Role of Gamma Glutamyltransferase and Alkaline Phosphatase Assay in Enzymatic Panel for Hepatobiliary Function in Patients Attending Kibungo Hospital, Rwanda

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ABSTRACT

Background: Liver complications show specific processes like hepatoxicity associated with drugs, primary neoplasm, or hepatotropic virus infections. Different markers based on laboratory testing help to diagnose and monitor liver related conditions. Mostly used tests are classed in a set known as hepatic panel or liver profile mainly consisting of body enzymes.

Objective: The objective of the present study was to ascertain the role of gamma glutamyltransferase (GGT) and alkaline phosphatase (ALP) assay in enzymatic panel for hepatobiliary function assessment among patients attending Kibungo hospital.

Methods: Two hundred twenty-five clients were included in the study. Demographic data were collected from December 2016 to March 2017. Blood sera were also collected and tested for serum GGT and ALP levels. Statistical package for social sciences (SPSS) was used in data analysis.

Results: Seventy-four point seven per cent of clients had normal GGT whereas 63.1% had normal ALP. The 0.9% of clients comprised low levels of ALP. The means were 53 and 153 U/L for GGT and ALP, respectively. Fifty per cent of alcohol consumers’ population had elevated GGT and ALP. An increase of 69.2 and 61.5% for GGT and ALP, respectively was observed in smokers’ population. The subpopulation of hepatitis C virus (HCV) was the most with elevated GGT and ALP levels. In HIV population, serum GGT and ALP were raised at 31.1 and 37.8%, respectively. In fact, hepatitis B virus (HBV), HCV, and HIV patients are clinically considered as immuno-compromised people. Alcohol consumption and smoking were also found to increase GGT and ALP concentrations. In addition, GGT and ALP levels were simultaneously elevated in 19.6% of the clients, indicating the frequency of cholestatic liver disease.

Conclusion: Elevated GGT and ALP revealed the occurrence of cholestasis among study participants due to factors that elevate serum GGT and ALP levels as a result of dysfunctional liver conditions. In hospital laboratories, GGT and ALP should always be included in the panel of tests for screening and bio-monitoring liver related conditions in Rwanda.

Key words: Cholestatic liver disease; Kibungo hospital; Enzymatic panel; Alkaline phosphatase; Glutamyltransferase

INTRODUCTION

Gamma glutamyltransferase (EC 2.3.2.2) catalyzes the transfer of gamma-glutamyl functional groups from substances like glutathione to an acceptor that may be an amino acid, a peptide or water forming glutamate. Alkaline phosphatase (EC 3.1.3.1) is a ubiquitous metalloenzyme that catalyzes the breakdown of monophosphate in the body by hydrolysis reaction. Both GGT and ALP are mostly produced in the liver. Complications of the liver usually show specific processes like hepatoxicity associated with drugs, primary neoplasm, or hepatotropic virus infections.

Liver diseases include viral hepatitis, alcoholic hepatitis and cirrhosis. Cholestatic liver diseases are primarily risks for cirrhosis. These diseases progress slowly in patients and may result in hepatocellular carcinoma (HCC). The long-term consequences of hepatobiliary and cholestatic diseases are major contributors to global mortality.
Apart from laboratory tests for parameters which may change in patients with liver and biliary diseases, the most sensitive and complementary biomarkers for such diseases are serum liver enzymes. The physiological applications of GGT are transport function. For instance, the transport of amino acids through reactions sequence to form a gamma-glutamyl cycle. GGT is also most important for the availability of the cysteine whose cycle of reactions lead to the glutathione synthesis. For the clinical use, GGT was investigated and accepted as a liver function test 50 to 60 years back. For example, it helps in hepatitis C and alcoholic-related liver diseases diagnosis. Other conditions like type 2 diabetes and obesity were associated with nonalcoholic steatohepatitis (NASH) as they share many clinical features with alcoholic liver disease; and in most patients with this condition, GGT is increased. The GGT increase was attributed to serum GGT release into the circulation as the result of bile acids acting on the cell membrane. The induction of GGT may also be ascribed to some extent specific for alcohol related disease. Therefore, hepatic GGT is increased in some types of liver diseases and the increase in serum GGT is not easily caused by the release of the enzyme from damaged cells.

