American Journal of Clinical Medicine Research, 2015, Vol. 3, No. 3, 37-41
Available online at http://pubs.sciepub.com/ajcmr/3/3/1

DOI:10.12691/ajcmr-3-3-1

Liver Function Biomarker IN Patients on Anticoagulant Therapy at Usmanu Danfodiyo Unversity Teaching Hospital, Sokoto, Nigeria

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Received April 08, 2015; Revised June 01, 2015; Accepted June 24, 2015

Abstract **Background**: Drug induced hepatotoxicity have been known to be a common cause of liver failure. Drugs can either have a short-term or long-term adverse effect. The risk of side effect varies from drug to drug and from patient to patient. Most of the patients that need anticoagulant therapy are on the drugs for a long period, hence liver function may be impaired during the course of therapy this study was designed to investigate the effect of anticoagulant drugs on liver function. **Methods:** Thirty patients who have been on anticoagulant therapy between 1to 20 years (X5.8years), 30 patients that were yet to commence anticoagulant therapy but with the same clinical condition and 30 apparently healthy subjects were recruited for the study. Effect of duration of therapy on liver function were also assessed. Patients with background liver disease from any cause were excluded from the study. Five ml of blood were collected from each of the participant and liver function biomarkers estimated using standard techniques. **Result**: Therewere statistically significant increases (P<0.001) in values of aspartate transaminase (AST), alanine transaminase (ALT), and gammaglutamyl transferase(GGT) in patients on anticoagulant therapy and patients that were not on anticoagulant therapy when compared with control subjects but the increases were within the reference range. There was no significant difference (P>0.001) in alkaline phosphatase (ALP), total protein (TP), albumin (ALB), total bilirubin (TB) and direct bilirubin (DB) values between the patients and the control group. **Conclusion**: The slight elevation in liver function biomarkers assessed in patients on anticoagulant therapy could not be linked to the effect of the drug because patients with the same clinical conditions that were not on anticoagulant therapy showed the same elevation of the biomarkers. We did not observe effect of duration of therapy on liver function. The liver function biomarkers assessed were within the reference range in both the patients on therapy and those not on therapy. From our findings, we did not observe hepatotoxicity among our subjects.

Keywords: *liver function, biomarkers, anticoagulant therapy, patients, adverse effect*

Cite This Article: Oduola Taofeeq, Bature Farida, Ndakotsu Mohammed Alhaji, Yakubu Abdulmumini, Dallatu Mohammed Kabiru, and Mainasara Abdullahi Suleiman, "Liver Function Biomarker IN Patients on Anticoagulant Therapy at Usmanu Danfodiyo Unversity Teaching Hospital, Sokoto, Nigeria." *American Journal of Clinical Medicine Research*, vol. 3, no. 3 (2015): 37-41. doi: 10.12691/ajcmr-3-3-1.

1. Introduction

The liver, located between the absorptive surface of the gastrointestinal tract and drugtargets throughout the body, is central to the metabolism of virtually every foreign substance. Most drugs and xenobiotics are lipophilic, enabling them to cross the membranes of intestinal cells. Drugs are rendered more hydrophilic by biochemical processes in the hepatocyte, yielding water-soluble products that are excreted in urine or bile [1]. This hepatic biotransformation involves oxidative pathways, primarily by way of the cytochrome P-450 enzyme system [2]. After further metabolic steps, which usually include conjugation to a glucuronide or a sulfate or glutathione, the hydrophilic product is exported into plasma or bile by transport proteins located on the hepatocyte membrane, and it is subsequently excreted by the kidney or the gastrointestinal tract [3,4,5]. Metabolism of drugs by this enzyme system leads sometimes to more active and toxic compounds which produce liver injury [6]. Liver disease is one of the acquired disorders that occur more frequently in several blood coagulation defects such as deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, congestive cardiac failure, artificial heart valve replacement and genetic or acquired hypercoagulability [5,7].

Anticoagulant drug is used to control and prevent thromboembolic disorders, the goal of anticoagulant

therapy is to administer the lowest possible dose of anticoagulant to prevent clot formation or expansion. The required degree of anticoagulation continues to evolve as studies provide more information about the efficacy and safety of lower doses [7-13].

