



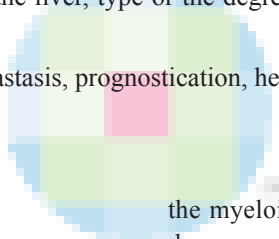
Plasma Hepatic Enzymes as Biopredictors of Type, Metastasis, and Prognostication of Hematological Malignancies

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Background and Aim: The present study evaluated the levels of some hepatic enzymes in the plasma of Nigerians affected with hematological malignancies, to determine if these enzymes could be established as predictors of possible metastasis to the liver, the degree of severity of the disease or prognostication of hematological malignancies. **Materials and Methods:** Twenty-seven consented subjects with multiple myeloma ($n = 4$), non-Hodgkins lymphoma ($n = 5$), Hodgkins lymphoma ($n = 5$), chronic myeloid leukemia ($n = 6$), and chronic lymphoid leukemia ($n = 6$) as well as control subjects ($n = 7$) were recruited having gotten the ethical approval from the authorities of the teaching hospitals used for the study. Evaluations of activities of enzymes (acid and alkaline phosphatases, alanine and aspartate transaminases, lactate, and glucose-6-phosphate dehydrogenases) were carried out in the samples collected. Statistical analysis was performed using SPSS version 20 software. **Results:** Statistically significant levels of the enzymes were found in chronic hematological malignancies such as chronic myeloid leukemia and chronic lymphoid leukemia. **Conclusion:** Evaluating the plasma levels of hepatic enzymes in Nigerians affected with hematological malignancies could assist in predicting possible metastasis to the liver, type or the degree of severity of the disease, or prognostication of hematological malignancies affected.

Key words: Hepatic enzymes, biopredictors, metastasis, prognostication, hematological malignancies



INTRODUCTION

The hepatologists or general physicians sometimes encounter hepatic manifestations of various hematologic disorders in daily practice, including various abnormalities in liver function tests or imaging studies of the liver. Some hematologic disorders also mimic liver diseases.¹⁻³ Neoplasms derived from hematopoietic and lymphoid tissues are classified according to their morphologic, immunophenotypic, genetic, and clinical features and by the type of originating cell lineage and differentiation stage according to the widely used and accepted the World Health Organization classification system of 2001, which was updated in 2008.⁴

The leukemias, lymphomas, and multiple myeloma (MM) though uncommon, are rare interrelated malignancies of

the myeloid and lymphoid systems of the body.⁵ When cell damage occurs due to malignancies of the myeloid and lymphoid systems or other diseases; the levels of plasma enzymes are dependent on the nature and extent of cell damage as well as the rate of release from damaged cells.⁶ However, the rate of release is dependent on the degree of induction of enzyme synthesis and the rate of cell proliferation is balanced by the rate of enzyme clearance, in the absence of cell damage.⁶

Metastasis to the liver can also affect its physiologic functions which may manifest in the form of elevation of hepatic enzymes.⁶ Hence, evaluations of levels of plasma enzymes could provide significant insight

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into the understanding of the nature and extent of cell damage in malignancies of the myeloid and lymphoid systems as well as possibility of metastasis.^{5,6} This study, therefore, evaluated the levels of lactate and glucose-6-phosphate-dehydrogenases, Acid and Alkaline Phosphatases, Alanine and Aspartate Transaminases in the sera of Nigerians affected with hematological malignancies, to determine if these enzymes could be established as predictors of possible metastasis to the liver, type, or the degree of severity of the disease or even prognostication of hematological malignancies.

MATERIALS AND METHODS

Ethical approval

Informed oral consents were sought and received from all individuals that participated in the study; and the study was carried out in accordance with the ethical guidelines of the Helsinki Declaration of 1975, as revised in 2000 with respect to the use of human blood samples for research purposes. In addition, ethical approval was received from the Faculty of Basic Medical Sciences of Olabisi Onabanjo University, Ogun State, Nigeria with respect to the use of human blood samples for research purposes.

Collection of blood samples

A volume of 5 ml of blood samples were each collected in lithium heparin bottle from 27 Nigerians affected with hematological malignancies from Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, Lagos State University College of Medicine, Ikeja, Lagos State, University College Hospital, Ibadan, Oyo State, Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun State and the University of Ilorin Teaching Hospital, Ilorin, Kwara State. There were 6 cases of chronic myelocytic leukemia (CML), 6 cases of chronic lymphocytic leukemia (CLL), 4 cases of MM, 5 cases of non-Hodgkin's lymphoma (NHL) and five (5) cases of Hodgkin's lymphoma (HL). Each case of the hematological malignancy was a cross-sectional subject group; hence, 5 cross-sectional subject groups were evaluated in the study whereas 6 apparently healthy students of Olabisi Onabanjo University, Ogun State were used as controls.

Handling of blood samples

A volume of 5 ml blood samples collected into lithium heparin bottles were centrifuged at 4000 revolution per minute for 5 min and the supernatant, which is the plasma was collected and stored in airtight Eppendorf bottle at -4°C in a refrigerator.

