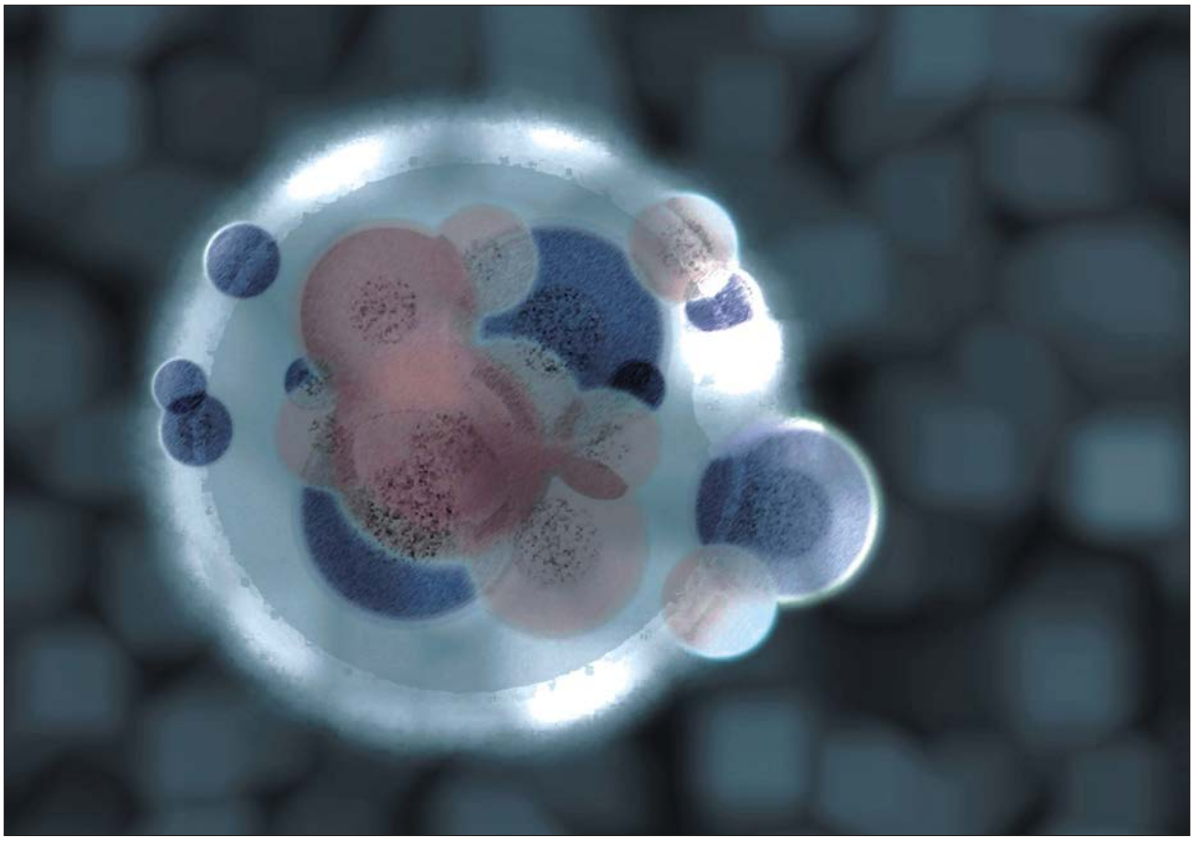

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Liver Functional Behavior During Thyrotoxicosis: A Review

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Abstract: Thyroid and liver are among two vital and important organs which are interrelated in health and disease. The cooperation of thyroid and liver is extremely vital for a proper functional behavior for both thyroid and liver. Liver crucial role in the basic metabolic rate, growth and development is due to the liver ability to transfer the thyroid hormone and deliver it to the various organs intracellular due to thyroid hormone transporting system which is mediated by the liver. Thyrotoxicosis defined as the clinical manifestation of hyperthyroidism, a symptom with various adverse effects on the liver, heart, vascular, nervous and gastrointestinal systems. There are many reports demonstrating the negative side effect of hyperthyroidism on liver function tests which occur due to the accompanying clinical manifestation of thyrotoxicosis. In severe form of hyperthyroidism in addition to liver biochemical alteration and elevated liver enzymes, damages to hepatocytes will occur. Therefore it is strongly recommended that subjects with either of hyperthyroid or liver dysfunction should be carefully examined simultaneously for both organs to have a clear cut diagnosis and to assist the patient with proper therapeutically treatments.

