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Chronic alcohol consumption affects serum enzymes levels in the HIV/AIDS patients on d4T/3TC/NVP treatment regimen during the 9 month follow up period

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ABSTRACT

Chronic alcohol use is a common problem globally including HIV/AIDS patients on ARV treatment regimens leading to severe liver damage and increase in serum enzymes. The study determined effect of chronic alcohol intake on serum enzymes in HIV/AIDS patients on d4T/3TC/NVP treatment regimen in Uganda using the WHO AUDIT tool and alcohol-use biomarkers. A case control study using repeated measures with serial measurements model was used. Alcohol-Use biomarkers were used to standardize gender differences in alcohol use. A total of 41 patients were screened for chronic alcohol use by the WHO AUDIT tool. The 21 patients were enrolled in the control group that were not chronic alcohol users and the other 20 patients in the chronic alcohol use according to the WHO AUDIT tool scores. Since the tool was not sensitive enough the patients in the control group were again sorted out using the chronic alcohol use biomarkers. Two studies with WHO AUDIT tool group and chronic alcohol use biomarkers were done. Alcohol-Use biomarkers were used to standardize the gender differences in alcohol use. A total of 41 patients (21 alcohol group and 20 control group) were followed up for 9 months with whole blood sampling done at 3 month intervals. The serum enzymes were determined using the Cobas Intergra 400 Plus analyzer machine. The mean GGT levels were higher in chronic alcohol use group as compared to control group though in both groups, the levels were above reference ranges during 6 month and three times higher during 9 month follow-up period for both chronic alcohol-use self reporting and biomarkers groups. Generally, the mean AST, ALT and AST/ALT levels were slightly higher in alcohol-use group as compared to control group and were slightly higher in both groups as compared to reference ranges during the 9 month follow-up period. Chronic alcohol consumption by HIV/AIDS patients on d4T/3TC/NVP drug regimen increased GGT and AST/ALT serum levels and hence used as chronic alcohol –use biomarkers.

KEYWORDS

Chronic alcohol use;
Serum enzymes;
HIV/AIDS patients;
ARVs.

Regular Paper

INTRODUCTION

Alcohol mainly ethanol is by far the most abused drug for centuries world over[1-3]. The types of alcohol consumed in alcoholic beverages include wine, spirits, liquors, beers and as traditional brew in the various countries of the world. The World Health Organization (WHO) estimates that there are about 2 billion people in both developing and developed countries globally who consume the different forms of alcoholic beverages[4-6]. Alcohol consumption is the leading risk factor for disease burden like HIV/AIDS especially in developing countries and the third largest risk factor in developed countries accounting for 4% of the burden of the diseases[4,7,8]. In Uganda, alcohol is consumed in various forms, including the home-made brews that are consumed in the country side and it is a serious problem and is ranked a top most country in alcohol consumption among the 189 WHO member countries and in the African region[9-12]. However, among the many people who consume alcohol are the HIV/AIDS patients, some of whom are on antiretroviral drugs like the d4T/3TC/NVP drug regimen[13,14]. The liver is the main site of ethanol metabolism though metabolism can also occur in other tissues such as the gastrointestinal tract (GIT) and other body tissues[15-19]. Chronic use of alcohol overwhelms the liver and thus damages the liver cells and together with the administered ARVs, the damage is exacerbated leading to massive release of liver enzymes into circulation and hence a rise in serum enzymes in the patients as a sign of liver toxicity. Also the metabolic ethanol intermediate products like acetaldehyde and free radicals can have a deleterious effects to the body tissues and organs where they may interfere with the normal metabolism of essential elements, leading to cellular damage through oxidation mechanisms and secondary oxidative stress as well as the endocrine function disturbances[20-22]. Chronic alcohol consumption not only harm liver cells but also interfere with the normal functioning of the liver that later have an impact on the distant organs like the brain leading to hepatic encephalopathy[23]. However, excessive consumption of alcohol leads to hepatocellular damage resulting in increased catalytic activities of serum AST and ALT[23-28]. Due to the high liver cell turnover, they are normally found in the blood. The ALT and AST are reported to be indicators of liver disease that may be due to alcohol induced liver damage. ALT is more specific to alcohol induced liver cell injury[24-28]. AST is also found in heart, muscle, kidney and brain cells[23-28]. Any injury or disease such as chemicals like drugs and aflatoxins and viral hepatitis[29,30] can increase the level of cellular injury or death in these organs will cause an elevation of these markers[23-28]. The ratio of AST to ALT has been reported to provide more meaningful information on ethanol use especially if the ratio cut-off is greater than 2[27,31-35]. The gamma glutamyl transferase (GGT) enzyme, a glycoprotein found in the liver, is the most widely used of all the liver enzymes to determine liver cell injury due to excessive alcohol consumption[27,31-35]. The study determined the effect of chronic alcohol use on the serum enzymes (GGT, ALT and AST) levels in the HIV/AIDS patients on d4T/3TC/NVP drug regimen using the chronic alcohol-use self-reporting WHO AUDIT tool method and the chronic alcohol-use biomarkers methods.

