

<http://www.pjbs.org>

PJBS

ISSN 1028-8880

**Pakistan
Journal of Biological Sciences**

ANSI*net*

Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

A Review of Literatures on the Adverse Effects of Thyroid Abnormalities and Liver Disorders: An Overview on Liver Dysfunction and Hypothyroidism

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Abstract: The healthy thyroid is vital for the liver metabolism. The liver also plays an important role in the metabolism of thyroid hormones. Thyroid and liver diseases can apparently have an adverse effects on each other organs. The main concept behind this present review is to analyze the coordination existed among thyroid and liver and the pathophysiology surrounding these two vital organs in human metabolism.

Key words: Liver, thyroid, liver dysfunction, thyroid hormones abnormalities

INTRODUCTION

Thyroid hormones metabolism is entirely depend on a healthy liver and a biologically healthy liver are crucial for well being of thyroid hormone. A healthy thyroid with good production of thyroid hormones are also essential for a good healthy liver. The various aspects of hormone metabolism including the synthesis of Thyroxine Binding Globuline (TBG), the peripheral production of triiodothyronine (T3) from tetraiodothyronine (T4) and inactive T3, named as reverse T3 (rT3) depend on healthy liver. The degradation of thyroid hormones, their excretion initiated by the liver and any harm happen to the liver will show its eventual effect on the thyroid hormone metabolism. As matter of interest it has been demonstrated that with all modifications on serum thyroid hormones concentration which may happened during liver disorders the thyroid statuses will mostly remain at euthyroid statuses.

One of side effects of liver dysfunctions on thyroid is the reduced serum T3 concentrations which is due to reduced activity of deiodinase enzyme which is catalyzing the T4 into T3 but the reverse T3 is not reduced, because the activity of responsible enzyme is not altered. As whole in liver diseases T3 is reduced firstly by lower activity of enzyme responsible for conversion of T4 into T3 and also the increased concentration of reverses T3, the inactive forms of T3. The conclusion out of liver diseases is the reduction in the amount of active form of thyroid hormone which is T3 and increased form of inactive form of thyroid hormones reverse T3 (Malik *et al.*, 2000; Oren *et al.*, 1996; Forbes *et al.*, 1998; Mansourian and Veghari, 2011; Mansourian 2010a, d, e; Fassler *et al.*, 1988).

As the severity of diseases is worsen the serum concentration of T4 and T3 reduced even further

(Evans, 1988; Ribeiro *et al.*, 1995; Mangelsdorf *et al.*, 1995; Umehara *et al.*, 1991; Ribeiro *et al.*, 1998a; Apriletti *et al.*, 1998; Kliewer *et al.*, 1992; Nagy *et al.*, 1997).

Thyroid assessment in liver diseases should be accompanied with laboratory estimation of thyroid function test. The laboratory procedure lay on the measurement of T4 and T3 in the form of total and free hormones, Thyroxine Binding Globulin (TBG), Thyroid Stimulating Hormone (TSH), at the front-line of laboratory investigation. Laboratory measurements confirm that in presence of chronic liver disorders, thyroid metabolic pathways altered adversely. But also thyroid hormone level stay almost at reference range but in expense of higher T4 and lower T3, mainly due to reduced activity of deiodinase enzyme within liver. As liver abnormality worsen the T3 production from T4 is also reduced and consequently the progression of liver disease can end up with as much lower T3, the more potent thyroid hormone. It is believed this reduction of T3 which mainly correspond to even lower basic metabolic rate, economically might be useful, because it prevent the consumption of an extra energy and keep it for the possible liver disease or any other related syndrome which needs more energy.

Although, euthyroid is manifested but thyroid normal pattern of metabolism adversely altered. T3 remain at low range of normal but serum T4 concentration is elevated which is due to the reduced activity of deiodinase-I enzyme, which is responsible for T4 to T3 conversion. It seems the serum T3 concentration directly related to liver disease progress. Other studies indicated that during various phase of liver disease the serum T4 concentration altered accordingly and related also to the disease progression.

One remarkable manifestation of thyroid hormone during liver abnormalities relay on the direct relation of bilirubine concentration and the level of thyroid disorders, also thyroid remain at euthyroid at most of the times. This unique clinical manifestation may be due to lower and higher range of T3 and T4 among liver disease patients. There are various report on the remarkable role of serum T3 concentration in predicting the status of liver abnormality in progressed phase of liver disease. T3 can be used as good laboratory index in evaluating the statues of liver disease, also the serum T3 concentration and those liver factors, such as bilirubine are now can be regarded as valuable index in following the trends in thyroid-liver pathophysiology. In other words the status of T3 can be considered as marker for the condition of liver disease.