Key words: Liver, thyroid gland, thyroid hormones, disease

INTRODUCTION

Thyroid hormones are interfering with all the aspect of intracellular human metabolism. The way metabolic pathways occur in healthy condition mainly dictated by thyroid hormones serum concentration of normal reference. Thyroid hormones including thyroxin or tetraidothyronin(T4) and triidothyronin(T3) play a crucial role in human metabolism. Although T4, T3 have an important metabolic responsibility in health, but any harm to the thyroid resulting into suppression or elevation of thyroid hormones leads to multiple disorders in human metabolism (Mansourian, 2013; Dratman and Gordon, 1996; Parma *et al*., 1995; Tolls *et al*., 1978; Mansourian 2010a, b; Mansourian *et al*., 2008).

Thyroid hormones are produced according to the physiological changes occurs in human metabolism and in fact thyroid adopting the hormone biosynthesis based on body requirements in different metabolic conditions (Mansourian, 2010c, d; Mansourian *et al*., 2010a, b; Shahmohammdi *et al*., 2008; Mansourian *et al*., 2011).

Thyroid Stimulating Hormone (TSH), is the key pituitary hormone which stimulate thyroid to produce T4, T3. There are an acceptable correlation between TSH and thyroid hormones and TSH production is controlled by the T4, T3 serum concentrations and in fact there is a negative feedback on the TSH-thyroid hormones axis. Serum T4, T3 concentration and the related serum TSH level have been determined worldwide and they are set up according to age, gender and geographical in each region of the world. Hypothyroidism and hyperthyroidism are condition when thyroid can not produce enough either T4, T3 or they are biosynthesized more than serum interval reference range respectively, keeping in mind the statistical variation in each region. Hyperthyroidism occur when T4, T3 are produced are elevated and if this case is continued, for enough period of time the normal path of metabolism is changed and various disorders in different organs including heart, liver, kidney, nervous system. Thyrotoxicosisis a definition which is given to the clinical manifestation of hyperthyroidism (Emerson and Utiger, 1972; Emrich *et al*., 1993; Studer *et al*., 1989; Studer and Ramelli, 1982; Mansourian *et al*., 2010a, b). In addition to metabolic disorders, thyrotoxicosis may show itself by some over dosage theraputical regiments, when the patient is given synthetic thyroxine for the treatment of hypothyroidism, but without proper follow up (Bogazzi *et al*., 1999; Mariotti *et al*., 1982; Kinney *et al*., 1988; Hedberg *et al*., 1987; Mansourian, 2010a, b, Mansourian *et al*., 2007; Mansourian, 2011a, 2012a, b; Mansourian and Ahmadi, 2010).

One of main visible clinical manifestation for thyrotoxic patient is the loss of weight, although the patient appetite remains the same or even increased. As it was stated as the serum concentration of T4, T3 reach to an elevated level and remain over the upper range of reference intervals it eventually end up with catastrophic metabolic condition affecting many organs and leading to

anxiety, hand tremors, heart beat, excess perspiration, sleep abnormality, skin, hair problems, muscular dysfunction, intolerance to heat, menstrual disorders and gastrointestinal dysfunction (Kim *et al*., 2009; Mansourian, 2010a, b; 2013; Mansourian *et al*., 2008; McDermott and Ridgway, 1998).

THE CLINICAL MANIFESTATION OF HYPERTHYROIDISM

Thyrotoxicosis is more prevalent among female and there are some reports indicating the ratio of thyrotoxicosis in male/female is about 1/10 (Mariotti and Pinchera, 1990; Kim *et al*., 2009; Berglud *et al*., 1996; Karger and Fuhrer, 2008; Cooper, 2003; Streetman and Khanderia, 2003; Schneeberg, 1983; Studer *et al*., 1989; Mansourian, 2012a-c).

Graves disease is among the most important factor for thyrotoxicosis toxic nodular which is a genetic based disorder and it is age-dependent is among other cause for thyrotoxicosis. In addition to multinodular goiter, single toxic adenoma, over dosage treatment with thyroid hormone substituted substances and also excess iodine as dietary or therapy can also the cause thyrotoxicosis. The excess production of TSH by pituitary or by ectopic source are among the elevated concentration of T4, T3 and eventual thyrotoxicosis (Persani *et al*., 2000; Kinney *et al*., 1988; Nayak and Burman, 2006; Maji, 2006; Shimatsu *et al*., 1999; Mansourian, 2010d; Mansourian *et al*., 2007; Mansourian, 2011c).