MATERIALS AND METHODS

Study design

The study was a case-control study that used repeated measures design model and it was conducted at St. Raphael of St. Francis Hospital, Nsambya, ART Private Clinic on the HIV/AIDS patients who were exposed to chronic alcohol and at the same time, they were initiated on the d4T/3TC/NVP drug regimen *[triomune 30 (lamivudine (3TC) 150 mg, nevirapine (NVP) 200 mg and stavudine (d4T) 30 mg tablets)]* for the last 6 months. The hospital handles about 1,500 HIV/AIDS patients. The d4T/3TC/NVP drug regimen was one of the drug regimen used in the suppression of the HIV virus in the patients during the study period. The serial measurements model was done on the HIV/AIDS on d4T/3TC/NVP drug regimen at 3 month intervals (0, 3, 6 and 9 months) for a period of 9 month for both the control group and the chronic alcohol exposed group. Both the control and chronic alcohol use groups were screened for alcohol use by using the WHO AUDIT tool method and the chronic alcohol-use biomarkers elevation (GGT values above 55.0 UI, MCV values above 96 fL and AST/ALT ratio above 2.0). About 1mL of whole blood was collected from the cubital vein for all the patients for the analysis of the biomarkers using the automated hematological Coulter

CBC-5 Hematology Analyzer equipment for MCV and the Cobas Intergra 400 Plus analyzer equipment for GGT, AST and ALT serum enzymes.

Study site and population

The study was conducted at St. Raphael of St Francis hospital, Nsambya, Private clinic and department of Pharmacology and Therapeutics pharmacokinetic laboratory. A total of 41 HIV/AIDS patients who are on d4T/3TC/NVP drug regimen were recruited. They were grouped into two arms with the first arm or the control group consisting of 21 HIV/AIDS patients who were self-reported for not being exposed to any type of alcohol or to chronic alcohol for the past one year. The second arm had 20 HIV/AIDS patients who were self-reported to be exposed to chronic alcohol.

Inclusion criteria

All the HIV/AIDS patients who were included in this study were HIV positive, on d4T/3TC/NVP drug combination regimen for the last 6 months at the time of enrollment. The adherence rates of all the patients recruited were measured using the self-reporting adherence and the pill counts at scheduled visits and all had an adherence rate of above 95%. This was to ensure that the patients were taking their drugs as per the prescription. Also those included were in the age range of 18 to 50 years old. In the test group, they must be exposed to chronic alcohol use at the time of recruitment and during the 9 months study period and in the control group, they were not exposed to any type of alcohol at all or for the last 6 to 12 months.

