Abnormal Serum Thyroid Hormones Concentration with Healthy Functional Gland: A Review on the Metabolic Role of Thyroid Hormones Transporter Proteins

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Abstract: Laboratory findings can definitely help the patients not to enter into status, where the damage might be happen due to a miss-diagnosis based on clinical assessment alone. The secondary disease accompanied with thyroid patients should also carefully check out due to the interference which some diseases can cause in the amount of serum thyroid hormone, particularly the free thyroxin. The dilemma over thyroid clinical diagnosis occur due to variation on serum thyroid hormone which initiated by other non-thyroidal disorders which can play an important roles in metabolic disorders of thyroid hormone due to the alteration which occur on the serum level of thyroid hormone transporter proteins. The majority of serum thyroid hormones of up to 95-99% are bound to the carrier proteins mainly to Thyroxin-Binding Globulins (TBG), some transthyretin already known as pre-albumin and albumin which are all synthesis in the liver and any modification which alter their production may alter the status of thyroid hormones. It seems TBG, transthyretin and albumin carries 75, 20, 5% of thyroid hormones within blood circulation, respectively. The dilemma facing the thyroid hormones following disruption of thyroid hormone transporter protein synthesis originate from this fact that any alteration of these protein contribute to the alteration of total thyroid and free serum thyroid hormones which are in fact the biologically active form of thyroid hormones. The subsequent of latter implication result in miss-understanding and miss-diagnosis of thyroid function tests, with possible wrongly thyroid clinical care, followed by undesired therapy of otherwise healthy thyroid.

Key words: Thyroxine binding globulin, transthyretin, albumin, non-thyroidal disease

INTRODUCTION

Patients with thyroid disorder either can be assessed either directory by the clinicians and are diagnosed only on the bases of clinical findings alone or they can be referred to the medical diagnostic laboratory and subsequently the patients can be evaluated on a joint approaches of clinical and laboratory tests results. In medical practice clinician usually decide if the patient therapy should be accompanied with laboratory findings.

The ideal bases for a proper treatment should only be established when the clinician assessment of thyroid patient accompanied with simultaneous laboratory findings for a comprehensive management and to have a clear understanding part of metabolic pathways of thyroid hormones which should be clearly treated (Wardle et al., 2001; Mansourian, 2010a; Mansourian, 2011). There are various studies in this region of clinical practice arguing that the patient initial route of medical treatment should be re-directed, flowing the thyroid laboratory assessments (Parle et al., 2001). There are other investigations indicated even on some cases, the entire medical treatment should be revaluated, due to misdiagnosis by

the initial therapeutic regiment based only on the clinician assessment alone (Klein and Ojamaa, 2001; Kahaly, 2000). The thyroid patient clinical manifestations which usually is expected to be observed among hypothyroid subjects occasionally are missed out on initial clinician assessments but the latter patients, are defined hypothyroid, when evaluated by laboratory findings, in other word a hypothyroid patient may be missed out it the therapy is not accompanied by the laboratory tests results (Fatourechi, 2001; Jones et al., 2010; Ferrari et al., 1987; Martin et al., 1993; Mansourian, 2010c).

The overt thyroid disorder clinical manifestations are not usually present, when the patients visit the clinician and if a medical decision was set up only by the observation of clinical manifestation of thyroid disorders, it is uncertain, whether it was an accurate diagnosis and in such conditions patients with thyroid abnormality of either of hypothyroid or hyperthyroid are left unattended if either of latter thyroid disorders are miss-out and miss-diagnosed the patients are left with sever consequences with eventual fatal outcome (Klein and Ojamaa, 2001; Kahaly, 2000; Mansourian, 2010c-e; Monzani et al., 1993). There are also some reports

