

## **Liver Dysfunction associated with Hyperthyroidism: Lessons from 2 Case Reports**

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## **ABSTRACT**

Deranged liver enzymes due to hyperthyroidism rather than intrinsic liver pathology are not uncommon. We present two cases that highlight the impact of hyperthyroidism on liver biochemistry tests and good response to treatment. A high index of suspicion is paramount in patients presenting with unexplained deranged liver enzymes or jaundice.

### **Keywords:**

Hyperthyroidism; Liver dysfunction; Liver enzymes

### **Key Clinical Message**

Hyperthyroidism may impact liver biochemistry negatively. Clinicians need a high index of suspicion in patients presenting with unexplained deranged liver enzymes or jaundice. Timely initiation of thionamides portends good prognosis.

## **Introduction**

Hyperthyroidism is commoner in females than males with a ratio of 5:1<sup>1</sup>. The overall incidence is estimated at about 0.05-1.3 % with majority of cases comprising of subclinical cases, and this increases to 4%-5% in older women<sup>1</sup>. Graves' disease tends to be commoner in younger women while toxic nodular goiter is more common in older women; also hyperthyroidism appears to be commoner in smokers<sup>2</sup>.

The two biologically active thyroid hormones: thyroxine (T4) and 3,5,3<sup>1</sup> triiodothyronine (T3) are synthesized solely in the thyroid gland in the case of the former; and both thyroid gland and other tissues by the latter<sup>3,4</sup>. Approximately 80 % of T3 is formed by 5<sup>1</sup>-deiodination of T4 in extrathyroidal tissue commonly the liver and kidney and rapidly degraded by deiodination at a rate of approximately 75% per day<sup>3,4</sup>.

The production rate of T4 is 80 to 100 mcg per day, all of which is produced in the thyroid gland and is degraded at a rate of 10% per day <sup>3,4</sup>. Approximately 80 percent is deiodinated: 40 percent to form T3 and 40 percent to form reverse T3 (rT3). The remaining 20 percent is conjugated with glucoronide and sulphate, deaminated and decarboxylated to form tetraiodothyroacetic acid (tetrac) <sup>3,4</sup>.

Over 99 % of thyroxine (T4) and triiodothyronine (T3) in serum are bound to serum proteins, thyroxine-binding globulin (TBG), transthyretin, albumin and lipoproteins, which are mainly produced in the liver. These aid to maintain the serum free thyroid hormones within narrow limits yet ensure immediate and continuous availability to tissues. It is the serum free T4 and T3 concentrations that determine the hormones biological activity <sup>3-5</sup>.

The liver is dependent on a functioning thyroid gland and as such adequate amounts of thyroid hormones are needed for its metabolic activity to manufacture its hormones and proteins while maintaining its normal function. The thyroid gland in turn, depends on the liver for its deiodinases for the conversion of T4 to majority of biological active T3 and for thyroid hormone metabolism <sup>3,4</sup>.

Hepatic dysfunction is common in patients with Graves' hyperthyroidism in clinical practice <sup>6</sup>. Majority of these patients may be asymptomatic and only a few of them suffer from severe liver damage leading to liver failure <sup>6,7</sup>. Reported prevalence of liver biochemical abnormalities in patients with untreated hyperthyroidism ranges from 15%-79% <sup>6</sup>.

There are six main putative mechanisms contributing to hepatic dysfunction in the context of hyperthyroidism. These include effects of excessive thyroid hormones, drug induced (anti-thyroid) related liver injury and the presence of underlying liver disease. These underlying mechanisms may be because of <sup>8-12</sup>:

- i. Long exposure to excessive thyroid hormones production with direct liver toxicity.
- ii. The hyper metabolic state results in increased energy consumption without concomitant increase in blood supply to the liver leading to hepatocyte anoxia with free radical damage.

- iii. Liver cell degeneration may result as thyrotoxicosis hastens liver glycogen and protein decomposition.
- iv. Autoimmune mechanisms might play a role in the process of liver injury.
- v. Cardiac complications of hyperthyroidism lead to hepatic congestion and hepatic necrosis.
- vi. Antithyroid medications also may have direct toxicity on the liver.

Resolution of liver derangements occurs in 77-83% of patients on early initiation of thionamides; however, about 1-2% of patients about 1-2% can progress to fulminant hepatitis <sup>9, 13</sup>. Timely management using appropriate therapy is essential to avert complications of the disease.

The rationale for publishing these cases is to increase awareness among clinicians on the negative impact hyperthyroidism has on liver function and how early initiation of treatment portends good prognosis. A high index of suspicion for hyperthyroidism as the cause of unexplained jaundice or deranged liver enzymes is warranted.

## **Case Presentations**

### **Case 1**

#### ***History, Physical Examination and Investigations***

A 44- year-old female health administrator known to have gastroesophageal reflux disease was referred to the Korle Bu Teaching Hospital Gastroenterology Clinic for a second health opinion with deranged liver enzymes, after declining an offer of liver biopsy in another facility outside the country to investigate the cause of a 6-month history of recurrent jaundice and deranged liver enzymes.