THE MECHANISM OF THYROTOXICOSIS

The mechanism behind T4, T3 biosynthesis is laid on the TSH effect on thyroid through activation of adenylate cyclase enzyme and subsequent production of (cAMP) cyclic adanosine mono phosphate (Sergi *et al*., 1993; Sanno *et al*., 2001; Smallridge and Smith, 1983; Goldstein and Hart, 1983; Parma *et al*., 1997; Takeshita *et al*., 1995; Lax *et al*., 1997; Pinducciu *et al*., 1988; Holtzapfel *et al*., 2002; Mansourian, 2011a-d). This cAMP activate various enzymes in thyroid glandes responsible for T4, T3 production. The active iodine uptake from blood circulation using the pump activated by ATPase, the oxidation of iodine and other sequential process of biosynthesis of T4, T3 on thyroglobuline and their secretion from thyroid all depend on the cAMP. The modification due to mutation on TSH receptor can also lead to excessive amount of T4, T3, again through cAMP pathways (Yovos *et al*., 1981; Tonachera *et al*., 2000; Takeshita *et al*., 1995; Trulzsch *et al*., 2001; Polak *et al*., 1991; Persani *et al*., 2000, Parma *et al*., 1995, Parma *et al*., 1997; Duperz *et al*., 1994; Derwahl *et al*., 1996; Deleu *et al*., 2000; Kopp *et al*., 1995; Lax *et al*., 1997; Ouchimoura *et al*., 1982; Nogueira *et al*., 1999).

There are some controversial arguments about the reasons behind thyrotoxicosis due to toxic adenoma and TSH receptor mutation and not all of the reports in this area of research are homogenous (Pinducciu *et al*., 1988; Derwahl *et al*., 1996; Parma *et al*., 1997; Takeshita *et al*., 1995; Lax *et al*., 1997; Nogueira *et al*., 1999; Trulzsch *et al*., 2001; Persani *et al*., 2000; Kopp *et al*., 1995).

Thyrotoxicosis due to multinodular and nodular are also genetically dependent and in case of iodine also the its deficiency can lead to hypothyroidism, but there are some studies indicated that iodine deficiency may eventually end up to thyrotoxicosis (Guters *et al*., 1998; Derwahl and Studer, 2001; Mansourian *et al*., 2007; Krohn and Paschke, 2002).

Laboratory examination reveal that the prevalence of thyrotoxicosis due to nodular among male and female is not similar and it is reported that it is more prevalent among female and also older age (Hamburger, 1980; Thomas and Croom, 1987; Bransom *et al*., 1979; Taylor, 1953; Becker and Cornette, 1971; Dige-Petersen and Hummer, 1977; Mariotti *et al*., 1982; Lisker-Melman *et al*., 1992; Ross *et al*., 1984).

Congenital disorders, genetically mutation and goitrogenous factors are also among other causative elements which eventually end up to throtoxicosis (Marine, 1924; Hamburger, 1980; Peter *et al*., 1985; Becker and Cornett, 1971; Hedberg *et al*., 1987; Al-Khafaji *et al*., 2005; Huang *et al*., 1994; Berghout *et al*., 1990; Holzapfel *et al*., 1997).

Other rare cases of thyrotoxicosis, with low prevalence are choricarcinoma, hydatidiform mole, struma avarii, polyostatotic fibrous dysplasia (Dowling *et al*., 1960; Ciccarelli *et al*., 2004; Anderson *et al*., 1979; Bransom *et al*., 1979; Becjer *et al*., 1963; Hershman and Higgin, 1971; Kenimer *et al*., 1975; Kempers *et al*., 1970; Kock *et al*., 1966; Galton, 1968; Misra *et al*., 2002; Simkin *et al*., 1999; Zalel *et al*., 2000).

THE BIOCHEMICAL PATHWAYS LEADING TO PHYSIOLOGICAL FUNCTION OF T4, T3 ON TARGET TISSUES

Thyroid hormones T4 and T3 enter nucleus with ultimate combination with thyroid hormone receptor. This combination of thyroid hormone-receptor bind to particular segment on the (DNA) deoxyribonucleic acid (Umesono *et al*., 1991; Ribeiro *et al*., 1998; Apriletti *et al*., 1998; Kliewer *et al*., 1992). DNA expression of particular

gene is the key message of thyroid hormone on the target tissues (Glass, 1994; Mangelsdorf *et al*., 1995; Umesono *et al*., 1991). T3 considered as a powerful thyroid hormone in body including liver. and DNA transcription occur through thyroid hormones action specifically by T3 with eventual protein biosynthesis of specific gene within target tissue (Nagy *et al*., 1997; Ribeiro *et al*., 1998).