indicating that even the manifestation of clinical symptoms of thyroid disease varies according to the onset of disease itself, patient age and body mass index, cardiovascular and respiratory disorders (Fatourechi, 2001; Jones *et al.*, 2010; Mansourian, 2010c, f; Saber *et al.*, 2009; Eftekhari *et al.*, 2007). On the base above statements, the elderly thyroid function and clinical manifestation should be reassessed and looked at separately from younger and middle age patients (Hansen *et al.*, 2003; Mansourian and Ahmadi, 2010; Mansourian *et al.*, 2010a, b; Marjani *et al.*, 2008). One should remember by emphasizing on the laboratory findings, do not mean to down-grade the vital role and clinician decision which is for well-being of a thyroid patient. By any standard the clinical decision making for any thyroid abnormality remain the sole responsibility of the clinician involved. The clinician can decide what should be done for the patient and it is in the patient interest to follow the clinician direction of therapy for a specific thyroid disorder. The other point which should be mentioned perhaps financially it is not logic to perform a laboratory test which can not be in any use by the clinician but the aim of this review is to emphasize the role played by the laboratory findings in a proper assessment of thyroid diseases and demonstrate that there are cases which are miss-diagnosed when the laboratory test findings either are not accompanied or, even ignored by the clinicians (Fatourechi, 2001; Jones *et al.*, 2010; Sawin *et al.*, 1994; Biondi *et al.*, 1993; Kelin and Ojamaa, 2001; Kahaly, 2000; Hansen *et al.*, 2003; Poyrazoglu *et al.*, 2008; Mansourian, 2010a; Mansourian and Ahmadi, 2010; Mansourian *et al.*, 2010a, b; Zarei *et al.*, 2009; Vern *et al.*, 2003). There are cases that can not be diagnosed solely on clinical manifestation but the thyroid disorder can only be diagnosed by the outcome of laboratory result (Mansourian, 2010c-f). The definition of sub-clinical means that the patient clinical symptoms does not demonstrate any clinical symptoms proving any disorder but the laboratory findings based on serum measurement of Thyroid of Stimulating Hormone (TSH) and Thyroxin (T4) and Triidothyronin (T3) demonstrate otherwise. In sub clinical hypothyroidism or sub clinical hyperthyroidism, the serum TSH level elevated suppressed, respectively (Weeke and Gunderson, 1978; Fatourechi, 2001; Jones *et al.*, 2010; Wesche *et al.*, 2000; Tunbridge and Vanderpump, 2000; Mansourian, 2010c-e).

In practice the sub clinically thyroid disorders, related to the type of moderate thyroid dysfunction without clinical symptoms and if these type of thyroid disorder remain un-attended eventually enter into the overt thyroid disorder. It is logic to prevent disease than cure it, therefore if the clinician accompany the therapeutic regiment with laboratory finding; it is possible to prevent overt thyroid disorders prior to the actual thyroid disease itself (MacDonald *et al.*, 1984; Biondi *et al.*, 1996; Wesche *et al.*, 2000; Bauer *et al.*, 2001; Mansourian, 2010c; Mansourian *et al.*, 2008, 2007).

Why laboratory findings in thyroid patient should be taken seriously?: As it was mentioned earlier, it is logic to treat a thyroid disorder prior to the overt abnormality occur to prevent the disastrous side effects for the he patients involved and also due to the cost and expenses accompanied with such disorders and if it is left un-treated, therefore otherwise the laboratory can give an assistant hand in the whole scenario. Initial thyroid function tests are predominantly are Thyroid Stimulating Hormone (TSH) and tetraiidothyronine or best known as Thyroxine (T4), tests are straight forward test these tests are the two important thyroid tests which usually are carried out in the clinical laboratories to assist clinician in draw the proper diagnosis to prevent a very adverse effects (Mariotti *et al.*, 1993; Stockigt, 1996; Hein and Jackson, 1990; Andersen *et al.*, 2002; Mansourian and Ahmadi, 2010; Mansourian *et al.*, 2010a, b) which can give an initial clear picture of thyroid function. The other concept behind the application of laboratory results is the various sorts of clinical manifestation which many be accompanied with either of hypo and hyperthyroidism and on such bases the clinicians can not make a comprehensive and clear-cut diagnosis. On such conditions laboratory measurement of TSH and T4 are the least laboratory indices which give a proper understanding of patient thyroid status. The cornerstone behind a proper understanding of thyroid function originates from the facts that there are various metabolic abnormities which are developed from thyroid dysfunctions. Thyroid hormones play an important role in many physiological conditions such a pregnancy infertility, neonatal and antenatal periods. Thyroid disorder in fact may be able to disrupt biochemical and physiological parameters. It is why the thyroid malfunction should be diagnosed before it is too late (Albaar and Adam, 2009; Costeira *et al.*, 2010; Bourcigaux *et al.*, 2010; Mariotti *et al.*, 1993; Mansourian *et al.*, 2010a, b; Mansourian and Ahmadi, 2010; Albaar and Adam, 2009; Lacka and Lakoma, 2002; Sapin and Schlienger, 2003; Lacka and Lakoma, 2002; Trainer and Howard, 1983; Stockigt and Lim, 2009; White and Barraclough, 1988; Saber *et al.*, 2009).