There also some studies indicating on how serum T3 concentration can predict the liver disease level and those index of liver function tests such as serum bilirubin, albumin and prothrombin time. It is reported that serum T3 concentration are correlated with above liver indexes. There also some controversial argument about the TBG, in which some studies indicated that this index is increases in liver disease but some other studies contradict that findings (Schussler *et al.*, 1978; L'age *et al.*, 1980).

Some studies indicated that in liver disease serum T3 and T4 concentration can remain at low and high range of reference range in various liver diseases including cirrhosis and chronic hepatitis. As it was mentioned earlier under any condition thyroid function remain at euthyroid status but with low and high free T3 and free T4 respectively. Laboratory study of thyroid status in liver disease include the determination of serum total T4 and free T4, total T3, free T3, total T3, Thyroid Stimulating Hormone (TSH), Thyroxine Binding Globuline (TBG) concentrations. Following the laboratory measurements various ratios can be applied to assess the thyroid hormone statues following liver disorders and these index can be used to differentiate the various type of liver disorders. It is a matter of interest that the data obtained from different studies indicates that chronic liver diseases can modify the thyroid hormone metabolism with subsequent reduction in the amount of T4 and manipulation in the concentration of TBG.

The abnormality in the amount of T3 production mainly is due to the reduced activity of deiodinase-I enzyme responsible for the biosynthesis of T3 from T4. The disorders of thyroid hormones and other related index directly related to the severity and deterioration of liver diseases (Nomura *et al.*, 1975; Hepner and Chopra, 1979).

HOW THYROID AND LIVER INTERRELATED IN HEALTH

Thyroid and liver are the two most important organs physiologically interrelated so deeply in many biochemical process and any defect to either them, can directly harm the other organ. The lipid metabolism is among such interaction existed between these two vital organs. Low Density Protein (LDL), a lipoprotein which carry the cholesterol to the liver for final degradation is thyroid hormone dependent for its metabolism. Prior to LDL penetration into liver cell, it should be bounded to the LDL receptor which is existed on the liver cell. Thyroid hormones T4 and T3 in particularly elevate the LDL receptor gene expression, therefore enhancing the numbers of available receptor on the hepatocytes. By doing that LDL entry into liver cells increased. One other thyroid hormone responsibility is to elevate the activity of those enzyme, mediating the catabolism of LDL. All these mentioned process including LDL receptor gene expression, enhanced activity of LDL catabolic enzymes eventually decrease the amount of LDL, which itself is defined as agent for cardiovascular damages. High Density Lipoprotein (HDL) is lipoprotein which is carrying the cholesterol and triglyceride and thyroid hormone increase the gene expression of apolipoprotein-a1 protein which is the core center for the formation of HDL (Ness *et al.*, 1998; Ness and Lopez, 1995; Mansourian *et al.*, 2008; Mansourian, 2010b). HDL is a lipoprotein collecting all the unwanted lipids, in this case cholesterol from peripheral tissues taking them into the liver and catabolic the undesired lipids, also LDL which is considered as risk factors for cardiovascular diseases is demolished following the simultaneous thyroid-liver operation and by doing that atherosclerosis and atrial arrhythmias can be prevented (Woeber, 1992; Dillmann, 1990). There various experimental studies elaborating the role of thyroid hormones in reducing the amount of cholesterol mediated by the liver (Leeson *et al.*, 1989; Baxter *et al.*, 2001; Mansourian, 2012a, b, c; Mansourian, 2013).

HYPOTHYROID DISEASES MANIPULATE LIVER FUNCTION

Some of clinical presentation of liver abnormalities can be similar to the those of thyroid hormones deficiency, myalgias, fatigue and muscle contraction are among such manifestation. In later situation the serum aspartate amino transferase concentration which considered the key enzymes and clinically is valuable index in the medical laboratory is elevated reflecting muscular disorder (Laycock and Pascuzzi, 1991). Comma