Thyroid hormone response in various organs depend to the thyroid hormone receptor, with specific affinity to a special segment of DNA to initiate the expression of specific protein (Baxter *et al*., 2001; Mansourian, 2010a, b, d; Kopp *et al*., 1995).

Serum thyroxine (T4) level is more than T3, but T3 binds to the thyroid hormone receptor in nucleus with more affinity to the receptor compared to the T4. T3 show about 5-10 times affinity to thyroid hormone receptors. T3 affinity and its potential activity overlap the higher serum T4 concentration and T3 considered for large portion of thyroid hormone physiological roles in human metabolism. T4 is considered as a banking system for T3 in the target organ and on condition and when the presence of T3 is improper, it will be converted to the non-active hormone namely reverse T3 (rT3). rT3 is produced when the T3 should not be available anymore and when rT3 is produced the T3 biological activity on the target tissue is not implemented (Larsen, 1975; Hassi *et al*., 2001).

THYROID AND LIVER IN HEALTH AND DISEASE

In healthy condition: The lipid metabolism in human metabolism is done by the coordination between the two most important organs within the body. Low density protein (LDL), transferring the cholesterol to the liver for eventual metabolism. Primarily LDL should be associated with the LDL receptor located on the liver cell. Thyroid hormones enhance LDL receptor gene expression and ultimately the available lipoprotein receptors on the hepatocytes and by doing that LDL uptake into liver increased. The activity of enzymes, responsible for the catabolism of LDL and ultimately decrease the LDL level, which is labeled as bad lipid due to its cardiovascular adverse side effects. High Density Lipoprotein (HDL) is lipoprotein which eventually excrete cholesterol through liver and ultimately by the intestine. Thyroid hormone elevate the gene expression of a protein considered as milestone for the HDL production (Mansourian, 2010c; Ness *et al*., 1998; Ness and Lopez, 1995; Taylor *et al*., 1997). HDL is a lipoprotein collecting all the undesired fats specifically cholesterol from peripheral tissues, directing them into the liver with subsequent catabolism. The simultaneous thyroid-liver physiological function, can be a pathways which can prevent atherosclerosis and atrial arrhythmias, which have been confirmed through experimental studies (Woeber, 1992; Dillmann, 1990; Leeson *et al*., 1989; Baxter *et al*., 2001).

As it was elaborate earlier T3 potentiality more effective thyroid hormone occurred due the specific requirement of target organs and liver is a major peripheral tissues for the excessive requirement of thyroid hormones, the conversion of T4 into T3 mostly happen in the liver. The deiodinase enzyme responsible for conversion of T4 into T3 demonstrate to show high activity (Sanders *et al*., 1997). In addition T4, T3 eventual metabolism from any other organs of the body eventually take place in the liver and excess thyroid hormones which are undesired in the body reach liver for eventual destruction.

Thyroxine Binding Globuline (TBG) which is produced in the liver is the main protein which carry thyroid hormones in circulation. Thyroid hormones in TBG is accounted for more than 95% of all thyroid hormones in human blood circulation. Thyroxin binding prealbumin and albumin are the other liver proteins carrying thyroid hormone in circulation. A trace amount of thyroid hormone are as free hormones playing the actual thyroid hormone physiological role in the target organ. Free hormones in circulation are therefore at the level which is needed for the body metabolism (McDermott and Ridgway, 1998; Hennemann *et al*., 2001; Mansourian, 2011b, d; Mendel *et al*., 1988).

The activity enzyme responsible for the conversion of T4 into T3 and the deidonase isomer converting the active form of T3 into rT3 and other inactive form T3 are crucial to control T3 activity when thyroid hormone biological function is not required any longer (Bianco *et al*., 2002). It seems the thyroid hormone transportation in circulation, thyroid hormone transportation in the target tissue, the proper passage of thyroid hormone to bind the thyroid hormone receptor, the structure of thyroid hormone receptors, the location receptor in the nucleus and the specific portion of DNA for the hormone-receptor complex, are all among other vital factors in proper pathways in thyroid hormone metabolism in addition to the normal level of T4 and T3 in human blood circulation.