As the body mechanism, the response of the liver to any obstructive biliary tree induces hepatocytes to synthesize ALP and newly formed coenzyme is released from the cell membrane by the action of bile salts and enters the blood circulation to increase the enzyme’s serum activity. This ALP increase tends to be noteworthy in extrahepatic obstruction than in intrahepatic obstruction and it is greater in the more complete obstruction. Serum ALP activity may reach ten up to twelve times the normal range and usually return to baseline on surgical removal of the obstructed part. The same raise is observable in patients with primary liver cancer or widespread secondary hepatic metastases. The increase of ALP at least greater than 2 folds the normal range may predict transplant-free survival rates of patients with primary biliary cirrhosis. Several hepatic tests are used to improve the detection of liver diseases. They basically differentiate clinically suspected disease and determine how severe the liver is damaged. Liver enzymes are commonly elevated in patients with liver diseases and therefore reflect the status of liver damage. Consequently, physicians use significant elevations of serum enzymes GGT and ALP levels as biomarkers of cholestatic predominant diseases, like obstructive biliary tree disease and biliary cirrhosis, leading to chronic liver failure. Unfortunately, no study about the use and diagnostic role of these enzymes has been done in Rwanda. Although GGT and ALP test reagents are ordered like other liver enzymes, they are rarely included in the enzymatic panel for liver function assay in many hospitals. However, results for this couple of tests should usually be analyzed together with other liver function tests in order to interpret in a wide diagnostic spectrum. Thus, the present study was carried out to determine the role of GGT and ALP assay in enzymatic hepatic panel when assessing the liver and biliary function among patients attending Kibungo hospital, in Rwanda.

METHODS

Kibungo hospital
Kibungo hospital was built in 1932 by China and it is among the oldest medical facilities in Rwanda. It is located in the Eastern Province of Rwanda, Ngoma District and was formerly known as a District hospital. Today, Kibungo hospital is under the Ministry of Health and was made a referral hospital and named Kibungo Referral Hospital. The hospital has a well-equipped modern laboratory bloc that makes possible for the hospital to meet international standard testing requirements. The hospital serves more than 15 health centers of all Ngoma District’s Sectors.

Ethical consideration
The study proposal was presented to ethic committees of both INES Ruhengeri and Kibungo hospital. Ethical approvals were obtained from both institutions’ ethics committees.

Inclusion criteria
Clients who attended Kibungo hospital laboratory during the study period and requested for any clinical chemistry laboratory test for liver conditions assessment were requested to participate in the study. Patients who met these criteria and who voluntarily consented to participate in the study were enrolled in the study. The participation of patients less than 18 years old was accepted after consent from their parents/guardians.

Exclusion criteria
Patients who were excluded from participation in the study included those who attended the laboratory for tests other than clinical chemistry; those who refused to consent for the participation and patients less than 18 years old, who did not have consent from their parents/guardians.

Sampling methods
Simple random probability sampling technique was adopted during the determination of the sample size for this study.

Demographic data and risk factors
The questionnaire was used to collect demographic, viz. sex, age, weight and marital status.
To ensure the confidentiality of clients’ information, only study numbers, and not names, were used on the data collection tools. Imperative risk factors that elevate GGT and ALP levels were assessed via the oral interview with the patient prior to blood draw. Short answer ended questions were used in risk factors assessment. Data were recorded in raw database on daily basis.

**Serum GGT and ALP levels determination**
Whole blood was collected and separated using clinical laboratory centrifuge (Z100A) to obtain serum. During the entire study, 225 blood sera were tested for GGT and ALP activity. The GGT and ALP levels were automatically generated by the chemistry analyzer Roche Cobas C311.

**Statistical analysis**
Results for GGT and ALP were grouped in classes. The interval was determined by subtracting the lower reference limit from the upper limit. ALP/GGT ratio was used to test the distribution of results using one sample Kolmogorov-Smirnov test. Basing on those results, the classification of results as normal, low or high (elevated) was done. Six (6) classes were formulated for each enzyme levels as follows (a) for GGT: < 5, [5-61], [62-118], [119-175], [176-232], and > 232; (b) for ALP: < 40, [40-129], [130-219], [220-309], [310-399], and > 399. The class intervals were 56 and 89, for GGT and ALP, respectively. The variability of GGT and ALP levels was studied based on reference limits for both enzymes. Obtained results were also interpreted according to risk factors. Karl Pearson’s correlation analysis was used to associate risks factors with enzymes’ elevation. From GGT and ALP levels, simultaneously elevated levels were scrutinized. Data were statistically analyzed using statistical package for social sciences (SPSS), version 24. P < 0.001 was considered as significant.