in Liver abnormalities associated with hypothyroidism might be presented which is due to elevated ammonia at pathological level, simultaneously with myxedema comma (Thobe *et al.*, 2000). Liver disease comma related hypothyroidism can be seen in myxedema ascites (Klein and Levey, 1984). Although, there are some studies elaborating on the role of heart abnormalities in initiating the ascites but on the other hand there are reports indicating ascites is the direct effect of hypothyroidism on causing the permeability of vascular tissue with subsequent ascites and other complicated in affected persons (Klein and Levey, 1984; Kinney *et al.*, 1989; Baker *et al.*, 1972). As it was mentioned earlier elevated protein concentration in myxedema ascites leading to exudates usually is considered as liver abnormality or some other clinical condition resembling liver disorder such as heart failure and the lesion which can inflict on liver function (Klein and Levey, 1984; Kinney *et al.*, 1989; Baker *et al.*, 1972). Studies show that in case of hypothyroidism ascites leading to exudate is the key responsible factor although the clinical manifestation is cleared off following thyroid hormone replacement therapy. There are various studies indicating that thyroid hormones suppression can have a serious manipulation on the structure and function of liver and as result of such liver modification due to hypothyroidism liver structure and function adversely affected leading to the destruction of liver tissue with the consequence of liver damage and interfering with normal metabolism of producing bilirubine and bile which is due to the cholestasis. The afflicted subject eventually will have the whole manifestation of jaundice due to damage occurred on liver tissue as result of hypothyroidism. It is demonstrated that as thyroid hormone reduction continued and overt hypothyroidism is ensued the direct bilirubine production within liver is reduced due to the key enzyme responsible for glucornic acid adhesion to the bilirubine which is already produced within spleen and reached into the liver facilitated by the albumin. The bilirubine produced in the spleen following red blood cells death and haemoglobin destruction with the disintegration of haem molecules into bilirubine and iron. The produced bilirubine in the spleen is not water soluble and it is in non-aqueous phase and therefore it is transported to the liver through blood circulation by the albumin which is itself a transporter protein biosynthesized within the liver. The bilirubine which is produced in the liver defined as non-conjugated bilirubine and as it was mentioned is not water soluble and it is hydrophobic in nature but as it reached the liver it will be converted into a hydrophilic substances named conjugated bilirubine which can be excreted into small intestine and eventually its oxidized form is seen in feces.

The hydrophobic bilirubine is congugated in the liver by glucuronic acid and the enzyme responsible for this conversion is UDP-glucuronyltransferase, which is an enzyme catalyzing the glucuronic acid addition on the hydrophobic bilirubine and converting it into water soluble substance. This later substance can be eliminated from human through bile duct pouring into small intestine and following oxidation and some supplementary pathways excreted through feces (Van Steenberg *et al.*, 1989).

Hypothyroidism can also interrupt bile acid and salt production which is mainly due to abnormality within the content of cholesterol in the hepatocyte of canalicular biological membrane of liver. This additional cholesterol in the membrane alter its fluidity and many liver physiological functions which are dependent on the well behavior of this membrane fluidity including the bile transporting system is disrupted. If the above mentioned pathways is diverted it will be followed by retardation of the bile excretion from the liver (Van Steenberg *et al.*, 1989). The other abnormalities following canalicular biological membrane of liver is the altering activity of some enzyme in the liver, Na^+/K^+ ATPase is among such enzyme, which may interfere with some of liver metabolic functions. The high cholesterol, interrupting bilirubine metabolism and gall bladder abnormality which all are seen in hypothyroid patients which can also eventually lead to production of gallstone which is as other clinical symptom of hypothyroidism (Inkinen *et al.*, 2000). Various studies indicated that the liver clinical symptom which are manifested due to thyroid hormone suppression can be overcome following the treatment of hypothyroidism or as result of therapeutic thyroid hormone substitution (Huang and Liaw, 1995; Gaitan and Cooper, 1997). Thyroid hormones T4 and T3 in particular play an important role in almost every organ metabolism growth in health and diseases. In other words the entire metabolism in human body in some ways regulated by thyroid hormone and any abnormality happen to the thyroid it can manipulate every aspect of biochemical pathways leading to a particular disorder in affected organ (Mansourian 2010a, c, 2011b; Mansourian *et al.*, 2011). T4 and T3 also have direct roles in the tissue development and organ development as result the liver metabolic pathways and growth also can be influenced by T4 and T3, the liver function, therefore ultimately is under the influence of thyroid hormones. As result of such thyroid hormone interference with liver function any thyroid disorder which lead to the abnormality T4 and T3 result into liver dysfunction which can be end-up with liver diseases. Liver is an vital organ and it is a center for every aspect of metabolism including thyroid hormone metabolism and

any damage to liver function also can alter adversely thyroid hormone metabolism. In other words there are interrelation and interaction between the thyroid and liver and any harm to any organ simultaneously manipulate the other in health and also in disease.