2. Subjects and Methods

2.1. Subjects

A total of 60 patients, 30 of them were on anticoagulant therapy (Warfarin) and the remaining 30 with the same clinical conditions that were yet to commence anticoagulant therapy were recruited for this study. The patients on anticoagulant therapy were also categorized into 4 depending on the duration of therapy; group 1 (1-5 years), group 2(6-10 years), group 3 (11-15 years) and group 4 (16-20 years). Thirty apparently healthy individuals of the same age and gender were recruited as controls.

Five ml of blood samples were collected from each subject into clean dry test-tubes by clean venipuncture. The samples were allowed to clot at room temperature and then centrifuged at 3000rpm for 5 minutes to obtain the sera. The separated clear sera were transferred into sterile plain bottles and were used for the assays of ALT and AST [14], GGT [15], TP [16], ALB [17], using Agape reagent kit (Agappe Diagnostics, Switzerland GmbH); ALP [16] TB and DB [16] using Randox reagent kit (Randox Laboratories Limited, UK) spectrophotometrically.

2.2. Ethics

This study was conducted in accordance with the Declaration of Helsinki. The study participants gave their informed consent and the research protocol was approved by the Ethics and Research Committee of Usmanu Danfodiyo University Teaching Hospital, Sokoto.

2.3. Statistics

The data obtained from this study were analyzed using the Sigma plot version 11.0 for the mean and standard deviation. Differences were considered significant when $p<0.001$.

3. Results

The mean ± standard deviation of serum AST (U/L) in controls, patients on therapy and patients not yet on therapy were 15.5 ± 4.86, 28.0 ± 17.01 and 33.0 ± 12.96; and ALT (U/L)10.45 ± 4.15, 24.27 ±16.58 and 23.01 ± 11.36 respectively. The mean ± standard deviation of serum GGT (U/L) in controls, patients on therapy and patients not yet on therapy was found to be 10.42 ± 3.36, 31.70 ±11.63 and 25.40 ± 11.83 respectively, (Figure 1).