Reagents

Enzyme assay kits for lactate dehydrogenase (LDH) and glucose-6-phosphate-dehydrogenase (G6PDH), acid phosphatase (ACP), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST) kits were products of Randox Laboratories limited; United Kingdom, and were supplied by LIMED International Limited, Idumota Lagos State, Nigeria.

Evaluations of activities of enzymes in plasma

Evaluations of activities of enzymes (ACP, ALP, ALT, AST, LDH, and G6PDH) were carried out as described in the protocols of Randox kits used for the assay of each enzyme.

Statistical analyses

Statistical analysis was performed using SPSS version 20. The mean $\pm$ standard error of mean value of each of the measured plasma enzymes (ACP, ALP, ALT, AST, LDH, and G6PDH) in Nigerians affected with hematological malignancies cross-sectional subjects' groups were compared with one another; and with the controls for any significant difference using the Student's *t*-test for unpaired samples. $P \leq 0.05$ were taken as statistically significant.

RESULTS

Mean ages of subjects and the control groups

The mean age for the control group was 27 ± 4 years, the mean age for the CML group was 34 ± 13 years, the mean age for the CLL group was 53 ± 11 years, the mean age for the MM group was 64 ± 11 years, the mean age for the NHL group was 13 ± 6 years, while the mean age for the HL group was 18 ± 9 years [Table 1].

Evaluations of plasma levels of lactate dehydrogenase

There was a significant increase ($P < 0.05$) in LDH level in HL group compared with the NHL group. There was

Table 1: Mean ages of subjects and the control groups

Type of hematological malignancy	Mean age (years) $\pm$ SD
MM	64 $\pm$ 11
NHL	13 $\pm$ 6
HL	18 $\pm$ 9
CML	34 $\pm$ 13
CLL	53 $\pm$ 11
Control	27 $\pm$ 4

SD=Standard deviation; MM=Multiple myeloma; NHL=Non-Hodgkin's lymphoma; HL=Hodgkin's lymphoma; CML=Chronic myelocytic leukemia; CLL=Chronic lymphocytic leukemia

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a significant increase ($P < 0.05$) in LDH level in the HL group compared with the MM group. However, there was a nonsignificant increase ($P > 0.05$) in LDH level in NHL group compared with the MM group. Furthermore, there was a significant increase ($P < 0.05$) in LDH level in the CML group compared with the CLL group. There were significant increases ($P < 0.05$) in LDH levels in the CML and CLL Groups compared with the HL, NHL, and MM groups. In addition, there were significant increases ($P < 0.05$) in LDH levels in the HL, NHL, MM, CML, and CLL Groups compared with the control Group [Table 2].

Evaluations of plasma levels of glucose-6-phosphate-dehydrogenase

There was a significant increase ($P < 0.05$) in G6PDH level in HL group compared with the NHL group. There was a significant increase ($P < 0.05$) in G6PDH level in the HL group compared with the MM group. However, there was a nonsignificant increase ($P > 0.05$) in G6PDH level in MM group compared with the NHL group. Furthermore, there was a significant increase ($P < 0.05$) in G6PDH level in the CML group compared with the CLL group. There were significant increases ($P < 0.05$) in G6PDH levels in the CML and CLL groups compared with the HL, NHL, and MM groups. In addition, there were significant increases ($P < 0.05$) in G6PDH levels in the HL, NHL, MM, CML and CLL groups compared with the control group [Table 2].

Evaluations of plasma levels of acid phosphatase, alkaline phosphatase, alanine transaminase and aspartate transaminase

There were significant increases ($P < 0.05$) in ACP and ALP levels in the CML group compared with the control group [Table 3]. However, there was a nonsignificant increase ($P > 0.05$) in ACP level in the MM group compared to the control group, whereas there was a significant decrease ($P > 0.05$) in ALP level in the MM group compared to the control group. There were significant increases ($P > 0.05$) in ALT and AST levels in the CML group compared with the control group. However, there was a nonsignificant increase ($P > 0.05$) in ALT level in the MM group compared to the control group, whereas there was a significant increase ($P > 0.05$) in AST level in the MM group compared to the control group [Table 3].

DISCUSSION

The hepatologists or general physicians sometimes encounter hepatic manifestations of various hematologic disorders in daily practice, including various abnormalities

Table 2: Plasma levels of lactate dehydrogenase and G-6-phosphate-dehydrogenase in the control, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, chronic myelocytic leukemia and chronic lymphocytic leukemia groups

Group	LDH (U/L)	G-6-PDH (U/L)
HL	417.15±49.85*	21.45±3.79*
NHL	326.66±36.85*	11.57±2.01*
MM	322.94±18.10*	14.72±2.39*
CML	1086.78±198.97*	280.90±75.36*
CLL	449.47±46.32*	102.88±10.79*
Control	219.73±12.59*	2.73±0.72*