BIOCHEMICAL PATHWAYS LEADING TO T4 AND T3 INFLUENCE ON HEPATOCYTE

The nature of thyroid hormones permit the penetration of T4 and T3 into the cytoplasmic and even the nucleus membrane with subsequent combination with thyroid hormone receptor. The combined hormone-receptor complex bind to specific site on the Desoxyribonucleic Acid (DNA), which is defined as thyroid receptor binding region. The binding receptor complex on the DNA take place through the mediation of Zinc element which is existed on the receptor molecule and receptor binding with DNA specific region can be in either monomer or dimer formation (Umesono *et al.*, 1991; Ribeiro *et al.*, 1998a; Apriletti *et al.*, 1998; Klierer *et al.*, 1992; Mansourian, 2012a, b, c). The vital responsibility of T4, T3 receptor is to trigger the transcription process occur on the DNA which ultimately lead to the DNA expression of particular gene (Glass, 1994). There is an particular segment on the DNA consist of 6 organic base of 1 adenine, 2 guanine, 1 thymine, 1 cytosine, 1 thymine with high affinity for the thyroid hormone receptor.

Transcription of this segment end up with the translation of specific protein, which is the end product of T4, T3 mission (Glass, 1994, Mangelsdorf *et al.*, 1995; Umesono *et al.*, 1991). Truly speaking it should be mentioned that the T4, T3 receptor is bounded to its specific segment on the DNA and in the absence of thyroid hormones it prevent the production of above mentioned proteins which is triggered by the T4, T3. The other fact which is true in the physiological term is the T3 hormone considered as a potent thyroid hormone in organs including liver, in other word T3 which is produced in thyroid and can be synthesized in other organ of body through diiodination of T4 is the main hormone stimulating the target tissues. To return to the above discussion T3 receptor binds with high affinity to the specific gene segment and by doing that the gene expression is prevented, utilizing the co-repressor molecule. Thyroid main function start with diminishing the activity of co-repressor molecule, following alteration in the three-dimensional structure of thyroid hormone receptor and letting the co-repressor substituent of thyroid hormone receptor cleared off the receptor. Following the departure of co-repressor, DNA

transcription begin with ultimate protein translation of particular gene (Nagy *et al.*, 1997; Ribeiro *et al.*, 1998b).

T3 receptor consist various isomers, with different concentration in various organs within the body, these variation is helpful tool in different tissues for the proper response which is expected for the physiological function of thyroid hormone in the different tissues according to the tissues requirements. Therefore the thyroid hormone response and its attenuation in different tissues mainly regulated by the nature of thyroid hormone receptor, with particular affinity of specific isomer to have on special segment of DNA to initiate the gene expression for biosynthesis of particular protein (Baxter *et al.*, 2001). T4 concentration within blood circulation is much higher than T3 but as it was mentioned it is the T3 which binds to thyroid hormone receptor strongly compared to T4 affinity to the receptor. It is believed that T3 exhibited, 5-10 times affinity and biological activity for the thyroid hormone receptors than T4 do. Although T4 concentration seems to be much higher than T3 concentration, T3 affinity and efficacy shown to overlap the high concentration of T4 and truly speaking it is the T3 which account for much of thyroid hormone biological activities. It is a matter of interest that the human body differentiate this differences and peripheral tissues produce T3 from T4 through the deiodination of T4. In other word T4 can be considered as large source for T3 within the target tissues. On occasion of non-requirement of T3, it can be converted to reverse T3 (rT3), which is a biologically non-active thyroid hormone and seems there is a fine regulation for the activity of thyroid hormone at target organ. T3 is biosynthesized from T4 when extra efficiency of thyroid hormone is required and rT3 produced whenever the target tissues do not require the activity of T3 any further (Larsen, 1975; Hassi *et al.*, 2001; Mansourian, 2010a, 2011a).

As it was mentioned T3 production from T4 is occurred due the specific requirement of target organs and it seems liver is a major peripheral organ for the high requirement of thyroid hormones, due to multiple metabolic functions which happen in the liver. Therefore it was found that liver is one of main site of deiodinase enzyme activity for T3 production from T4 (Sanders *et al.*, 1997). Liver also play an important role in the production of potent hormone T3 but other biological pathways for T4, T3 metabolism and their transportation in the liver and blood circulation is the sole responsibility of liver function (Mansourian, 2011c).