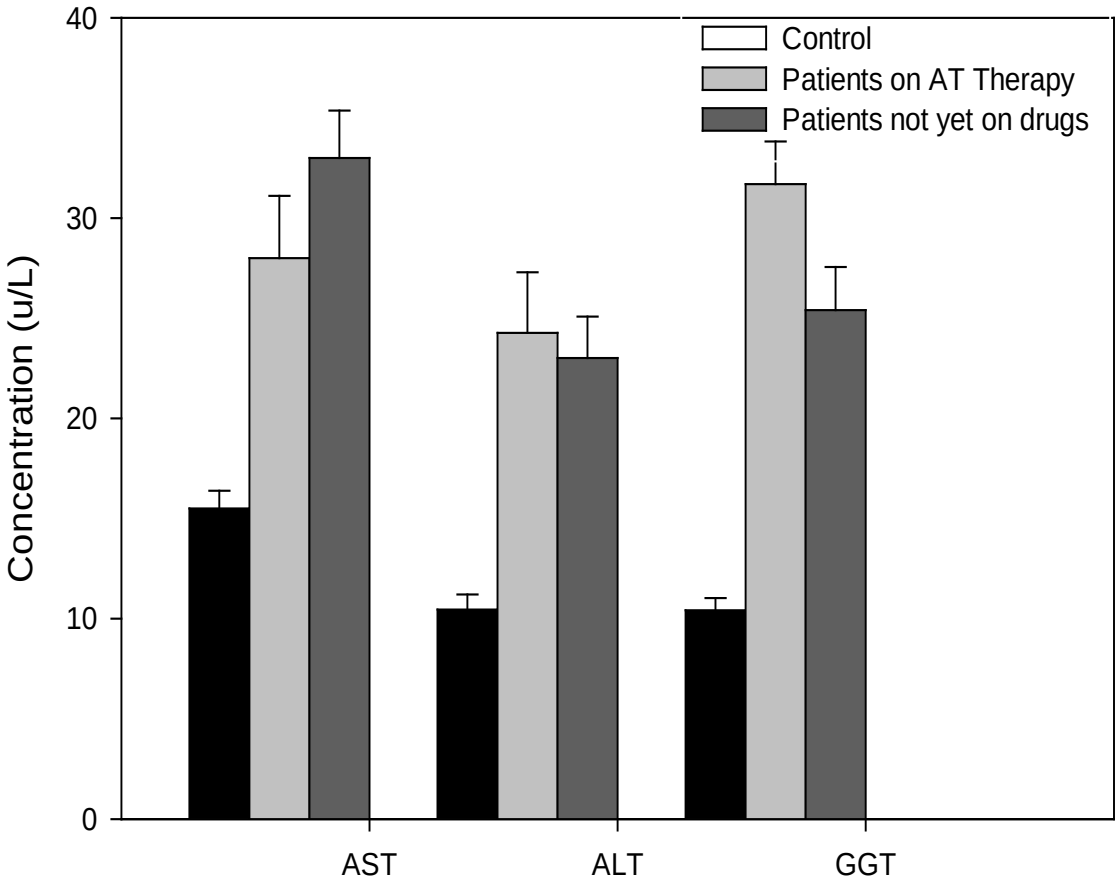

Figure 1. Bar chart showing values of AST, ALT and GGT in controls, patients on therapy and patients not on therapy

The mean ± standard deviation of serum ALP (U/L) in controls, patients on therapy and patients not yet on therapy were 126.07 ± 31.67,144.47 ± 54.08 and 137.43 ± 55.99 respectively, (Figure 2).

The mean ± standard deviation of serum total bilirubin (mg%) in controls, patients on therapy and patients not yet on therapy were found to be 0.40 ± 0.27, 0.63 ± 0.35 and

0.99 ± 0.68 and conjugated bilirubin (mg%) 0.15 ± 0.06, 0.22 ± 0.11 and 0.38 ± 0.33 respectively, (Figure 3).