Liver crucial role in the basic metabolic rate, growth and development is due to the liver ability to transfer the thyroid hormone and deliver it to the various organs intracellular due to thyroid hormone transporting system which is implemented by Thyroxine Binding Globulin (TBG), pre-albumin and albumin, all are liver proteins. Thyroid and liver metabolism are associated and correlate

in a manner which any harm to this association eventually leading to adverse effect on the normal physiological pathways of metabolism. T4, T3 are playing vital role in general metabolism but some diseases manipulating the physiological pathways force thyroid to adjust itself to the outgoing pathological condition and biosynthesis T4 and T3 as it is needed through the reduced activity of the deidinase and ultimate reduced production of T3 from T4. On this way T4 can be conserved and the loss of thyroid hormone prevented in diseases such as non-thyroidal chronic diseases.

Thyroid hormones are the main regulator of basic metabolic rate and that is occur through complex pathways. The prevention of energy loss during diseases is justifiable and thyroid hormone must produced to cover the new condition and to prevent the loss of energy through prevention of the T4 into T3 and also available T3 into rT3. Liver abnormalities exhibit a physiological demonstration on thyroid function and it will have its adverse effect on the thyroid hormone, but various forms of liver diseases may be presented with different laboratory measurement of liver function tests (Bianco *et al*., 2002; Camacho and Dwarkanathan, 1999; Stathatos and Wartofsky, 2003; Mendel *et al*., 1988).

In disease condition: Studies indicated that thyroid and liver can also be associated in disease states as well and some pathological condition affect liver and thyroid simultaneously. Autoimmunity and inflammation can adversely interfere with both organs, benign and cargonic can also do the same and affect both liver and thyroid (Inoue *et al*., 1999; Wirtzfeld *et al*., 2001; Thieblemont *et al*., 2002). Iron overload also in liver and thyroid can affect both organs, in other words the accumulation of iron in the thyroid and subsequent hypothyroidism can show its effect on liver and reveres is occur as well.

The side effects of hypothyroidism due to iron overload will exhibit adverse physiological behavior not only on liver function test but on the organs of the human (Gillmore *et al*., 2001; Phillips *et al*., 1992; Shirota *et al*., 1992; Magro *et al*., 1990). Malignancy in either of liver and thyroid affect both on the same time. The drug therapy in some diseases was found to implement adverse effect on both thyroid and liver, but the thyroid and liver dysfunction can be overcome following the cessation of therapeutically regiments (Sanoski *et al*., 1998; Croft and Herxheimer, 2002; Isojarvi *et al*., 2001; Van Santen *et al*., 2002; Oren *et al*., 1998).

Thyroid status in liver disorders can be followed through serial measurement of laboratory determination of TSH, T4, T3, TBG, thyroid auto antibodies and studies in this regard show manipulation of thyroid function tests and it has been shown serum T3 production is lowered, to conserve energy loss, which seems a positive course to face the liver diseases by lowering the rate of basic metabolism.

Cirrhosis: Laboratory measurement show T3 production in the liver is reduced, but rT3 concentration is increased due to the responsible enzymatic manipulation in the liver to adjust to the new condition to preserve energy expenditure The laboratory indexes for the serum thyroid hormone level, can be used mathematically to predict what biochemical modification are to be followed for thyroid hormone metabolism in liver diseases including cirrhosis. There is a higher ratio of rT3/T3 when the serum levels of T4, T3, rT3 are evaluated. Studies indicated the serum T3 level is reduced in the cause of liver dysfunction to overcome energy loss for giving hand the liver at the time energy most wanted to face the liver disease (Bianchi *et al*., 1991; L'age *et al*., 1980; Faber *et al*., 1981; Guven *et al*., 1993; Van Thiel *et al*., 1985; Oren *et al*., 2000; Oren *et al*., 1998).

Acute liver diseases: TBG biosynthesized by the liver transport thyroid hormone in the circulation. TBG is increased as result of protein produced by the liver during acute diseases.. As result of elevated TBG concentration of total thyroid hormones produced within the thyroid gland is increased, this manifestation is seen in early acute liver abnormality, but TBG level is reduced later as result of liver even worsen liver dysfunction, which is followed by total thyroid hormone reduction. It can be stated that in the initial state of acute liver diseases total T4 increases and subsequently reduced in later stage of liver diseases due the higher and lower TBG levels, respectively. In general although there are some modification in the amount of thyroid hormones during liver diseases but thyroid condition of euthyroid although T4, T3 level altered and T3 concentration fall, but this is in favor of human metabolism at the time of liver dysfunction to preserve energy for ailing liver (Oren *et al*., 1998; Hegedus; 1986).