Laboratory findings can definitely help the patients not to enter into status, where the damage is done due to a miss-diagnosis which was based on clinical assessment

alone. Not only hypothyroidism and hyperthyroidism all are accompanied with sever side effects but the sub-clinical hypothyroidism and hyperthyroidism, occasionally having similar adverse effects as an overt thyroid disorders such as cardiovascular dyslipidemia associated with subclinical thyroid disorder all well-established (Ross, 1994; Guo *et al.*, 1997; Mansourian, 2010c-e). Arterial fibrillation, cardiac disorder osteoporosis type of bone disorder and eventual risk of hyperthyroidism are possible side effect of sub-clinical hyperthyroidism (Monzani *et al.*, 1993; Wardle *et al.*, 2001; Surks and Sievert, 1995; Borst *et al.*, 1983; Hamblin *et al.*, 1986; Mansourian, 2010c, d). The other hand atherosclearosis, cardiovascular diseases, hyperlipidemia, depression and if remain ineated, the overt hypothyroidism with all of its clinical manifestation accompanied with sub-clinical hypothyroidism (Marjani *et al.*, 2008; Mansourian *et al.*, 2008; Mansourian, 2010c-e).

If remain ineated, the overt hypothyroididsm with all of its clinical manifestation accompanied with sub-clinical hypothyroidism (Man *et al.*, 1969; Stockigt, 2001; Lewis *et al.*, 1991; Stockigt, 1996; Hein and Jackson, 1990; White and Barraclough, 1998; MacDonald *et al.*, 1984; Ransohoff and Feinstein, 1978; Weetman, 1997; Nordyke *et al.*, 1998; Snyder and Utiger, 1972; Vagenakis *et al.*, 1974; Meier *et al.*, 1993; Meikle *et al.*, 1988; Andersen *et al.*, 2002; Weeke and Gudersen, 1978; Pietrangelo *et al.*, 1992; Mansourian, 2010c; Mansourian *et al.*, 2008).

Thyroid Stimulating Hormone (TSH) is the front runner in laboratory tests for thyroid function assessments: Thyroid stimulating hormone is a pituitary hormone which stimulate thyroid gland to produce T4 and T3 (Meier *et al.*, 1993; Marshall *et al.*, 1974; Mansourian, 2010a).

T4 predominantly is the main hormone produced by the thyroid also T3 is produced by the thyroid simultaneously but the main portion of serum T3 is produced in peripheral tissue by deidonation of T4, the released iodine in prepherial tissues can be re-vitalized and integrated in the structure of thyrosyle residues of thyroglobuline within thyroid gland in complex process to produce T4 and T3. It should be mentioned that significant iodine deficiency may eventually lead to hypothyroidism with sever side-effects from fetus to elderly life (Mansourian, 2010a, d; Mansourian *et al.*, 2007, 2010a, b; Christensen and Davis, 2004). It is generally accepted that TSH is the most single laboratory test which can explain the status of thyroid gland (Nordyke *et al.*, 1998; Weetman, 1997; Mansourian *et al.*,

2010a, b; Mansourian and Ahmadi, 2010; Mansourian *et al.*, 2007; Christensen and Davis, 2004) it is also usually a routine practice to determine T4 simultaneously with TSH to have a proper function of thyroid gland (Surks and DeFesi, 1996; Mansourian and Ahmadi, 2010; Mansourian *et al.*, 2010a, b). On the bases above statements TSH alone, can not be definitely secure a proper diagnosis based on laboratory findings. Therefore it is suggested the serum evaluation of TSH and T4 should be the least two hormones in assessing the gland and can be to some extend reliable approach to set up laboratory investigation into thyroid function to prevent any miss-jujment raised otherwise (Ransohoff and Feinstein, 1978; Meikle *et al.*, 1988; White and Barrclough, 1988).