**RESULTS**

**Demographic data and risk factors**
Demographic data and risk factors for participants are presented in Table 1. The females were in higher number compared to males, and most of the studied population, about two third, was married. Risk factors were assessed for all participants. Most of the population (around 80-90%) do not smoke, not consume alcohol, and do not have viral hepatitis. Sixty seven percent (67%) of them do not have HIV.

| Description          | Number | Percentage |
|----------------------|--------|------------|
| **Sex**              |        |            |
| Female               | 121    | 53.8       |
| Male                 | 104    | 46.2       |
| Total                | 225    | 100.0      |
| **Marital status**   |        |            |
| Infant               | 14     | 6.2        |
| Single               | 58     | 25.8       |
| Married              | 150    | 66.7       |
| Widow                | 3      | 1.3        |
| Total                | 225    | 100.0      |
| **Alcohol consumption** |      |            |
| No                   | 183    | 81.3       |
| Yes                  | 42     | 18.7       |
| Total                | 225    | 100.0      |
| **Smoking**          |        |            |
| No                   | 212    | 94.2       |
| Yes                  | 13     | 5.8        |
| Total                | 225    | 100.0      |
| **Viral hepatitis**  |        |            |
| None                 | 202    | 89.8       |
| HBV                  | 6      | 2.7        |
| HCV                  | 17     | 7.6        |
| Total                | 225    | 100.0      |
| **HIV status**       |        |            |
| No                   | 151    | 67.1       |
| Yes                  | 74     | 32.9       |
| Total                | 225    | 100.0      |
Serum GGT and ALP levels among participants

Serum levels for GGT and ALP among participants are presented in Table 2. For GGT, most of the patients had levels falling within the normal range. No patient was found with levels below normal range, however, 25.3% had levels above limit. Similarly, for ALP, most of the participants had levels within the normal range, with 0.9 and 26% below and above normal ranges, respectively.

### TABLE 2. GGT and ALP levels

| GGT (U/L) | Frequency | Percent | ALP (U/L) | Frequency | Percent |
|-----------|-----------|---------|-----------|-----------|---------|
| <5        | 0         | 0       | <40       | 2         | 0.9     |
| [5-61]    | 168       | 74.7    | [40-129]  | 142       | 63.1    |
| [62-118]  | 36        | 16.0    | [130-219] | 46        | 20.4    |
| [119-175] | 13        | 5.8     | [220-309] | 13        | 5.8     |
| [176-232] | 1         | 0.4     | [310-399] | 11        | 4.9     |
| >232      | 7         | 3.1     | >399      | 11        | 4.9     |
| Total     | 225       | 100.0   | Total     | 225       | 100.0   |

GGT and ALP according to alcohol consumption

The serum GGT and ALP levels in drinkers’ subpopulation were determined (Tables 3 and 4). In both cases, 50% of the clients consuming alcohol were found to have higher values of both enzymes. No client found to have levels below normal range for GGT, whereas 1 was below average level for ALP.

### TABLE 3. GGT levels among patients according to their sub populations

| GGT Levels (U/L) | Alcohol consumers | Cigarette smokers | Viral hepatitis patients | HIV patients |
|------------------|-------------------|-------------------|--------------------------|--------------|
|                  | HBV               | HCV               | Total                    |              |
| <5               | 0                 | 0                 | 0                        | 0            |
| [5-61]           | 21                | 4                 | 4                        | 12           |
| [62-118]         | 13                | 5                 | 1                        | 6            |
| [119-175]        | 5                 | 1                 | 1                        | 2            |
| [176-232]        | 0                 | 0                 | 0                        | 0            |
| >232             | 3                 | 3                 | 0                        | 1            |
| Total            | 42                | 13                | 6                        | 17           |
|                  |                   |                   | 23                       | 74           |