AUTOIMMUNE LIVER DYSFUNCTION

There are autoimmune liver diseases including hepatitis and cirrhosis associated biliary liver diseases associated with chronic hepatitis in such liver dysfunctions thyroid gland is affected adversely with autoimmune disorders. The thyroid autoimmunity can be as result of thyroid disorder or as direct negative effect of liver disorders which is the main source for the

autoimmunity to the thyroid. In such condition TSH, T4, T3, thyroid auto antibodies should be checked by the clinical laboratory to give a hand to manage the patient of liver dysfunction and for the sake of proper treatment.

Thyroid and liver metabolism are so closed that abnormality in one organ can be followed the other organ and in some cases it can be mistaken by the other, which should be looked at it with deep eye to prevent any misdiagnosis. Autoimmunity to the liver can also have its side effects on the thyroid and liver autoimmunity can finally demonstrate its adverse effect on the thyroid by some auto-antibodies which will be raised against thyroid, but thyroid remain at euthyroid status (Mansourian, 2010d, e; Crowe *et al*., 1980; Krawitt, 1996; Sherlock and Scheuer, 1973; Elta *et al*., 1983; Saarinen *et al*., 2000; Borzio *et al*., 1983). The drug therapy for the liver dysfunction may be end up with autoimmunity to the thyroid, including to the TSH receptor (Benelhadj *et al*., 1997; Shimizu *et al*., 1994; Fonseca *et al*., 1991; Kopp *et al*., 1995). It is strongly advised to check thyroid function tests by the clinical laboratory measurements of TSH, T4, T3, TBG and thyroid auto antibodies, prior and during to any treatments for the liver hepatitis to avoid mistreatment and misdiagnosis in such vital human organs (Roti *et al*., 1996; Koh *et al*., 1997; Bell *et al*., 1999; Lisker-Melman *et al*., 1992; Deutsch *et al*., 1997; Melman, 1994).

HYPERTHYROID DISEASES ALTER THE LIVER STRUCTURE AND FUNCTION

As it was stated thyrotoxicosis is definition which is given to the clinical manifestation of hyper active thyroid, when producing an even larger amount of thyroid hormones. There are major complications which are accompanied with in thyrotoxicosis and in fact all tissues in human are adversely affected by hyperthyroidism including liver structure and functions. Thyrotoxicosis is a symptom with various adverse effects on the liver, heart, vascular, nervous and gastrointestinal system. On the other hand it should be stated that the cooperation of thyroid and liver is extremely vital for a proper functional behavior for thyroid and liver. The aminotransferase are the key liver enzymes, which are affected adversely following hyperthyroidism and there are studies indicated an increase in the above enzymes in some cases. The reason behind such adverse biochemical alteration lay on the specific nature of throtoxicosis and increased metabolic rate in liver following hyperthyroidism. On such condition although blood circulation in the liver remain mainly steady but oxygen requirement is increased, but in the absence of any oxygen supplementation the liver adversely affected, leading to tissue destruction and the elevated aspartate aminotransferase and alanine aminotransferase enzymes. It seems only sever form of hyperthyroid can cause such alteration in the liver enzymes (Mansourian, 2010b; Thompson *et al*., 1978; Mansourian and Veghari, 2011).

In severe form of hyperthyroidism in addition to biochemical alteration and elevated liver enzymes, damages to hepatocytes in liver will occurs and liver damages mainly happen in the area with lower amount of required oxygen. The extent of liver damages biochemically can be assessed by measuring the serum level of isocitrate dehydrogenase enzyme which is releases following liver lesion as result of thyrotoxicosis. It seems excess thyroid hormone can not go to that extend, which leaving the affected person with liver failure, but there are also some study indicating hepatocytes damage and liver failure can be a result of thyrotoxicosis. Although heart abnormality simultaneously is participated in the whole scenario if such liver failure practically is happened (Lum *et al*., 1983; Huang and Liaw, 1995; Chung *et al*., 2001; Choudhary and Roberts, 1999). T4 and T3 are metabolized within the liver through conjugation with glucoronic acid and sulfuric acid are the key factors in the bilirubine excretion by congugating glucoronic acid with hydrophobic bilirubine converting it into hydrophilic compound. The conjugated bilirubine produced by the function of glucuronyl tranferase, which is activated through T4 and T3.Bile acid and their eventual loss through bile duct and small intestine, on the other hand occur by T4 and T3 (Fagiuoli and Van Thiel, 1993). The catastrophic adverse effect of thyroid hormone abnormalities on liver is reported in late 19th century, through demonstration of cardiovascular and liver diseases. with fatal outcome on patients with thyroid over activity in producing elevated amount of thyroid hormones (Habershon, 1874). The alkaline phosphatase although is not specifically produced in the liver and the bone tissues is the alternative source of the above mentioned enzyme it is another liver enzyme which is biochemically increased during hyperthyroidism. The other liver specific biochemical factors including Gamma glutamyl transpeptidase enzyme and bilirubine are among substances which should have been taken into consideration, when liver function and in particular cholestasis is being assessed. The hepatocytes liver damage in here looks similar to the other lesion and only it seems in severe cases of hyperthyroidism, the bilirubin concentration reach to the level which one can be labeled as jaundice patient, even at that time other intervening elements such as heart and liver damages which