Patient admitted to having lost 10kg of weight in three months, 6- week history of abdominal pain, nausea and anorexia. On physical examination, she had tachycardia but regular and hyperdynamic pulse. Patient was noticed to be fidgety with proptosis and pretibial myxedema with grade 2 goitre. There was however no digital clubbing or lymphadenopathy. All other systems were unremarkable.

A diagnosis of Grave's disease was made following some baseline investigations as shown in Table 1.

### ***Treatment and Follow Up***

Treatment was initiated using propranolol 40mg twice a day and carbimazole 30mg daily, referred to the endocrine clinic for follow up and co-management.

Her liver enzymes and thyroid function showed a downward trend over the following 8 months (Table 2) and subsequently patient opted for a thyroidectomy for cosmetic reasons and is currently doing well.

## **Case 2**

### ***History, Physical Examination and Initial Investigations***

She was a 29-year-old student initially worked up for ovarian malignancy by the gynecological department and defaulted follow-up. She reported to the emergency room with cough of six months duration productive of blood-streaked sputum. Subsequently, her sputum became yellowish after two months. She had worsening dyspnoea, pleurisy and pedal oedema in the last month prior to presentation.

Physical examination showed a chronically ill patient in respiratory distress, for which she was propped up at almost 90 degrees with oxygen 10 litres via a non-re-breather mask which recorded her oxygen saturation (SPO<sub>2</sub>) between 89%-96%. Patient was deeply jaundiced with moderate anaemia and appeared wasted with prominence of zygomatic bones. There was however no evidence of clubbing. She had anasarca and lymphorrhoea in her lower limbs.

Patient's blood pressure recorded was 135/80mmHg with a pulse rate of 146 beats per minute, of regular and good volume. Jugular venous pressure was raised at 9cm of water and apex beat was displaced and located in the 6th left intercostal space mid-clavicular line. Her heart sounds 1 and 2 were present with a loud pulmonary sound (P2) and a grade 4 pan-systolic murmur.

There were signs suggestive of right-sided pleural effusion on examination, which was confirmed on chest x-ray. She had massive ascites without any stigmata of chronic liver disease. The central nervous system was negative for a flap but showed mild proximal myopathy.

All other systems were essentially normal.

### ***Differential Diagnosis, Treatment and Follow Up Investigations***

Patient was stabilized immediately: pleural effusion was drained and samples sent for microbiology, biochemistry and cell count examination. She was initially started on management for heart failure to rule out liver disease. Samples were sent for hepatitis B and C screen, autoimmune hepatitis. Patient remained with persistent tachycardia despite improvement with anti-failure medications, which raised a suspicion of thyroid involvement and then further investigations subsequently yielded laboratory results (Table 3) in keeping with hyperthyroidism secondary to Graves' disease complicated with deranged liver enzymes and heart failure. A neck ultrasound done was suggestive of heterogeneous thyroid gland with increased vascularity with a differential diagnosis of Graves' disease. Echocardiography revealed normal wall thickness with a dilated left ventricle and left atrium. No motion wall abnormalities and a good left ventricular systolic function (ejection fraction 55%). Grade III diastolic dysfunction was noted with severe eccentric mitral regurgitation, with a mild tricuspid regurgitation. Estimated pulmonary arterial systolic pressure (PaSP) 35 mm Hg. There was no pericardial effusion nor intracardiac mass nor thrombus seen. The findings were consistent with thyrotoxic heart disease.

Carbimazole was initiated at 30mg daily and patient's symptoms resolved drastically with a downward trend in liver function tests as well (Table 3).

On account of financial constraints, patient was unable to afford all her labs initially requested. However the laboratories most helpful to clinch the diagnosis for effective management were done. Pleural aspirate yielded no bacterial growth and was indicative of a benign transudate aspirate. Gene xpert® for mycobacteria tuberculosis was negative. Full blood count showed mild anaemia of 10.3 g/dl with a microcytic hypochromic picture and marginal thrombocytopenia of  $149 \times 10^9 /L$  ( $150-450 \times 10^9 /L$ ). There was no evidence of infection and she had an erythrocyte sedimentation rate (ESR) of 10mmfall/hr. There was evidence of liver dysfunction with elevated

International normalized ratio (INR) of 1.5 and prothrombin time of 17.9 seconds with albumin of 26.8g/dl

### ***Follow up***

Patient clinical condition and liver function tests improved remarkably on antithyroid and antifailure medications (refer Table 3). Patient is currently stable and doing well.

### **Discussion**

We illustrate 2 cases of liver dysfunction in hyperthyroidism. The first case was a patient who was managed on an out-patient basis and had direct effect of hyperthyroidism on the liver with overt signs of hyperthyroidism such as proptosis, pretibial myxedema and grade 2 goiter. The second case presented heart failure from thyrotoxic heart disease with jaundice (from hepatic congestion) and no overt signs of hyperthyroidism or obvious goiter.