Dilemma of thyroid assessments based solely on TSH and thyroid hormones measurements: There are also disagreements in this area of research and some believe that TSH and thyroid hormones measurement alone can not be trusted totally in some circumstances, due to other hormonal interference. Some hormones such as cortisol and some sex hormones and metabolic states such as renal disorders which have an a negative adverse effect on TSH production with subsequent alteration of thyroid hormones (Ritter *et al.*, 1993; Tahboub and Arafah, 2009; Qi *et al.*, 2011; Gilles *et al.*, 2008; Albaar and Adam, 2009).

Other parameter such a nutritional, physiological status and also some diseases, my have direct effect on having an abnormal serum TSH level (Beck-Peccoz *et al.*, 1984; Despres and Grant, 1998; Gilles *et al.*, 2008; Bartalena and Robbins, 1992; Sorger *et al.*, 1992).

The secondary disease accompanied with thyroid patients should also carefully checked out due to the interference which some diseases can cause in the amount of serum TSH and T4 (Bartalena and Robbins, 1993). There are also disagreement on the comprehensive application and using sole TSH and T4 measurements and initiating a clinical diagnosis based on solely the serum thyroid hormone level within blood circulation alone (Bartalena and Robbins, 1992; Ferrari *et al.*, 1987). The dilemma occur due to variation which initiated by other non-thyroidal diseases and possible interference by other metabolic disorders which is why other parameters of non-thyroid origin can play an important roles in metabolic disorders of thyroid hormones (Langsteger, 1996). It should be mentioned that thyroid transport proteins which are responsible for thyroid hormone transport within blood circulation are synthesized within the liver and can be manipulated by some diseases and abnormal hormones serum level and possible intervention particularly of estrogens and

androgen which can play an significant role on the production of abnormal thyroid transport protein with adverse effects on the level of thyroid hormones and particularly of freeT4 and free T3 which in fact are the true biologically active form of thyroid hormones responsible for metabolic process within human body (Langsteger, 1996; Bartalena and Robbins, 1993; Rosner, 1991; Yamauchi and Ishihara, 2009; Tahboub and Arafah, 2009; Lin *et al.*, 2010). In apparently healthy subjects it is a matter of importance that whenever total thyroxin is reduced, TBG measurement should be the clinical strategy to find out whether this carrier protein production is metabolically disordered (Langsteger , 1996; Bartalena and Robbins, 1992; Bartalena and Robbins, 1993; Rosner, 1991). Although the TBG deficiency itself can not make any clinical disruption but it is based a foundation for miss dignosis of thyroid function due to the demonstration of low total thyroid hormones particularly total thyroxine. The consequence such scenario will be hormonal therapy which mistakenly advised with possible sever adverse effects (Stockigt and Lim, 2009; Beck-Peccoz and Persani, 1994; Beck-Peccoz *et al.*, 1996; Davey, 1997; Caldwell *et al.*, 1985; Bartalena *et al.*, 1996; Byfield *et al.*, 1983; Sorger *et al.*, 1992; Ferrari *et al.*, 1987).

How thyroid hormone imply its effect (Free thyroid Hormones): Thyroxine (T4) and Triidothyronine (T3) stimulation of target tissues mainly depends on the amount of thyroid hormones that arrive at the cells, in addition to the thyroid hormone receptors which are located in the cytoplasm and most probably within the cell nucleus (Mansourian, 2010a; Sapin and Schlienger, 2003).