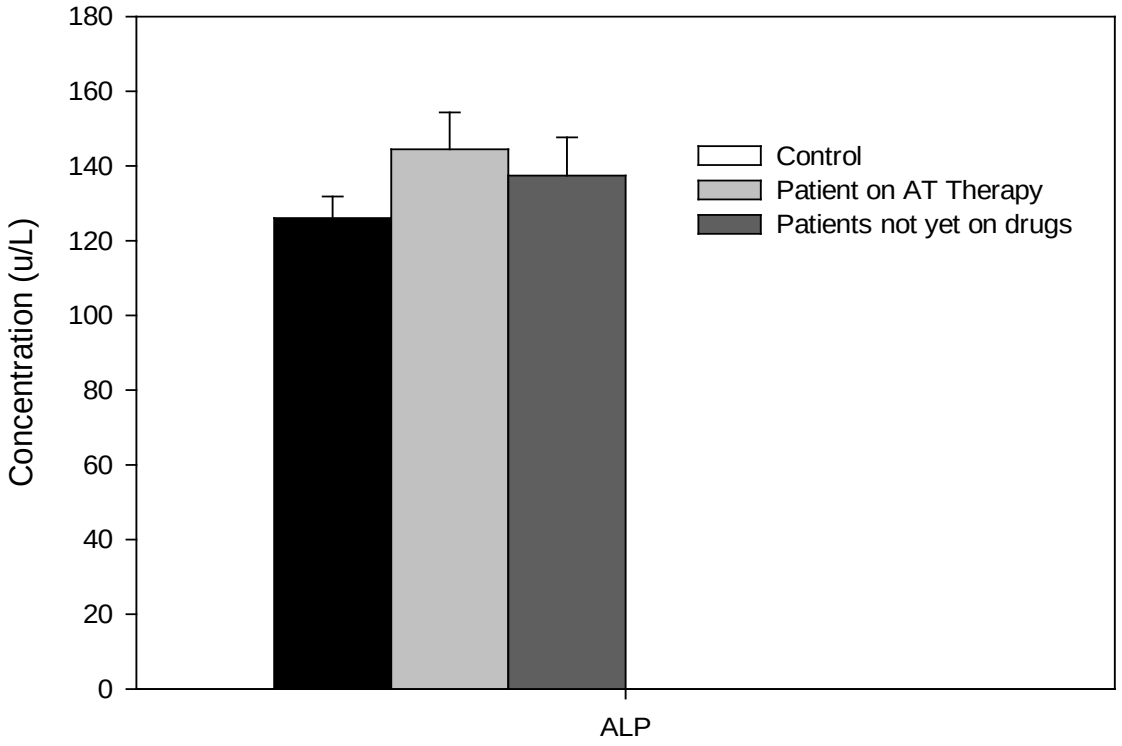

Figure 2. Bar chart showing values of ALP in controls, patients on therapy and patients not on therapy

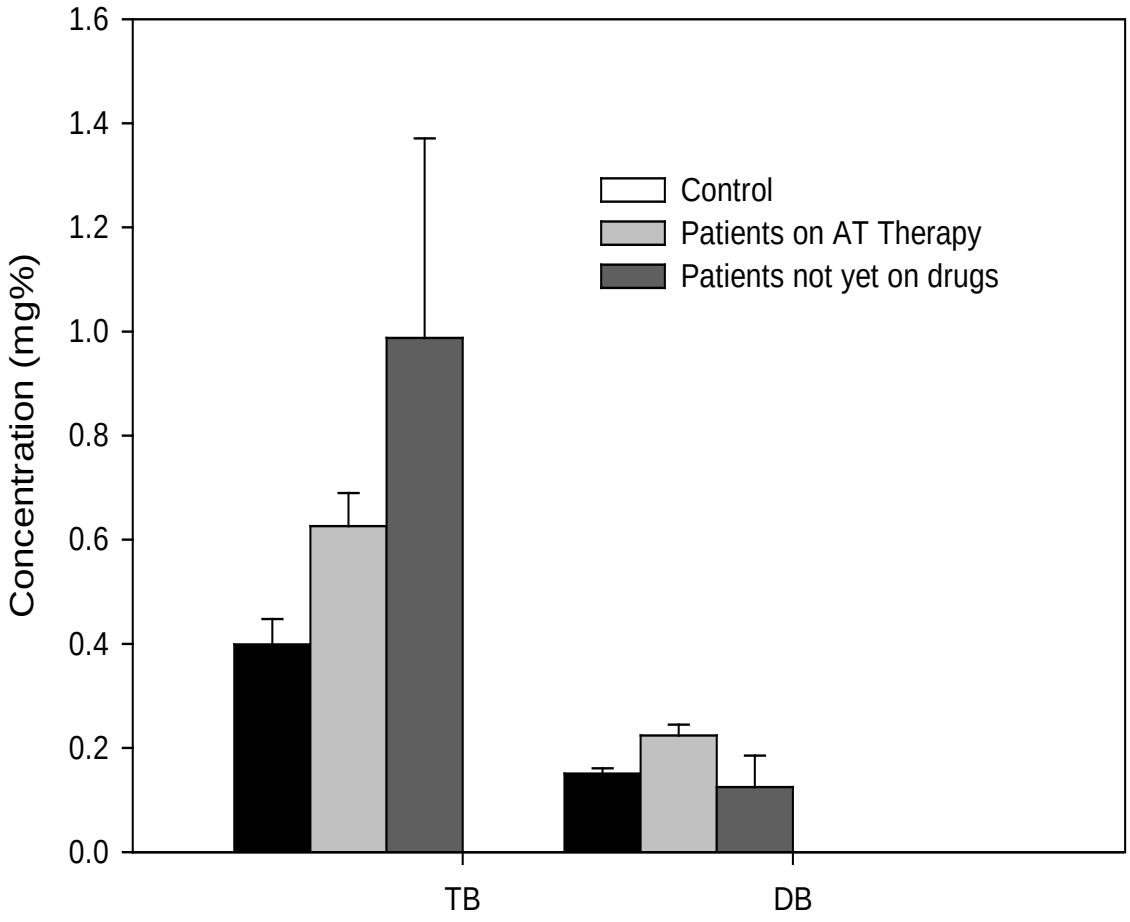

Figure 3. Bar chart showing values of total bilirubin and conjugated bilirubin in controls, patients on therapy and patients not on therapy

The mean ± standard deviation of serum total protein (mg/dl) in controls, patients on therapy and patients not yet on therapy were 6.61 ± 0.78,6.78 ± 0.84 and 6.46 ± 1.24 and albumin (mg/dl)4.15 ± 0.60,4.33 ± 1.07 and 3.98 ± 0.84 respectively, (Figure 4).