* $P < 0.05$ (comparison between subjects and control). LDH=Lactate dehydrogenase; PDH=Phosphate-dehydrogenase; HL=Hodgkin's lymphoma; NHL=Non-Hodgkin's lymphoma; MM=Multiple myeloma; CML=Chronic myelocytic leukemia; CLL=Chronic lymphocytic leukemia; G-6-PDH=G-6-phosphate-dehydrogenase

Table 3: Plasma levels of acid phosphatase, alkaline phosphatase, alanine transaminase, aspartate transaminase in the multiple myeloma, chronic myelocytic leukemia, Hodgkin's lymphoma, and control groups

Group	ACP (U/L)	ALP (U/L)	ALT (U/L)	AST (U/L)
MM	3.79±0.86*	36.39±7.35*	7.80±1.16*	72.75±6.43*
CML	7.40±0.66*	140.00±5.30*	19.72±2.00*	17.40±2.25*
HL	1.77±0.48*	32.2±8.8*	5.08±1.25*	18.5±1.66*
Control	2.78±0.48*	80.30±15.20*	6.25±1.26*	5.30±0.92*

* $P < 0.05$ (comparison between subjects and control). ACP=Acid phosphatase; ALP=Alkaline phosphatase; ALT=Alanine transaminase; AST=Aspartate transaminase; MM=Multiple myeloma; CML=Chronic myelocytic leukemia; HL=Hodgkin's lymphoma

in liver function tests or imaging studies of the liver. Some hematologic disorders also mimic liver diseases.¹⁻³ When cell damage occurs due to malignancies of the myeloid and lymphoid systems or other diseases; the levels of plasma enzymes are dependent on the nature and extent of cell damage as well as the rate of release from damaged cells.⁶ Liver infiltration of malignant cells has been reported in 14% of patients with HL. Hepatomegaly is found in 9% of patients with disease Stages I–II and in 45% of patients with Stages III–IV.⁷

There is paucity of data which evaluated the levels of LDH, G6PDH, ACP, ALP, ALT and AST in hematological malignancies. In this study, mild elevation of ALT was found in subjects with MM when compared with that of the controls. Moderate elevation was found in subjects with CML while levels in other hematological malignant groups were not significantly elevated. AST level was very high in subjects with MM, but moderately elevated in subjects with CML and HL. ALP was equally moderately elevated in CML. The mild

elevation of aminotransferases and moderate elevation of ALP can occur due to tumor infiltration or extrahepatic bile duct obstruction.⁷ This cholestasis can be caused by direct infiltration of lymphoma cells, extrahepatic biliary obstruction, viral hepatitis, drug hepatotoxicity, or vanishing bile duct syndrome.⁸ Liver function tests of NHL patients show mild to moderate elevation in serum ALP.⁷

Plasma LDH levels were found to be significantly elevated in CML, moderate in CLL and mildly elevated in HL, NHL, and MM. Similar findings is also often seen in patients with NHL, especially in highly aggressive type such as Burkitt or lymphoblastic lymphoma, reflecting high tumor burden, extensive infiltration of the liver, and coincident immune-mediated hemolytic anemia, which are associated with poor prognosis.

In this study, plasma G6PDH levels were also found to be significantly elevated in CML, moderate in CLL and mildly elevated in HL, NHL and MM. Primary NHL of the liver is a rare condition, accounting for <1% of all extranodal lymphomas. Two-thirds of cases occur in men aged approximately 50 years. Presenting symptoms include abdominal pain, fever, hepatomegaly, and abnormal liver function tests with elevation of LDH higher than that of ALT.^{9,10} The most common histological subtype of primary hepatic NHL is diffuse large B-cell lymphoma, comprising 80%–90% of cases. This disease may present with nodules in the liver or diffuse portal infiltration and sinusoidal spread.¹¹ All these will eventually lead to intrahepatic obstruction and consequently cholestasis.

Liver involvement is often observed in several hematological disorders, resulting in abnormal liver function tests, abnormalities in liver imaging studies, or clinical symptoms presenting with hepatic manifestations. In hemolytic anemia, jaundice, and hepatosplenomegaly are often seen mimicking liver diseases. In hematologic malignancies, malignant cells often infiltrate the liver and may demonstrate abnormal liver function test results accompanied by hepatospleno-megaly or formation of multiple nodules in the liver and/or spleen. These cases may further evolve into fulminant hepatic failure. In the chronic phase, approximately 50% of patients with CML show mild to moderate hepatomegaly at presentation, with no liver function abnormalities.¹² In this study, however, there was moderate disturbance of hepatic function in CML as manifested by the moderate to significant changes found in all the hepatic enzymes assayed for. It has also been discovered that at the time of blastic crisis, liver sinusoidal infiltration by immature cells may lead to liver enlargement and elevated serum ALP levels.¹³

CONCLUSION

From interpretation of data obtained in this study, evaluation of plasma levels of hepatic enzymes such as

Lactate and Glucose-6-phosphate-dehydrogenases, Acid and Alkaline Phosphatases, Alanine and Aspartate Transaminases in Nigerians affected with hematological malignancies could assist in studying the prognostication of hematological malignancies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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