It is therefore obvious, that the first step in thyroid hormones effect is the thyroid hormones (T4, T3) combination with the hormone receptor inside the cell either of cytoplasm or nuclei locations. It is well known that it is the Free Thyroxin (fT4) and Free T3 (fT3) which can penetrate the cytoplasm and nucleus membrane and combined with the hormone receptors. The combination of hormone-receptor complex bind to the specific promoter site on the deoxyribonucleic acid and trigger the unique gene with ultimate protein production related to the effect of hormone-receptor sole combination. It should be mentioned that on binding of thyroid hormones to the related receptors conformational change of receptor is followed which is the initial steps to the hormone action on the target tissues. In healthy subjects the serum level of fT4 and fT3 is strictly controlled through a tiny regulated system available between the thyroid gland and hypothalamus-pituitary axis which keep the free hormones at constant level within the blood circulations

(Bartalena *et al.*, 1996; Byfield *et al.*, 1983; Sorger *et al.*, 1992). On conditions when this latter mechanism collapses the thyroid disorder of either of hypothyroidism or hyperthyroidism clinically manifested. In other hand the failed mechanism, lead to the either of suppressed or elevated free hormone with various metabolic disorders accompanied with adverse clinical manifestation on either of hypo or hyper activities of target tissues of thyroid hormones (Ferrari *et al.*, 1987; Langsteger, 1996; Mansourian, 2010c-e).

Total thyroid hormones: As it was mentioned earlier, it is the free thyroid hormone which stimulates the target tissues. Therefore it is the free hormones that pass through the cell membrane and not total hormones which often measured in patient clinical managements due to the technical difficulties but it is normally accepted that there is an acceptable correlation between total and free hormones. It seems the free hormone measurement, should be the base for thyroid function assessments and it is due to much comfortable and more accurate determination of total hormones than the free T4 and T3 are replaced to a large extend with free hormones (Trainer and Howard, 1983; Stockigt and Lim, 2009).

Thyroid hormones binding proteins: The majority of thyroid hormones up to 95-99% of T4 and T3, are bound to the carrier proteins mainly to Thyroxin-Binding Globulins (TBG), some pre-albumin and albumin which are all synthesis in the liver and their synthesis within the liver modified by male and female hormones namely of testosterone and stradiol (Nelson *et al.*, 2008; Rosner, 1991; Yamauchi and Ishihara, 2009). It seems TBG, Pre-albumin and albumin carry 75, 20 and 5% of thyroid hormone within blood circulation respectively. The abnormality of sex, corticosteroid hormones and, drugs, chemical compounds lead to manipulation of total T4 and T3 within human serum due to direct effect of latter hormones on liver function and producing abnormal level of thyroid hormone transporter proteins which their concentration mainly control and dictate the serum level of thyroid hormones metabolic activity within blood (Tahboub and Arafah, 2009; Lin *et al.*, 2010; Stockigt and Lim, 2009; Dallaire *et al.*, 2009). It seems that proper thyroid function tests mainly can be assessed through accurate measurements of free throid hormones and particularly free T4 and thyroid disorder mainly originated in particular by the fluctuation of free thyroid hormone (Nelson *et al.*, 2008; Sapin and Schlienger, 2003; Bartalena *et al.*, 1996; Byfield *et al.*, 1983; Ferrari *et al.*, 1987; Sorger *et al.*, 1992). Thyroid hormonal change and

alteration in the thyroid hormones serum concentration due to TBG and other transporter proteins variations eventually accompanied with some metabolic disorder of either of hypo and hyperthyroidism related to the adverse physiological changes (Trainer and Howard, 1983; Rosner, 1991; Bartalena and Robbins, 1993; Gilles *et al.*, 2008; Mansourian, 2010c-e).

Thyroid hormone carrier proteins mainly are responsible for the proper economy and preserving nearly entire concentration of thyroid hormones except of ting concentration which remain as free hormones. There are not a definite understanding of as why the thyroid hormone carrier are required and there are much contradictory discussion about the role played about the thyroid transporter proteins (Bartalena and Robbins, 1992; Bartalena and Robbins, 1993; Bartalena *et al.*, 1996; Byfield *et al.*, 1983; Langsteger, 1996).

Among all these controversial argument it can be concluded that the thyroid hormones transporter proteins, mainly controlling the level of active hormones which in healthy subjects required being preserved (Rosner, 1991; Langsteger, 1996; Bartalena and Robbins, 1992; Bartalena and Robbins, 1993). By doing that hypo and hyperthyroidism prevented they can also play an important role in preserving the body iodine as donated tyrosyle residues namely T4 and T3, as storage proteins of thyroid hormone which otherwise they would have been secreted through kidney as urine components (Costeira *et al.*, 2010; Bourcigaux *et al.*, 2010; Gilles *et al.*, 2008; Mansourian *et al.*, 2007; Mansourian, 2010a).