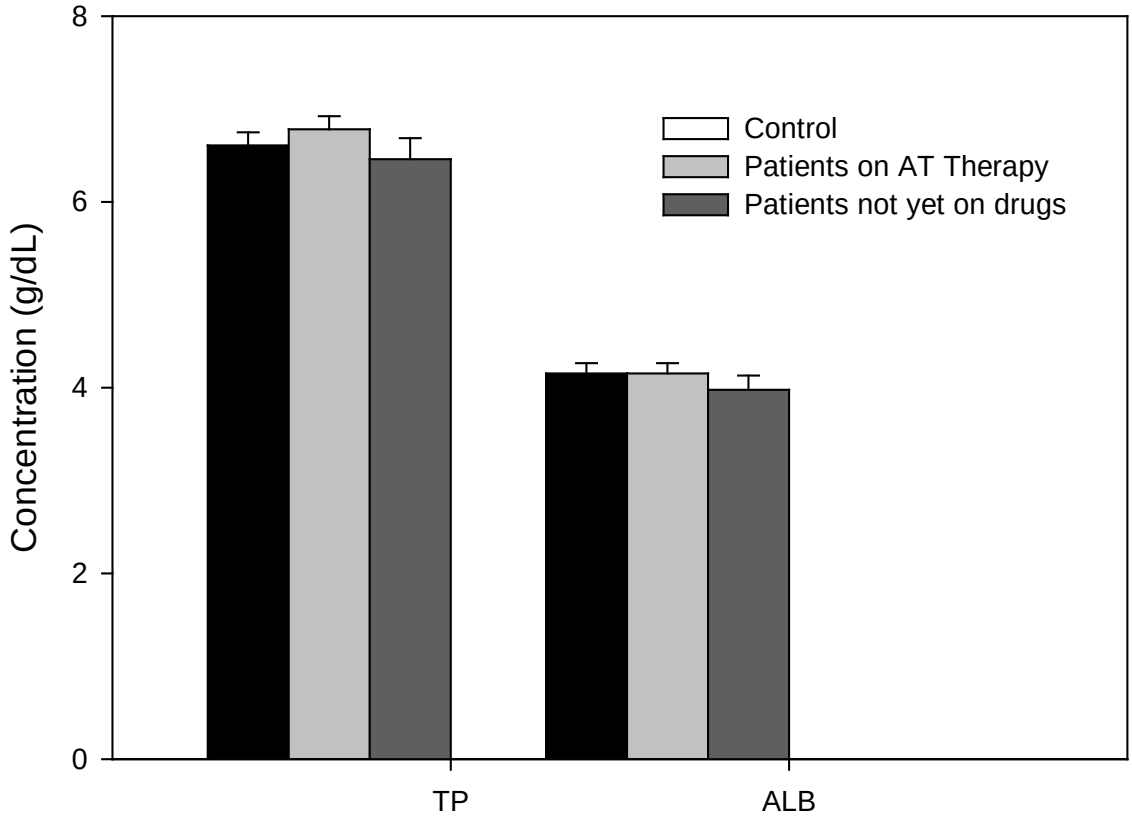

Figure 4. Bar chart showing values of total protein and albumin in controls, patients on therapy and patients not on therapy