A protein called Thyroxine Binding Globuline (TBG) which is synthesised within liver is the main transporter protein which carry thyroid hormones. TBG is accounted for more than 95% of thyroid hormones in circulation, also

thyroxine binding prealbumin and albumin also are among the liver proteins responsible for thyroid hormone transportation. Only a trace amount of thyroid hormone existed as free hormones is applying thyroid hormone physiological function in the target tissues.

It seems the conjugated act as banking system for the thyroid hormones and the level of free thyroid hormone which is the active form can be regulated through this system.

On the base of such mechanism, the active form of thyroid hormone remain at the level which is required with constant concentration (Mendel *et al.*, 1988; Hennemann *et al.*, 2001; Mansourian 2011b, c, Shahmohammdi *et al.*, 2008). Particular requirement of T4, T3 for specific tissues is one other interesting aspect in this regard, although the free hormone concentration within blood circulation remain the same but how the different concentration of various tissues are met, which seems to be an vital question in this area of thyroid hormones metabolism (Croft and Herxheimer, 2002). The concept behind this query lay on the amount of hormone which required and transported into a particular tissues and also strongly relay on the activity enzyme responsible for the conversion of T4 into T3 plus that type deiodinase which convert the active form of T3 into rT3 and other inactive isomers of T3 (Croft and Herxheimer, 2002). Even in persons with healthy thyroid which produce sufficient amount of thyroid hormone, there are also various other elements which manipulate the normal passage of thyroid hormone metabolism. It seems the thyroid hormone transportation in circulation and also thyroid hormone transportation within the target tissue, the proper passage for the adhesion of thyroid hormone to the receptor, the proper structure of thyroid hormone receptors, its proper location within nucleus and the exact segment of DNA, are among other crucial elements in well being of thyroid hormone metabolism as whole. It seems in addition to a healthy thyroid, liver can also play an important role in the basic metabolic rate, growth and development of the human body.

Liver do this due to its ability to transfer the thyroid hormone within circulation and intracellular in target tissue due to thyroid hormone transporting system which is mediated by TBG, pre-albumin and albumin, all are synthesized within liver.

It looks thyroid gland and liver metabolism are interrelated so closely and any harm to this interaction eventually lead to catastrophic scenario affecting the normal biochemical-physiological status of entire metabolism leaving the affected person in badly pathological state. Thyroid hormone are so vital in metabolism and thyroid hormones play a role in every

aspect of metabolism in health and diseases. Also T4, T3 are involved in entire metabolism but it should be mentioned that other organ diseases affecting the normal physiological function of thyroid gland to adopt itself to the new pathological state and produce T4 and T3 accordingly. In addition to the alteration in thyroid gland intracellular metabolism, other non-thyroidal manipulation such as reduced activity of the deiodinase which lead to the suppression of T3 production from T4 can interfere and T4 can be conserved and the loss of thyroid hormone can be prevented in the chronic diseases. One of the main function of thyroid hormones are the regulation of basic metabolic rate and energy expenditure within human body which is controlled through a tiny and sophisticated pathways. It seems logic to conserve energy at time the patient combating a disease and for doing that, thyroid gland and thyroid hormone must adopt themselves to the new economical condition to prevent the loss of energy.

The above alternative pathways are done by controlling the T3 production from T4 and converting the available T3 into rT3, a non-active form of 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.

It seems various type of liver diseases may clinically and Para-medically are presented with different pattern at least by laboratory measurement of liver function tests (Camacho and Dwarkanathan, 1999).

THYROID AND LIVER IN DISEASES

Thyroid and liver is deeply interrelated that some pathological agents even can interfere with both of these vital organs. The immune system which can adversely affect both organs are among such abnormalities, other diseases of benign and carginic are also reported, which affect both organs (Inoue *et al.*, 1999; Wirtzfeld *et al.*, 2001; Thieblemont *et al.*, 2002; Mansourian *et al.*, 2011). Other studies concentrated on the role of inflammatory diseases which can cause problems for the thyroid and liver and study show how inflammatory treatment can be a useful procedure in this regards. The iron storage within the body either of primary as in genetic diseases or through excessive iron therapy, are behind many hormonal dysfunction including thyroid leaving the affected person into hypothyroidism due to unrelated iron storage within the thyroid gland.

This thyroid dysfunction accompanied with simultaneous liver disorder due to excessive overload of iron storage inside the liver tissues itself.