Eligibility criteria and enrolment of study participants

The study was conducted on the HIV/AIDS patients who were initiated on the d4T/3TC/NVP drug regimen for the last 6 months. At the time of enrollment, a total of 41 HIV/AIDS patients on d4T/3TC/NVP were screened for chronic alcohol use using the WHO Alcohol Use Disorder Identification Test (AUDIT) tool. The 20 patients (13 males and 7 females) were identified to consume alcohol chronically using the tool and were enrolled into the chronic alcohol use group after signing the consent forms. The 21 patients (17 males and 4 females) were identified by the tool as non-alcohol consumers by the tool and were enrolled in the control group still after consent. The WHO AUDIT is currently an important tool which is non-invasive and it's routinely used worldwide to screen patients on chronic alcohol consumption[36]. The AUDIT tool has a set of 10 questions, each with responses and scores which the individual responds by self-reporting. A total score of 8-15 indicates hazardous alcohol use, 16-19 indicates alcohol use problem and scores above 20 indicates alcohol use dependence[36]. All the patients recruited in the chronic alcohol group had a total score of above 8 according to the WHO AUDIT tool interpretation of the scores. The patients enrolled in the control group had a score value of less that 8 according to the WHO AUDIT tool interpretation of the scores. However because the WHO AUDIT was not sensitive enough to actually detect some of the patients in the control group who were consuming alcohol chronically, the chronic alcohol-use biomarkers (GGT, MCV and AST/ALT ratio) were used to further sort out the patients in the control group who were being exposed to chronic alcohol and could not be detected by the WHO AUDIT tool. Therefore the 41 HIV/AIDS patients were again grouped according to the chronic alcohol use biomarkers into 2 arms with the chronic alcohol use arm having 26 patients (22 males and 4 females) and the control group with 15 patients (8 males and 7 females). These HIV/AIDS patients in both the control and chronic alcohol exposed group were followed-up for 9 months starting from March 2008 to November 2008. Each HIV/AIDS patient was explained well about the study and any questions raised were answered. All those patients who participate in the study signed the consent forms. The baseline serum enzyme concentrations (GGT, ALT and AST) at time 0 month just before they were initiated on the d4T/3TC/NVP drug regimen of all the patients that participated in the study were collected retrospectively from the patients records.

Whole blood sample collection and processing

The whole blood samples from the recruited HIV/AIDS patients were collected from cubital vein every 3 months for a period of 9 months (0, 3, 6 and 9th month). The third category of vacutainers was containing a clot-activator and 3ml of whole blood were collected in them for serum extraction that was used for liver enzyme assays. The serum samples were extracted by centrifuging the clot-activator vacutainers with whole blood at 2000 revolutions per minute (rpm) for duration of 5 minutes. After which a clear supernatant of serum were

Regular Paper

transferred to the clean cryovials. The serum samples were immediately refrigerated at -70oC prior to analysis. The others are the liver function tests like the serum enzymes such as alanine amino transferase (ALT), aspartate amino transferase (AST) and the gamma glutyl aminotransferase (GGT) since these were used as biomarkers of chronic alcohol consumption. The liver function test study was carried out at the Mulago National Referral Hospital Clinical Chemistry laboratory with the use of the Cobas Intergra 400 Plus analyzer equipment using standard methods and laboratory standard operating procedures (SOPS). The serum samples extracted from the HIV/AIDS patients' venous whole blood on d4T/3TC/NVP treatment regimen into the clot-activated vacutainer were used. The print-out of each sample was made. The results were entered into the excel spreadsheet from there which they were analyzed statistically.

Data analysis

All the data was entered in the Microsoft excel and was then sorted using the chronic alcohol-use self-reporting WHO AUDIT tool method for the use of chronic alcohol as well as basing on the chronic alcohol-use biomarkers method to produce 2 sets of data which were then compared statistically. It was then imported into the SAS 2003 version 9.1 statistical package for statistical data analysis. The data was analyzed at 95% confidence interval. The repeated measures fixed model was used in the statistical data analysis. The t-test was used to compare the means for HIV/AIDS patients who were in the chronic alcohol use (chronic alcohol use group) and the control group at different time intervals. The outcome measures were the mean difference of the measured parameters between the chronic alcohol use and non-alcohol use basing on the chronic alcohol-use self-reporting WHO AUDIT tool method and the chronic alcohol-use biomarkers. The p value of less than 0.05 was regarded as statistically significant.