intrinsically can interfere should be taken into consideration, when such clinical manifestation is presented itself (Sola *et al*., 1991; Doran, 1978).

There are many reports demonstrating the negative side effects hyperthyroidism on liver function tests. Liver abnormalities during hyperthyroidism occur due to the accompanying clinical manifestation of thyrotoxicosis, cardiovascular disorders originated from hyperthyroidism and hyperthyroidism itself and finally the liver diseases which is a accompanying nature of hyperthyroidism (Fong *et al*., 1992; Huang *et al*., 1994; Runyon, 1998; Giallourakis *et al*., 2002). It seems there are not homogeneity in the pattern of clinical manifestation and organs involved and in reality the hyperthyroid patients can be subdivided into hyperthyroid patients suffering from heart dysfunction, non heart problems and subjects with accompanying liver abnormality without cardiovascular origin (Fong *et al*., 1992).

Liver histopathological studies revealed there are heptocyte tissues modification and injury in patients suffering from thyrotoxicosis. The liver biochemical abnormalities of hyperthyroid patients accompanied with cardiovascular diseases is even worse, liver function is adversely altered even with heart dysfunction in the absence any thyrotoxicosis (Fong *et al*., 1992; Upadhyay *et al*., 2004; Myers *et al*., 2003; Runyon, 1998; Venkat *et al*., 2011). Clinically it seems liver disorder can only manifest itself when the hyperthyroidism remain unattended, and, studies indicated liver complication practically reversed following thyroid treatments (Lum *et al*., 1983; Sola *et al*., 1991; Fong *et al*., 1992).

Depending on the different categories the degrees of liver malfunction varies accordingly, although there are not clear cut reports on association of liver biochemical measurements and thyroid hormones levels and it seems thyroid remain at euthyroid state (Huang *et al*., 1994; Kubota *et al*., 2008; Hull *et al*., 2007).

Although there are controversial arguments in how hyperthyroidism can adversely modify liver function, but various experimental studies indicated that liver abnormality during hyperthyroidism is might be through the changes in hepatocyte mitochondria. There are reports indicating on conditions of recovery from hyperthyroidism, liver function returns to normal (Upadhyay *et al*., 2004; Klion *et al*., 1971; Kalderon *et al*., 1995).

Thyrotoxicosis due to autoimmunity such as Graves disease can be correlated with some hepatic dysfunctions such as primary biliary cirrhosis, hepatitis due to autoimmunity. In fact thyroid autoimmunity as Graves disease is associated with many types of chronic liver diseases, which also might be accompanied with heart dysfunction (Boelaert *et al*., 2010; Czaja *et al*., 1993; Venkat *et al*., 2011; Vierling, 2004; Tsuneyama *et al*., 1995; Michieletti *et al*., 1994; Baethge *et al*., 1988; Morita *et al*., 1995; Petri *et al*., 1991).

Unfortunately, there can be some drug adverse effect happen on the liver function of some patients when hyperthyroidism is undergoing treatment. The liver abnormality show itself with elevation of key liver enzyme of AST, ALT, initially but reduced later on in the course of thyroid recovery and successful treatments, but it seems one cannot take all these changes as serious liver complications and liver returns to its normal physiological function following thyroid treatment eventually, although there some studies indication a catastrophic scenario in some exceptional case particularly among female in their twenties. On the base all uncertainty, liver should be assessed routinely whenever thyrotoxicosis is diagnosed and also when thyroid therapeutic treatment is initiated. (Lum *et al*., 1983; Siegers *et al*., 1983; Szilagyi *et al*., 1993; Smith *et al*., 1983; Smolle *et al*., 1983; Willianıs *et al*., 1997; Kim *et al*., 2001; Levy, 1993; Gurlek *et al*., 1997; O'Grady *et al*., 1993; Blom *et al*., 1985; Aynsa *et al*., 1986).