All these scenarios are happened at the time in which the body itself engaged with a type anemia and hypoxia as result of hypothyroidism due to iron deposition within thyroid leaving thyroid with all the consequences of hypothyroidism not only for the liver but also for entire body as whole (Gillmore *et al.*, 2001; Phillips *et al.*, 1992; Shirota *et al.*, 1992; Magro *et al.*, 1990).

Some other diseases in human can adversely affect both organs thyroid and liver simultaneously, malignancy can be considered among such illness, which may affect thyroid and liver, with are clinically manifested by thyroid enlargements and abnormal liver function tests.

In medical practice there are some therapeutic regiments which adversely affect both thyroid and liver in human and their side effects may remain even after the therapy is terminated (Sanoski *et al.*, 1998; Croft and Herxheimer, 2002; Isojarvi *et al.*, 2001; Van Santen *et al.*, 2002; Malik *et al.*, 2000; Oren *et al.*, 1996, 1999).

SERUM CONCENTRATION OF T4, T3 MODIFICATION IN LIVER DISEASES

Thyroid assessment in liver diseases should be accompanied with laboratory assessments of thyroid function test. The laboratory procedure lay on the measurement of T4 and T3 in the form of total and free hormones, TBG, Thyroid Stimulating Hormone (TSH), at the front-line of laboratory investigation.

In fact laboratory measurements of thyroid hormones and autoantibodies to thyroid enzyme and thyroglobulines are recommended not only for liver diseases but also in various human abnormalities.

The importance of references intervals for thyroid hormones should be kept in mind for a, laboratory investigation to confirm the presence of chronic liver disorders. Also thyroid hormone level stay almost at reference range but at expense of higher T4 and lower T3, mainly due to reduced activity of deiodinase enzyme within liver. As liver abnormality worsen the T3 production from T4 is also reduced. It is believed this reduction of T3 which mainly correspond to even lower basic metabolic rate, economically can be useful due to preventing extra energy waste and keep it for the onset of liver disease or any other related syndrome which consume further energy. Paramedical examination of cirrhosis by sonography show an enlarged thyroid gland. Laboratory examination indicated that the T3, the most potent hormone concentration is reduced and the same time the concentration of rT3 concentration is increased, which is mainly due to lower activity of deiodinase enzyme, which mediate the production of T3 from T4. As

it was mentioned the elevated rT3 concentration is also can be due to reduced transformation of active form of T3 into inactive form of T3, which is defined as (rT3) in on hand and in the other hand as the production of T3 from T4 is reduced, the biosynthesis of rT3 from T4 is due to the higher activity of other isomer of deiodinase enzyme namely deiodinase enzyme-II, contrary to the reduced activity of deiodinase enzyme-I, which is responsible for the biosynthesis of T3 from T4. Using the laboratory index for the serum thyroid of different hormone concentration, one can produce some mathematical equation in the laboratory and based on those value it can be predicted what biochemical alterations was happened on thyroid hormone metabolism following liver disorders such as cirrhosis. As liver function deteriorates the T3 production is reduced and rT3 concentration is elevated, therefore, there is higher rT3 to T3 ratio is demonstrated when the serum concentration of various thyroid hormone are measured in the medical laboratory. There are many studies in this area of research indicating that this useful alteration in the amount of T3, has a positive physiological role in harmonizing the human liver metabolism lowering energy expenditure in liver diseases (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).

Thyroid hormones are transported within blood circulation by a protein called thyroxine binding globuline which is synthesized within liver which is abbreviated as TBG. It seems the biosynthesizing of TBG is increased during the acute liver diseases. TBG production is simultaneously elevated as result of the acute onset of disease along side of proteins which are produced due to liver acute illness. Therefore following enhanced concentration of TBG the level of total T4 is increased, which is the manifestation of early acute liver abnormality. On condition of more TBG reduction as result of progressed liver disease the T4 level is also reduced.

In other word it can be stated that in the initial state of acute liver diseases the total T4 production increases and subsequently as liver function is worsen it will reduced due the higher and lower concentration of TBG respectively. From laboratory point of view it can be shown that as acute liver disease progressed, the T3 concentration fall, may be as result of lower activity of deiodinase-I and again there is a mathematical equation for T3 to T4 ratio, which can be applied further to look for an index to evaluate the liver progress of disease. It should be mentioned in the entire discussion of this review that also there are fluctuation in the amount of thyroid hormones but the thyroid remain in euthyroid state.