### TABLE 4. ALP levels among patients according to their sub populations

| ALP Levels (U/L) | Alcohol consumers | Cigarette smokers | Viral hepatitis patients | HIV patients |
|------------------|-------------------|-------------------|--------------------------|--------------|
|                  | HBV               | HCV               | Total                    |              |
| <40              | 1                 | 0                 | 0                        | 0            |
| [40-129]         | 20                | 5                 | 1                        | 6            |
| [130-219]        | 9                 | 2                 | 1                        | 6            |
| [220-309]        | 4                 | 2                 | 3                        | 6            |
| [310-399]        | 3                 | 1                 | 1                        | 2            |
| >399             | 5                 | 3                 | 0                        | 3            |
| Total            | 42                | 13                | 6                        | 17           |
|                  |                   |                   | 23                       | 74           |
Role of glutamyltransferase and alkaline phosphatase assay in enzymatic panel

**GGT and ALP according to smoking**

GGT and ALP levels according to smoking were investigated and 69.2% had elevated GGT levels (Table 3) while 61.5% had raised ALP (Table 4). No patient was found with levels below normal ranges for both enzymes.

**GGT and ALP according to viral hepatitis**

In the current study, 2.7% participants had HBV infection and 7.5% had HCV infection. Among patients with HBV and HCV infections, none had levels below normal range for both GGT and ALP enzymes. Among HBV patients, 33.3% and 83.3% had high levels for GGT and ALP, respectively. In HCV patients, 52.2% and 70.6% had elevated levels for GGT and ALP, respectively (Table 3 and 4).

**GGT and ALP according to HIV status**

The levels of GGT and ALP according to HIV status were assessed and 68.9% and 62.2% were in normal ranges for GGT and ALT levels, respectively. No clients were found to have levels below normal ranges (Table 3 and 4).

**DISCUSSION**

The present study was carried out to highlight the role of GGT and ALP assay in enzymatic hepatic panel when investigating the liver and biliary function among patients attending Kibungo hospital. The target population for the present study was 673 but data were collected from 225 participants who were chosen randomly. By considering the population and sample size, 1 participant in the study represented 3 clients in the target population.

Levels of GGT and ALP vary from person to person, depending on demography and factors like alcohol consumption, tobacco use, viral hepatitis, and living with HIV. Previous studies have shown that alcohol consumption, cigarette smoking, viral hepatitis, and HIV infection are associated with elevation of GGT and ALP levels. It has also been established that serum GGT and ALP are predominantly biomarkers of cholestatic disease. The normal ranges for GGT and ALP are within 5-61 and 40-129 U/L, respectively. In the present study, serum levels for GGT and ALP among participants were analyzed and values within normal ranges were found to be high whereas values less than normal limits were low for both GGT and ALP.

The normal distribution was significant (P < 0.001) as shown by the ratios of ALP to GGT, which were used to test that distribution. High levels of ALP were observed in infants and males. ALP levels also correlated with the weight of participants. Demographically, ALP levels are higher in males than females and the levels correlate with the weight of the person. ALP levels are also high in neonates and children with accelerated bone growth. In this study, classes formed served to find abnormal values of studied enzymes. High levels were classified in 4 classes as it specifies the degree of enzyme levels elevation. For example, participant in the 6th class had elevated levels greater than 3 times.

The means levels for 225 clients were 53 for GGT and 153 U/L for ALP. The mean level of GGT was within the reference limits but tended to surpass its peak. In contrast, the mean level of ALP exceeded its upper limits. Results were significant and basing on averages, participants were probably having some of the factors, which result in elevation of ALP levels. Indeed, all forms of cholestasis were dominant among participants. King and Armstrong evaluated ALP among subjects and the elevation was significant in patients with liver diseases. The mean of levels in statistical distribution viewed the normality and abnormality of GGT and ALP, respectively. 0.9% of participants had low ALP levels. Zinc is a coenzyme of ALP catalyzed reactions, and persistent low levels of ALP may mean low zinc levels of serum. Despite hepatobiliary diseases, other disorders in the body can interfere in the levels of ALP. To analyse ALP with GGT together as a couple test may help to detect cholestasis among participants.

According to Wolf, in alcoholic liver disease GGT raises 8-20 times the upper limits and persistence elevation is an indicator of cirrhosis. In the present study, the serum GGT level was high in 50% clients consuming alcohol. The same percentage (50%) for elevated ALP levels was obtained for drinkers’ population. GGT and ALP were significantly elevated (P < 0.001). The high alcohol intake can lead to chronic liver failure, a condition requiring liver transplantation in most cases as the prognosis for chemotherapy is frequently worse. Drinking alcohol may therefore be associated with hepatobiliary disease.