KEY POINTS

- Thyrotoxicosis is originated form a hyperthyroidism as result of excess thyroid hormones of T4 and T3
- Thyrotoxicosis is occurred mainly as result of toxic adenoma, nodular and multinodular goiter, acute thyroiditis, autoimmunity related thyroiditis including Hashimati's thyroiditis, thyrotoxicosis factitia thyrotoxicosis originated from pregnancy and tumor producing Thyroid Stimulating Hormone (TSH)
- Toxic nodular and multinudular thyroiditis, excess thyroid hormones replacement therapy are the major and common form of thyrotoxicosis and excessive iodination of dietary regiment or iodide based drugs, neonate hyperthyroidism and overproduction of TSH due to pituitary adenoma and pituitary biochemical resistance by T4 and T3, thyroid cancer, struma ovarii choricarcinoma are among other minor common causes of thyrotoxicosis
- In addition to physical examination of throid by the clinician the clinical diagnose of thyrotoxicosis done by the Laboratory measurements of thyroxine (T4) trriothyronine (T3) and Thyroid Stimulating Hormones (TSH) and thyroid auto antibodies. In thyrotoxicosis serum T4, T3 level is increased although T3 can be at normal range in some cases but serum TSH is always suppressed but except rare case of throtoxicosis due to tumor producing TSH or ectopic TSH production

- The laboratory measurement and other paramedical examinations obviously are requested by Clinicians and Endocrinologist following careful clinical examinations of thyroid gland to give the definit diagnosis
- Thyrotoxicosis mainly modify the metabolism of all organs including liver cardiovascular, neuromuscular, reproductive, dermatological, bone, gastrointestinal
- Thyroid and liver are the two most important organs which metabolically are related in many pathways and any defect to either of them ultimately affect the other organ
- Thyroid hormones disorders either of hypothyroidism or hyperthyroidism can have adverse effects on liver function tests. Liver dysfunction can also interfere with thyroid hormones normal pathways of metabolism
- The immune system which can adversely affect both organs are among such abnormalities, other diseases of benign and cacogenic tumors are also reported in these area of studies, which affect both organs
- Thyroid and liver closely interrelated in such way that pathological agents can interfere with both of these vital organs at the same time. Some diseases in human can adversely affect both thyroid and liver simultaneously, malignancy can affect thyroid and liver, by thyroid and abnormal liver function tests
- Some therapeutic regiments adversely affect both thyroid and liver and their side effects persist even after the therapy is terminated
- The aminotransferase is the key liver enzymes which is modified following hyperthyroidism. The reason for this biochemical alteration is due to throtoxicosis and increased metabolic rate in the liver. In addition in the absence of any oxygen supplementation the liver adversely affected and liver tissue damage occur followed by aspartate aminotransferase and alamine aminotransferase enzymes
- The extent of liver damages by thyotoxicosis biochemically can be assessed by measuring the serum level of isocitrate dehydrogenase enzyme which is releases following liver lesion as result of thyrotoxicosis. Although in liver diseases thyroid remain at euthyroid state but normal hormonal pattern of adversely altered. T3 remain at low range of normal, but serum T4 concentration is elevated which is due to the reduced activity of deidonase-I enzyme, which is responsible for T4 to T3
- Liver abnormalities at any stage can have its influence on thyroid function tests and no matter the form of liver abnormality it will have its adverse effect on the thyroid hormone metabolism, but it seems various type of liver diseases may clinically and Para-medically are presented with different pattern at least in laboratory investigations
- In liver diseases thyroid remain at euthyroid state but normal serum T4, T3 are changed. Serum T3 level remain at low range of normal, but serum T4 concentration is elevated as result of reduced activity of deidonase-I enzyme, responsible for the conversion of T4 into T3
- From laboratory point of view whenever there is corresponding association between liver and thyroid abnormality, laboratory indices such as total, T4, T3, TBG and TSH, free T4, are elevated but remain at reference range of normal

CONCLUSION

On the base all of above metabolic alterations, which may occur following either of thyroid or liver dysfunction on the each other biochemical functions, laboratory measurements of thyroid and liver function tests seems important to be performed simultaneously whenever either liver or thyroid are under medical care for the sake of clear and comprehensive understanding of clinical setting and prevent any possible misdiagnosis.

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