group (41-50 years) with a zinc element. (Table 4,5).

Table 4: Traces of zinc element and mean ratio of Zinc in three studying group.

Chemical Parameters		Cirrhosis n (%)	HCC n (%)	HCV n (%)	p value
Zinc	Increase	3 (10%)	2 (6.7%)	12 (40%)	0.005
	Decrease	14 (46.7%)	11 (36.7%)	3 (10%)	
	Normal	13 (43.3%)	17 (56.7%)	15 (50%)	
Zinc Mean ± SD		5.5 ± 4.32	5.2 ± 3.04	9.1 ± 4.96	

Table 5: Correlation between age group and zinc element in three study groups

Age group	Cirrhosis Mean ± SD	HCC	HCV	p-value

> 60 years	(7) 6.7 ± 5.56	(17) 4.9 ± 3.11	(3) 6.5 ± 1.22	0.521
51- 60 years	(12) 5.0 ± 4.43	(7) 5.3 ± 1.73	(2) 9.2 ± 5.23	0.368
41-50 years	(7) 4.6 ± 1.90	(5) 5.8 ± 4.78	(9) 9.9 ± 5.61	0.073
31-40 years	(4) 9 ± 5.52	0	(7) 9.9 ± 5.53	0.408
20- 30 years	0	(1) 6.200	(9) 8.5 ± 5.16	0.683

DISCUSSION

In recent years the investigation of blood traces caught the attention of researchers after having a severe impact on patients with hepatitis C, hepatocellular carcinoma, and cirrhosis. Different studies found low, high, and constant blood trace elements among patients[22]. Studies reported a low level of element traces, especially zinc, which worsen the condition of the patient and the patient becomes more vulnerable to liver disorders. In the progression of the hepatitis C virus, a reduction in metabolism of trace elements was found in recent years which enhance morbidity ratio[23]. In our study, we found a reduction of zinc element among the cirrhosis and hepatocellular carcinoma cases whereas increased zinc level was reported in chronic viral hepatitis cases. Our results are in contradiction of previous studies of Qasim et al[23], Ko et al[24] and Nagase et al[25] but also support the argument of Solis et al[26] and others[27-36]. In a study by Qasim[23] and Ko et al[24], they found a low level of zinc among the cases of chronic viral hepatitis. During observations, we observed a reduction in mean zinc value which was also reported in the previous study by Mezey et al[37], Solis et al[26] and others[27-36]. On the other hand, Nagase et al[25] observed a high zinc ratio among the cirrhosis cases. Low zinc ratio is directly associated with the poor binding of protein, testicular atrophy, cerebral and immune dysfunction. Toxicity of zinc may cause hepatic failure when combined with a high ratio of copper and iron.

The direct relationship between blood zinc level and HCC was drawn in the study of Costello and Frankin[38]. They observed that blood zinc level is directly associated with the development and progression of hepatocellular carcinoma. In our study, we observed a reduction of zinc levels among HCC patients. Our study result were as Poo et al[39], and others[40,41]. At the same time, our study was in contradiction of El Fotouch at el[42] in which they observed a high amount of zinc among HCC patients. Poor diet and intestinal absorption, high urinary loss, and less liver storage are considered as the root causes of low zinc level whereas impaired hepatic function especially less albumin production dramatically changes the zinc level in many cases[43]. In cirrhosis cases, a high zinc ratio is required to synthesize nucleic acid protein and enzymes during cell damage and inflammation which causes a deficiency of zinc among patients[44]. In the recent years many scholars have observed reduction in metallothionein protein in cirrhotic patients due to the overall low protein synthesis among them[45].

Zinc is also responsible for the development of chronic hepatic liver disease. Qasim et al reported a huge contribution of zinc in the development and replication of hepatitis C virus among patients[46]. In many cases, non-stable zinc levels cause many obstacles in the identification of malignant cell activities. A normal level of zinc has a tumor suppressor effect on malignant cells. To avoid this effect malignant cells alter the zinc transporters which results in low zinc levels[47]. These observations were reported in HCC tissues with low zinc levels in cancerous cells while comparing with normal hepatocytes. Development of tumors required low zinc levels for their development. For chronic hepatitis cases, physicians recommend zinc treatment to control or prevent malignancy[48].

CONCLUSION

Zinc plays an anti-cancerous role in liver cirrhosis, HCC, and HCV infection. It can be concluded from our study that the reduction in the zinc element acts as a trigger for many liver complications. Hepatitis C virus becomes more active when the zinc ratio increases. The reduction and toxicity of Zinc may cause severe liver complications and over burden the healthcare sector. There is a need to diagnose patients at an early stage to reduce morbidity and mortality ratio. Dietary plans are required to be practiced in our country to reduce the risk of liver disorders.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

FUNDING: The work was not financially supported by any organization. The entire expense was taken by the authors.

ACKNOWLEDGEMENTS: We are thankful to all who were involved in our study.

AUTHORS' CONTRIBUTIONS: All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST: No competing interest declared

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