TABLE 1. Effect of duration in therapy on liver biomarkers

Duration	AST (Up to 49 µ/l)	ALT (Up to 49 µ/l)	ALP (98-279 µ/l)	GGT M=10-45µ/l F=5-32 µ/l	TP (6.0-8.0 g/dl)	ALB (3.5-5.0 g/dl)	TB (Upto1.4mg %)	DB (Upto 0.4 mg%)
0 - 5 Years	39.00 ± 15.65	13.19 ± 21.89	134.61 ± 41.04	27.07 ± 5.70	4.57 ± 0.95	3.56 ± 1.22	0.69 ± 0.44	0.32 ± 0.13
6 - 10 Years	34.00 ± 19.55	12.53 ± 13.79	120.85 ± 67.84	24.34 ± 13.13	3.94 ± 0.68	3.17 ± 0.89	0.61 ± 0.26	0.28 ± 0.09
11 - 15 Years	36.30 ± 6.29	12.86 ± 9.23	127.73 ± 52.04	25.71 ± 10.72	4.26 ± 0.81	3.37 ± 1.22	0.65 ± 0.19	0.30 ± 0.07
16 - 20 Years	34.93 ± 10.61	12.69 ± 11.81	124.29 ± 25.46	25.03 ± 7.78	4.10 ± 0.23	3.27 ± 0.14	0.63 ± 0.42	0.29 ± 0.21
Control	15.50 ± 4.86	10.45 ± 4.15	126.07 ± 31.67	10.42 ± 3.36	6.61 ± 0.78	4.15 ± 0.60	0.40 ± 0.27	0.15 ± 0.06

4. Discussion

Hepatotoxicity have been reported to be a rare complication of coumarin anticoagulants [18], except for bleeding complications, relevant adverse effects of coumarin anticoagulants are comparatively rare considering the widespread use of these substances [19].

From the present study, the values obtained for AST and ALT in patients on drug and those that were not on drug were significantly higher ($p<0.001$) than values obtained for the control groups, however there was no significant difference ($p=0.130$) in the values obtained for patients on drug and those not on drug. Nipun et al [20] has previously described elevated levels of transaminases in patients on anticoagulant therapy;association of anticoagulants with asymptomatic elevation of serum transaminases, clinically significant hepatitis, and fatal liver failure have also been reported [21,22,23,24]. Levels of transaminases, ALT and (AST) are sensitive indicators of drug-induced hepatocellular injury. Elevations in ALT and AST can occur from conditions other than liver injury, but ALT is relatively more specific because it is synthesized primarily by the liver [20]. In this study, we could not associate increased level of transaminases to drug intake because our observations in both categories of patients were similar. The elevations in AST and ALT in patients on drug could also be due to their clinical state since this elevation was also observed in patients not on drug. The specific mechanism of transaminase elevation after anticoagulant use has not been identified [20], but coumarin drugs can be linked with direct damage of hepatocytes by reactive metabolites, which may result in augmented antigenicity and consequent immunoallergic reaction. It can also be associated with high-energy reactions involving cytochrome P-450 enzymes, causing decline of adenosine triphosphate levels, loss of ionic gradients, cell swelling, and rupture [25].

The values obtained for GGT in patients on drug and those not on drug were significantly higher ($P<0.001$) than values obtained for the control groups. Also the GGT values of patients on drug were significantly higher ($P<0.001$) than those not on drug. These elevations may be due to anticoagulant therapy because anticoagulant drugs are known to be enzyme-inducing [20].

Although the values obtained for serum ALP in patients on drug and those not on drug were higher than that of the

control group, the values were not statistically significant (p= 0.338), hencewe did not observe cholestatic reaction to anticoagulant drug in our subjects, however a case of cholestasis following exposure to warfarin therapy has been reported [26].

The values obtained for total protein and albumin in patients on drug and those not on drug were not statistically different from the control groups. This observation might be that the drug has no adverse effect on synthetic function of the liver. The values obtained for total and direct bilirubin in patients on drug and those not on drug were higher than the control groups, although the increases were not statistically significant. The values obtained for all the groups were within the reference range.

In conclusion, our study did not reveal any adverse effect of anticoagulant therapy on liver function and we did not observe association between duration of exposure to therapy and liver function. Our observations may be due to small sample size of our subjects, it is recommended that this study is conducted on large number of patients.

Acknowledgement

The authors are grateful to all our study participants.

Conflict of Interest

There was no conflict of interest in any form.

Source of Funding

The authors did not receive financial support from any source.

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