ALT and GGT levels in smokers were evaluated and both GGT and ALP levels in smokers were found to be significantly elevated. Similar findings were also reported by Boonstra et al. and Wannamethee and Shaper. Levels of GGT and ALP correlate in liver disease principally of cholestatic type. Mohammad demonstrated a relationship of elevated serum GGT levels to cigarette smoking, and the significantly increased serum GGT in smokers seemed to increase the harmful effects of cigarette smoking on the liver.

Viral hepatitis often results in liver injury and can lead to chronic liver disease. In the present study, higher levels above normal ranges were observed for ALP compared to GGT among HBV and HCV patients. Elevated hepatic enzymes were mostly found among patients with HCV. The present study was carried out to highlight the liver and biliary function among patients attending Kibungo hospital. The target population for the present study was 673 but data were collected from 225 participants who were chosen randomly. By considering the population and sample size, 1 participant in the study represented 3 clients in the target population.

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infection. HBV population had less elevation of these enzymes and results were statistically significant. In previously reported studies viral hepatitis was correlated with elevation of GGT and ALP. Cholestatic liver disease in viral hepatitis patients was confirmed. Regular assessment of GGT and ALP in this population can help in monitoring the prognosis.

In this study, 32.9% were HIV patients and clinically considered immuno-compromised. Data showed that 31.1% and 37.8% had high GGT and ALP levels, respectively. The elevation was significant, and ALP was more elevated than GGT with the difference of 6.7%. These findings are in agreement with those reported by Markowitz et al., who associated HIV infection with high levels of GGT and ALP. Similarly, HIV infection and HIV and HCV coinfection has also been associated with GGT and ALP elevation. Being HIV positive is decided as a risk factor for elevating GGT and ALP levels. Indeed, cholestatic liver disease is frequent in HIV population hence GGT and ALP should be used in biomonitoring of HIV infection progression among patients.

Elevated serum GGT and ALP levels indicate the predominance of cholestatic hepaticobiliary disease. According to Friedman et al., increased levels in serum ALP and GGT were associated with liver disease of intra and extra hepatic cholestasis as well as in destruction of hepatocytes membranes. In this study, 19.6% of clients had a simultaneous elevation of GGT and ALP levels. In clinics, this elevation hints at the malfunction of hepatico-biliary system among clients.

Among subjects with uniformly elevated GGT and ALP in the present study, 27% were infants. It has been reported that neonates and infants up to one year likely experience high GGT and ALP levels. They were suspected to have maternal jaundices that should be cleared in 2 to 3 weeks of birth. Simultaneously, elevated GGT and ALP levels showed biliary disorders of birth among infants and children less than 1 year.

In 44 participants with high levels of studied enzymes, 36 were adults. Twenty adults were males whereas 16 were females. Thirteen were alcohol consumers, 6 were smokers, 2 were HBV positive, 7 were HCV positive, and regrettable among participants with simultaneously elevated GGT and ALP, 20 were HIV patients. High levels of both GGT and ALP were found among some of the study. Elevated enzyme levels were frequent in four classes above the normal reference limits for both GGT and ALP. D’Agata and Balistreri observed that in cholestatic conditions, there is an accumulation of compounds whose excretion fails as a result of biliary tree obstruction. GGT and ALP require a clear biliary tree for elimination, and they will simultaneously be elevated in this condition rather than in hepatocellular injury. Among the clients with simultaneously elevated GGT and ALP levels 19.6% had cholestasis, and this percentage is similar to the frequency of cholestatic liver diseases among clients of Kibungo hospital. GGT and ALP can help in diagnosis and monitoring of the conditions related to liver function.

CONCLUSION
The role of GGT and ALP assay in enzymatic panel for hepatobiary function assessment was studied. Alcohol consumption, smoking, viral hepatitis, and HIV were found to be associated with GGT and ALP elevation. Simultaneously elevated GGT and ALP, among clients of Kibungo hospital, were strong indicators of both the cholestatic liver disease and the frequency of cholestasis among clients of Kibungo hospital. GGT and ALP should always be included in the panel of tests for screening and bio-monitoring liver related conditions in Rwanda since statistics showed these tests as significant predictors of liver related conditions.

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