The scenario which possibility could have end up with thyroid disorder of thyroid hormone deficiency which is defined as hypothyroidism (Gilles *et al.*, 2008; Mansourian 2010c, d; Trainer and Howards 1983). As s conclusion to these latter concept the thyroid hormone transporter protein naturally and logically are required to manage, preserve and pave a proper dialogues between the thyroid gland hormones and other targeting tissues as a whole (Chan *et al.*, 1972; Refetoff *et al.*, 1970; Mendel *et al.*, 1987; Pemberton *et al.*, 1988; Jirasakuldech *et al.*, 2000; Langsteger *et al.*, 1996; Bartalena and Robbins, 1993; Bartalena and Robbins, 1992; Byfield *et al.*, 1983). It should be also mentioned that in true scenario, the total T4 concentration is about 10 times higher than T3 but in the other hand the free T3 is about 10 times of freeT4 and in real term the hormonal activity of T4 and T3 are equal (Refetoff *et al.*, 1970; Farer *et al.*, 1962).

Thyroid hormones transporter carrier proteins: As it was mentioned above, in the absence of thyroid transporter proteins the extra thyroidal active from of T4

and T3, can cause damage beyond repair for a person to remain healthy and slight variation in the concentration of thyroid hormones carrier protein in disease state can cause major harm to person involved in addition to serious misdiagnosis on thyroid function on otherwise healthy thyroid (Bartalena and Robbins, 1993; Bartalena and Robbins, 1992; Chan *et al.*, 1972; Refetoff *et al.*, 1970; Mendel *et al.*, 1987; Pemberton *et al.*, 1988; Jirasakuldech *et al.*, 2000; Refetoff *et al.*, 1970; Farer *et al.*, 1962). The main transporter proteins which carry the large portion of thyroid hormone is named Thyroxin Binding Globulin (TBG) but Thyroxine-binding Pre-albumine (TBPA) or recently known as transthyretin and serum Albumine, are also transport some portion of T4 and T3. Also there are a very minute amount of thyroid hormones which may attaches to some lipoproteins within the blood circulation but it can not be considered as seriously to have any side effect on thyroid hormones metabolism. As whole as it was mentioned TBG, transthyretin (TBPA) and Albumin carry 75, 20 and 5% of thyroid hormone within the human blood circulation (Palha, 2002; Sousa *et al.*, 2005; Sapin and Schlienger, 2003; Ferrari *et al.*, 1987; Langsteger, 1996).

Thyroxin binding globulin: Thyroxin binding globulin which is a macroprotein and in real term is a glycoprotein which binds, T4 and T3 as well and crry about 75% of thyroid hormones. As it was mentioned above the main portion of thyroid hormone of (3/4) is bound to this transporter protein, therefore any alteration of this protein, can have also major effect on the thyroid hormone fluctuation (Sapin and Schlienger, 2003; Bartalena *et al.*, 1996; Zhou *et al.*, 2006; Domingues *et al.*, 2009).

TBG is protein synthesized within the liver and it is glycosylated, post transitionally for accurate tertiary structure and exodus from the liver (Zhou *et al.*, 2006; Kambe *et al.*, 1992; Gartner *et al.*, 1981). It is shown that thyroxine can be carried out by various hydrophobic interactions which is to be produced at the surface of TBG and also some hydrogen binding which is occurred between the T4 and TBC. On condition that any substance can substitute these weak bounds between thyroid hormones and thyroid hormone transporter, eventually leads to alteration of free thyroid hormones with serious side-effects (Bartalena and Robbins, 1992; Sapin and Schlienger, 2003; Bartalena *et al.*, 1996; Sorger *et al.*, 1992; Palha, 2002; Trainer and Howard, 1983; Dallaire *et al.*, 2009; Stockigt and Lim, 2009). In real term thyroxine binding globulin can have two biochemical conformations and the two-three-dimensional conformations which allow the TBG exhibit the high and