The modification in the amount of thyroid hormone leading into reduced T3 and increased rT3, are in advantage of patient with liver diseases, to conserve and adapt the metabolic rate at lower level, when energy requirement for fighting the disease as its highest threshold. As whole it should be remembered that although following liver disease the thyroid getting into trouble and some fluctuation in the serum concentration of T4, T3, may occur but the clinical manifestation of thyroid abnormality are not presented and thyroid remain at euthyroid states (Oren *et al.*, 1998; Van den Berghe *et al.*, 1998).

THYROID HORMONES ALTERATION IN LIVER AUTOIMMUNITY

In addition to hepatitis, cirrhosis, there are other forms of autoimmune related liver diseases or cirrhosis associated biliary liver disorders which all are associated with chronic hepatitis, thyroid gland is affected adversely and it is prone to be afflicted with autoimmune disorders (Krawitt, 1996; Crowe *et al.*, 1980; Mansourian, 2010a). This latter thyroid abnormality arises from the fact that the autoimmunity may be as result of thyroid disorder itself or can be a direct adverse effect of liver dysfunction which can be original source for the thyroid autoimmunity. There are also other studies indicated that autoimmune hypothyroid related disorder can also be associated with cirrhosis associated biliary liver disorders. In such hypothyroid patients total T4 is elevated mainly due to higher concentration of TBG, since total T4 is elevated but in such affected patients free T4 is reduced. So it is vital to measure the free T4, Thyroid Stimulating Hormone (TSH) and any other laboratory test which may be in any help to avoid misdiagnosis of a hypothyroid patients suffering from liver diseases. In addition to TSH, free and total T4 and T3, the determination of autoantibodies to the thyroid including antithyroid peroxidase, antithyroglobuline autoantibodies are also recommended for the proper determination of thyroid liver statuses, to avoid misdiagnosis in a such crucial and vital human metabolism. The rises of autoimmunity against thyroid is common in some form of liver abnormality and particularly with cirrhosis associated biliary liver disorders. It seems the thyroid and liver metabolism are interrelated that in some cases that even the abnormality in one organ can subsequently follow the other and possibly can mimics each other, which can be consider it carefully to avoid any possible misdiagnosis. Even any autoimmunity to the liver can have influence on the thyroid gland and there are studies indicating liver autoimmunity eventually can have its adverse effect on

the thyroid through arising some autoantibodies to the thyroid glands and other related inflammation to the thyroid gland (Crowe *et al.*, 1980; Krawitt, 1996; Sherlock and Scheuer, 1973; Elta *et al.*, 1983; Saarinen *et al.*, 2000; Mansourian, 2010e).

From laboratory point of view whenever there is not a corresponding association between liver and thyroid abnormality, laboratory index such as total T4, T3, TBG and TSH, free T4, are elevated but are remain at reference range of normal and the thyroid clinical manifestation is of euthyroid statuses (Borzio *et al.*, 1983).

Thyroid dysfunction may occur as result of some liver therapeutic treatment with possible side effects of autoimmunity to the thyroid gland, but if it is a true scenario all the thyroid related factors even autoimmunity to the TSH receptor in thyroid may be targeted (Benelhadj *et al.*, 1997; Shimizu *et al.*, 1994; Fonseca *et al.*, 1991; Mansourian, 2011b). The possible role played by iodine concentration within the thyroid gland and the possible adverse effect of iodine concentration within the thyroid can also have been taken into considerations (Mansourian, 2011d; Mansourian *et al.*, 2007). In other study anti-peroxidase auto-antibody which may have been biologically active even before the liver treatment started can be initially a predisposing factor in the occurrence of thyroid malfunction. To avoid any mistreatment it is suggested that thyroid hormones laboratory measurement should be done before any liver treatment initiated.

The laboratory measurement of thyroid hormones and others related parameters including thyroids auto-antibodies are checked and measured while liver hepatitis is under treatments.

In general as it was mentioned in the course of this present review it seems predominantly thyroid statuses remain at euthyroid during liver diseases, this is confirmed by the laboratory measurement of TSH, T4, T3, the three main hormones in evaluating thyroid function.

Thyroid hormones serum concentration are at high and low range of normal, indicating the euthyroid condition but extra care should be taken in such sensitive occasion by recommending other laboratory tests including thyroid autoantibodies and TBG when thyroid function is evaluated simultaneously with liver diseases (Roti *et al.*, 1996; Koh *et al.*, 1997; Bell *et al.*, 1999; Lisker-Melman *et al.*, 1992; Deutsch *et al.*, 1997; Melman, 1994; Mansourian, 2011d; Mansourian *et al.*, 2010a, b; Mansourian and Ahmadi, 2010).