Hyperthyroidism can affect multiple systems such as the cardiovascular, gastrointestinal, nervous amongst others <sup>9</sup>. It can alter both the structure and function of the liver. The interaction of the thyroid and liver is crucial to maintain homeostasis <sup>14</sup>. Many reports have highlighted deranged liver enzymes ranging from 15%-76% in the setting of hyperthyroidism <sup>9, 14</sup>.

An increase in metabolic activity increases oxygen demand by the liver and as such can lead to tissue ischemia and infarction of the hepatocytes <sup>9, 14, 15</sup>. This is evidenced by the rising levels of the liver enzymes, aspartate amino transferase and alanine aminotransferase <sup>9, 14-16</sup>. In the liver, thyroid hormones are glucuronidated and sulphated, and then excreted into bile; in addition these same hormones maintain the metabolism of bilirubin by regulating the level of ligandin amongst others <sup>4, 14</sup>. Thus, it is not surprising that hepatic dysfunction is common in hyperthyroidism.

It is worth noting that the liver is a major site for the manufacturing of proteins that bind thyroid hormones such as the albumin, transthyretin and thyroxine binding globulin <sup>3, 5</sup>. These hormones, if not in right amounts will fail to serve their normal function of maintaining the serum free T4 and T3 concentrations within narrow limits, yet ensure their immediate release and continuous availability to tissues <sup>3, 5</sup>.

Other mechanisms noted to cause deranged liver enzymes are as follows; direct toxic effect of hyperthyroidism <sup>8-12</sup>. Excess amounts of triiodothyronine induce apoptosis of hepatocytes by the mitochondrial dependent pathway <sup>8-12</sup>. Hyperthyroidism and its complications such as malnutrition, heart failure are major contributory factors to liver dysfunction, as well as associated rare autoimmune conditions and anti-thyroid medications such as carbimazole <sup>8-12</sup>.

In the case of the first patient, her derangement in liver enzymes can be attributed to direct toxic effects of hyperthyroidism as discussed above, while the second patient presented with complications of thyrotoxic heart failure. The latter case almost clouded a prompt judgment and diagnosis of hyperthyroidism. Heart failure in the absence of underlying cardiac disease or arrhythmia, such as in the case of purely hyperthyroidism is thought to be as a result of rate-related cardiomyopathy. As such when hyperthyroidism is treated as in the situation of case two, the heart function returns to normal and cardiomyopathy improves <sup>17</sup>.

More often than not such patients, similar to our patient in case two, may exhibit pulmonary hypertension. Pulmonary artery pressure average twice normal values and can even go as high as 50 mmHg <sup>17</sup>. Tricuspid and/or mitral regurgitation have also been described in patients with hyperthyroidism of all causes <sup>17</sup>.

Carbimazole was initiated in a timely fashion, which resulted in a downward trend in liver enzymes over the period. Prognosis is usually good upon treatment <sup>17</sup>.

### *Diagnostic and Management Challenges*

We believe our patients had hyperthyroidism long before presentation. However, the culture in many developing countries does not encourage routine hospital reviews and laboratory investigations. Patients, on the other hand do not seek early medical attention till their condition has deteriorated. In addition clinical features of hyperthyroidism may be subtle, and not always present classically but rather with non-specific symptoms as was the case in both of our patients. Without a high index of suspicion, hyperthyroidism as a cause of deranged liver enzymes and unexplained diagnosis may be missed. Thus, delayed initiation of thianomides would impair reversal in liver damage leading to more complications and sometimes untimely death.



## **Conclusion**

Hepatic dysfunction in a patient with thyrotoxicosis is not an uncommon presentation, but often this abnormality may dominate the clinical picture and cause complications of the primary disease. Multifactorial mechanisms are involved in the development of liver derangement in hyperthyroidism. The challenge is sometimes to establish the definitive factor causing liver injury in a particular patient.

Notwithstanding, the importance of identifying the relationship of both the liver and thyroid and focusing on definitive treatment in a timely manner directed at saving both vital organs cannot be over emphasized; using a multidisciplinary approach is key.

## **Ethical Approval**

All patients provided written informed consent. Ethical and Protocol approval for the study was sought from the University of Ghana College of Health Sciences Ethics and Protocol Review Committee with reference number URF/9/ILG-076/2015-2019.

## **Author contribution**

NAAS O-A, AAN and EY conceived the study, participated in its design, data collection, analysis, drafted the manuscript. EY collated all drafts. All authors read and approved the final version of the manuscript.

## **Conflict of interest statement**

There is no conflict of interest involving any of the authors of this manuscript.

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## **Data Accessibility/Availability**

The data used to support the findings of this study are available from the corresponding author upon request.

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## **List of abbreviations**

ANA: Antinuclear antibody

Anti-TG Ab: Antithyroglobulin antibody

Anti-TPO Ab: Antithyroid peroxidase antibody

ALT: Alanine transferase

AST: Aspartate transaminase

GGT: Gamma glutamyl transferase

rT3: reverse T3

T3: 3,5,3<sup>1</sup> triiodothyronine

T4: Thyroxine

TBG: Thyroxine-binding globulin

TFTs: Thyroid function tests

TSH: Thyroid stimulating hormone

LFTs: Liver function tests

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