Ethical consideration

The research work was approved by the Faculty of Medicine Higher degrees, Research and Ethics committee of Makerere University Institution Review Board (IRB) (IRB#-2007-060), IRB of St. Raphael of St Francis hospital, Nsambya (no. IRB 03: 01/03/2008) where the study participants were recruited from and the Uganda National Council for Science and Technology (UNCST)(no. HS 387), a government body that oversee all the research activities done in the country. In this study, a written informed consent was obtained from each human subject and that all the procedures used were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983. They were given study code numbers which were used all through the study period in order to protect their privacy and confidentiality. Their names or any identifier were not used anywhere in the study.

RESULTS

The effect of chronic alcohol consumption on the liver (serum) enzymes (ALT, AST and GGT) levels of the HIV/AIDS patients on d4T/3TC/NVP drug regimen were determined during the 9 months period of follow up using the chronic alcohol-use self reporting WHO AUDIT tool and the chronic alcohol-use biomarkers methods. The mean GGT levels in the 6 and 9 month were higher than the reference ranges of 0 – 55IU in both groups (TABLE 1 and 2). For the chronic alcohol-use self reporting WHO AUDIT tool, the mean GGT levels in the control group were higher than in the chronic alcohol use group except in the 9 month and the difference in all were not statistically significant ($p \geq 0.05$) (TABLE 1). For the chronic alcohol-use biomarkers group, the mean GGT levels in 6 and 9 month for the control group and 0, 3, 6 and 9 month in the chronic alcohol use group were higher than the reference ranges (TABLE 1). The levels in the chronic alcohol use group were generally higher than in the control group and the difference was statistically significant ($p=0.046$ and $p=0.009$) in the 6 and 9 month respectively (TABLE 1). The overall mean GGT levels in chronic alcohol use group were higher than in control group for both the chronic alcohol-use self reporting WHO AUDIT tool and the chronic alcohol-use biomarkers methods but the difference was only statistically significant ($p=0.029$) in chronic alcohol-use biomarkers method and hence used as biomarker for chronic alcohol use (TABLE 2).

The mean AST levels were generally within the normal reference ranges of 0 - 46IU except in the 0 month

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TABLE 1 : Variation of mean serum (liver) enzymes with time among the control and chronic alcohol-use group using alcohol-use self-reporting

Mean serum enzyme levels		Time of follow-up (months)				Ref . values
		(Baseline)0	3	6	9	
Chronic alcohol use self reporting with WHO AUDIT tool						
GGT±SE (Ul)	Control	52.86±29.72	53.87±28.7	79.0±44.58	104.08±70.84	0-55
	Alcohol	48.5±29.17	49.4±28.2	74.35±29.75	148.17±105.89	
p value		0.59	0.59	0.69	0.12	
AST±SE (Ul)	Control	48.43±28.7	38.57±25.0	39.79±16.9	42.29±55.43	0-46
	Alcohol	43.7±27.11	44.75±23.65	51.8±37.65	28.54±8.19	
p value		0.58	0.46	0.20	0.27	
ALT ±SE (Ul)	Control	41.6±46.32	23.9±15.33	27.0±11.21	33.81±22.75	0-40
	Alcohol	34.16±17.26	24.65±14.91	27.35±14.17	26.82±12.1	
p value		0.46	0.95	0.88	0.17	
AST/ALT	Control	1.65±1.23	1.77±0.73	1.61±0.64	1.22±0.56	<2.00
	Alcohol	1.41±0.66	2.0±0.66	1.95±0.72	1.19±0.43	
p value		0.55	0.25	0.03	0.86	
Chronic alcohol use biomarkers group						
GGT±SE (Ul)	Control	46.33±24.22	44.0±27.82	60.62±21.12	68.04±36.37	0-55
	Alcohol	54.17±32.63	55.04±32.97	84.62±41.21	155.17±97.39	
p value		0.66	0.32	0.046	0.009	
AST±SE (Ul)	Control	41.34±20.57	32.31±17.88	32.77±9.22	29.15±11.82	0-46
	Alcohol	49.87±32.14	47.52±26.18	52.54±34.09	38.55±47.92	
p value		0.73	0.11	0.06	0.81	
ALT ±SE (Ul)	Control	35.09±36.14	22.13±12.22	25.15±10.61	28.82±18.29	0-40
	Alcohol	40.22±34.82	25.64±16.55	28.19±1.64	31.06±18.66	
p value		0.87	0.37	0.17	0.93	
AST/ALT	Control	1.47±0.53	1.60±0.53	1.45±0.57	1.13±0.56	<2.0
	Alcohol	1.58±1.25	2.06±0.69	1.95±0.7	1.24±0.56	
p value		0.76	0.13	0.09	0.50	