Key points:

- Thyroid and liver are interrelated physiologically in health and diseases and these clinical manifestations

are clinically confirmed through serials determinations of thyroid and liver function tests in the laboratory. Although thyroid gland remain at euthyroid statuses but at expenses of lower free T3 and higher free T4

- This unique clinical manifestation of thyroid to remained at euthyroid may be due to lower and higher range of T3 and T4 among liver disease patients. There are various reports on the remarkable role of serum T3 concentration in predicting the status of liver abnormality in progressed phase of liver disease
- One remarkable manifestation of thyroid hormone during liver abnormalities relay on the direct relation of bilirubine concentration and the level of thyroid disorders, also thyroid remain at euthyroid at most of the times
- Free T3 concentration corresponding with the state of liver disease and it seems the serum T3 concentration directly related to liver abnormalities progress. Other studies indicated that during various phase of liver disease the serum T4 concentration altered accordingly and related also to the disease progression
- T3 can be used as good laboratory index in evaluating the statues of liver disease, also the serum T3 concentration and those liver factors, such as bilirubine are now can be regarded as valuable index in following the trends in thyroid-liver pathophysiology
- It is vital to measure the free T4, Thyroid Stimulating Hormone (TSH) and any other laboratory test which may be in any help to avoid misdiagnosis of a hypothyroid patients suffering from liver diseases. It can be stated that in the initial state of acute liver diseases the total T4 production increases and subsequently as liver function is worsen it will reduced due the higher and lower concentration of TBG, respectively
- In addition to TSH, free and total T4 and T3, the determination of autoantibodies to the thyroid including antithyroid peroxidase, antithyroglobuline autoantibodies are also recommended for the proper determination of thyroid liver statues, to avoid misdiagnosis in a such crucial and vital human metabolism
- The rises of autoimmunity against thyroid is common in some form of liver abnormality and particularly with cirrhosis associated biliary liver disorders. It seems the thyroid and liver metabolism are interrelated to the level which in some cases that even the abnormality in one organ can subsequently follow the other and possibly can mimics each other, which should be considered it carefully to avoid any possible misdiagnosis
- Thyroid abnormality arises from the fact that the autoimmunity may be as result of thyroid disorder itself or can be a direct adverse effect of liver dysfunction which can be the original source for the thyroid autoimmunity. There are also other studies indicated that autoimmune hypothyroid related disorder can also be associated with cirrhosis associated biliary liver disorders
- Even any autoimmunity to the liver can have influence on the thyroid gland and there are studies indicating liver autoimmunity eventually can have its adverse effect on the thyroid through arising some autoantibodies to the thyroid glands and other related inflammation to the thyroid gland
- The modification in the amount of thyroid hormone leading into reduced T3 and increased rT3, are all can be argued to be in advantage of patient with liver diseases, to conserve and adapt the metabolic rate at lower level, to prevent the adverse outcome of human metabolism as whole when energy requirement for fighting the disease as its highest threshold
- Liver abnormalities at any stage can have its influence on thyroid function tests and it will have its adverse effect on the thyroid. It seems various type of liver diseases may clinically and para-medically are presented with different pattern laboratory measurement of liver function tests
- It was found that liver is one of main site of deiodinase enzyme activity for T3 production from T4. Liver also play an important role in the production of potent hormone T3 but other biological pathways for T4, T3 metabolism and their transportation in the liver and blood circulation is the sole responsibility of liver function
- It seems in addition to a healthy thyroid, liver can play an important role in the basic metabolic rate, growth and development of the human body in general due to its ability to transfer the thyroid hormone within circulation and in target tissue intracellular due to thyroid hormone transporting system which is mediated through Thyroxine Binding Globulin (TBG), pre-albumin and albumin, all are synthesized within liver
- For avoiding any mistreatment it is suggested that thyroid laboratory examination and measurement for the thyroid gland should be done before any liver treatment and this laboratory measurement of thyroid hormones and others related thyroid parameters including thyroids auto-antibodies are to be checked and measured while liver hepatitis is under treatments

- In general as it was stated in the course of this present review it seems predominantly thyroid statuses remain at euthyroid during liver diseases, which is confirmed by the laboratory measurement of TSH, T4, T3, the three main hormones in evaluating thyroid function. Their serum concentration are at high and low range of normal, indicating the euthyroid condition but extra care should be taken in such sensitive occasion by recommending other laboratory tests including thyroid autoantibodies and TBG when thyroid function is evaluated simultaneously with liver diseases

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