Key: Ref: Reference values; SE: standard error; GGT: gamma glutamyl transferase; AST: aspartate amino transferase; ALT: alanine aminotransferase

for the control group and in the 6 month for the chronic alcohol use group (TABLE 1). For the chronic alcohol-use self reporting WHO AUDIT tool, the levels were higher in the 0 and 9 month for the control group and in 3 and 6 month for the chronic alcohol use group but the difference was not statistically significant ($p \geq 0.05$) (TABLE 1). For the chronic alcohol-use biomarkers methods, the mean AST levels in the chronic alcohol use group were higher than the reference ranges in the 0, 3 and 6 month follow up period (TABLE 1). Generally the mean AST levels in the chronic alcohol use group were higher than in the control group but the difference was on statistically significant ($p \geq 0.05$). The same effect was observed in the overall mean AST levels in both the chronic alcohol-use self reporting WHO AUDIT tool and the chronic alcohol-use biomarkers methods (TABLE 2).

For the ALT levels, the mean ALT values were within the normal reference ranges of 0 – 40IU except in the 0 month for the control group in the chronic alcohol-use self reporting WHO AUDIT tool method and in 0 month for the chronic alcohol use group in the chronic alcohol-use biomarkers methods (TABLE 1). The mean ALT levels in the chronic alcohol use group were higher than in the control group in the 3 and 6 month but the difference was not statistically significant ($p \geq 0.05$) in the chronic alcohol-use self reporting WHO AUDIT tool method (TABLE 1). For the chronic alcohol-use biomarkers method, the mean ALT levels in the chronic alcohol use group were higher than in the control group

Regular Paper

TABLE 2 : Comparison of mean serum enzymes among the chronic alcohol-use self reporting WHO AUDIT tool and chronic alcohol-use biomarkers groups during the follow-up period

Mean serum enzyme	Control group	Chronic alcohol consumption	p value
Chronic alcohol-use self reporting WHO AUDIT tool			
GGT±SE (Ul)	115.03±23.22	151.39±21.81	0.263
AST±SE (Ul)	44.45±10.5	28.67±9.87	0.282
ALT ±SE (Ul)	35.37±4.77	26.98±4.48	0.208
Chronic alcohol-use biomarkers group			
GGT±SE (Ul)	69.18±30.62	153.09±19.36	0.029
AST±SE (Ul)	28.03±15.29	41.05±9.67	0.478
ALT ±SE (Ul)	27.0±6.07	30.62±3.84	0.619

Key: Ref: Reference values; SE: standard error; GGT: gamma glutamyl transferase; AST: aspartate amino transferase; ALT: alanine aminotransferase

in the 0, 3, 6 and 9 month period of follow up but the difference was not statistically significant ($p \geq 0.05$) (TABLE 1). The overall mean ALT levels in the control group were higher than in the chronic alcohol use group but the difference was not statistically significant ($p \geq 0.05$) in the chronic alcohol-use self reporting WHO AUDIT tool method. While for the chronic alcohol-use biomarkers method, the overall mean ALT levels in the chronic alcohol use group were higher than in the control group though still the difference was not statistically significant ($p \geq 0.05$) (TABLE 2). For the mean AST/ALT ratio, the value was higher than 2.0 in the 3 month in the chronic alcohol use group for both the chronic alcohol-use self reporting WHO AUDIT tool method and the chronic alcohol-use biomarkers method and hence used as a chronic alcohol consumption indicator when it exceed 2.0.

DISCUSSION

The increased mean GGT levels in the HIV/AIDS patients on d4T/3TC/NVP drug regimen in the chronic alcohol use group was due to chronic alcohol consumption and its metabolic ethanol intermediate products like acetaldehyde and free radicals that can have a deleterious effects to the body tissues and organs where they may interfere with the normal cellular metabolism, leading to cellular damage through oxidation mechanisms and secondary oxidative stress as well as the endocrine function disturbances[20-22]. Chronic alcohol consumption not only harm liver cells but also interfere with the normal functioning of the liver that later have an impact on the distant organs like the brain leading to hepatic encephalopathy[23]. The effects of the ingested ethanol on different organs depend on the ethanol concentration achieved in the tissue or organ and the duration of exposure. However excessive consumption of alcohol leads to liver cell injury resulting in increased catalytic activities of serum GGT, AST and ALT enzyme elevation. The ALT and AST are felt to be an indicator of liver disease in general and less specific to alcohol induced liver damage[24-28]. The increased byproducts of alcohol during the chronic alcohol consumption affect the liver cells by the increased destruction of the hepatocytes[25,34,35]. Also the increase in the mean GGT levels has been reported to be due to the prostate GGT, pancreas and kidneys[25,34,35]. It can also be due to the adverse effects of the drugs like stavudine (d4T) such as acute pancreatitis and hepatitis[37-41]; lamivudine (3TC) such as hepatomegally and lactic acidosis[37-41] and nevirapine such as hepatitis and hepatic failure[37-41]. The observed increased levels of the mean AST and ALT indicate a sign of the liver cell injury or destruction leading to increased release of these liver enzymes in blood causing their increased catalytic activities. These enzymes metabolize amino acids and due to the high liver cell turnover, they are normally found in the blood circulation[25,35,42-44]. The ALT and AST are reported to be indicators of liver disease and less specific to alcohol induced liver damage. However, ALT has been reported to be more specific to alcohol induced liver cell injury than AST which can also be found in heart, muscle, kidney and brain cells. Any injury or disease that can increase the level of cellular injury or death in these organs can cause an elevation of these enzyme markers[25,35,42-44]. The liver disease can be caused by a variety of agents including chemicals like alcohol and its metabolites[27], toxins like aflatoxins[30], drugs like the anticancer and antiviral drugs like the ARVs in this case stavudine[37,38,40,41], lamivudine[37,38,40,41] and nevirapine[37,38,40,41], injuries, anticancer and antiviral agents[37,38,40,41], aflatoxins[30] and infections like the viral hepatitis[29]. However, since the study was an effective type of study where all the pa-

tients were observed in their natural settings, the confounders in the study that may have affected the serum enzyme concentrations in both the control and chronic alcohol use groups were assumed to be the same. Therefore the variable chronic alcohol use could have caused the observed elevation of the GGT, ALT and AST serum enzyme concentrations in chronic alcohol use group for both the WHO AUDIT tool and chronic alcohol-use biomarkers groups in the study. Chronic alcohol consumption leads to increased GGT, ALT and AST serum enzymes levels as well as the ratio of AST to ALT greater than 2.0[27,33,34] that has been reported to be associated with chronic ethanol use and the problems may be exacerbated by the HIV/AIDS disease itself, the antiretroviral drugs used as well as the other concomitant medicines like the herbal preparations which the patients may be using during the 9 month follow up period.

CONCLUSION

The serum/liver enzymes (GGT, AST and ALT) were monitored in this study as a way to determine the status of the liver since it is the main organ that metabolizes the many substance in the body such as drugs like the ARVS, chemicals like ethanol and other xenobiotics. The enzymes increase in circulation when the liver and other tissues and organs are damaged by the drugs, chemicals, chronic alcohol use, viral hepatitis infection and many others. These enzymes are used as biomarkers of chronic alcohol use and therefore they can be used in the therapeutic monitoring of the HIV/AIDS patient on chronic alcohol use as well as the adverse drug reactions associated with the ARVs. In this sub-study chronic alcohol use greatly affected the GGT levels and to some extent the AST levels during the 9 month period of follow up in both the alcohol-use self reported group and alcohol-use biomarkers group though the difference was more observed for the alcohol-use biomarkers group especially with the GGT levels.

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