low affinities toward to thyroid hormone. This process allow for the tiny regulated pathway for thyroid hormones (Zhou *et al.*, 2006; Grasberger *et al.*, 2002). TBG is a protein synthesized in the liver and genetically studies was shown to detect a transcription element with particular activity within the liver (Hayashi *et al.*, 1993; Domingues *et al.*, 2009). The genitical characteristic of which end to Thyroxin Binding Globulin, are much the same to Cortisol Binding Globuling (CBG) and it is why some times cortisol which is adrenal cortex hormone may show affinity to cross-react and bind to the other transporter protein and TBG as well within the blood circulation (Hayashi *et al.*, 1993; Lin *et al.*, 2010; Qi *et al.*, 2011).

Also TBG can bind to T4, T3 and even cortisol as it was mentioned above but the main legend for TBG is T4 which can bind to the TBG with equimolar ratio of 1:1 (Hocman, 1981; Cody, 1980). It is of grate interest that some compound can bind to TBG, instead of the true legend which is T4. It is postulated that some substances can manipulate on the level of free thyroid hormone with serious sides effects manifesting non-thyroidal metabolic disorders (Nelson *et al.*, 2008; Bartalena and Robbins, 1993; Bartalena and Robbins, 1992; Gilles *et al.*, 2008; Albaar and Adam, 2009; Bartalena *et al.*, 1996). In case proper concentration, of such chemical compound are present in the blood, they can competitively inhibit the TBG in binding to T4 and T3 the true legend of TBG causing the thyroid metabolic disorders with non-thyroidal origin (Oppenheimer and Tavernetti, 1962; Larsen, 1972; Bartalena *et al.*, 1996). Any conformational alterations which may happen irreversibly eventually deplete the TBG binding capacity of the thyroid hormone with sever address effects. In normal physiological conditions the reversible TBG conformation changes is considered as permission for this transporter protein to behave as donor and acceptor to T4 and T3 (Janssen *et al.*, 2003; Sapin and Schlienger, 2003). In case of irreversible conformational change which may occur on the TBG protein structure as results of various factors such as a protease enzyme the ability of TBG for binding T4 and T3 is eventually lost but the TBG present in the circulation still can be assessed using serological studies (Refetoff *et al.*, 1984). In normal healthy thyroid subjects 2/3 of thyroxine binding globuline is not occupied with thyroid hormone. This latter observation seems to have a significant biochemical function when the amount of thyroid hormones are elevated for any particular, reasons and it may end with serous side-effect otherwise because the TBG is able to collect the extra T4 and T3 and to some extend it prevent the adverse effect which may be followed otherwise (Cavalieri *et al.*, 1975; Refetoff *et al.*, 1976).

Biochemically TBG is a protein with tertiary structure and contain about four hundreds and fifteen aminoacids. In fact it is a glycoprotein, composed of sialic acids (Murata *et al.*, 1986; Kambe *et al.*, 1992). TBG biochemically is at peak of its activity for about a five days and subsequently it is metabolized in the liver. The sialic acid residue of TBG play an important role for its true half life and on condition of sialic acid depletion the TBG disintegrate with much faster speed (Cavalieri *et al.*, 1975; Refetoff *et al.*, 1976; Refetoff *et al.*, 1975).

It seems that thyroxine binding globuline, produced at early stage of pregnancy truly in first-trimester of pregnancy and its concentration fluctuated at elderly stage starting from fetus to elderly life (Andreoli and Robbins, 1962; Robbins and Nelson, 1958; Stubbe *et al.*, 1978). Also TBG main site of biological action is the human serum but the tiny amount of this protein is also can be traced in other biological fluid of human body (Burman *et al.*, 1976; Hagen and Elliott, 1973; Gavin *et al.*, 1979).

As it was mentioned earlier estrogen and particularly stradiol the main female sex hormone in either of pathological condition or in hormonal therapy and contraceptive regiments enhance the over production of TBG, in addition to other protein produced by the liver (Doe *et al.*, 1967; Sorger *et al.*, 1992). The male sex hormone androgen and in particular testosterone in contrary to stradiol suppress the production of TBG by the liver. It seem these sex hormones effect occur through the manipulation of supplementary chemical residues of TBG such as carbohydrates and sialic acids which eventually determine TBG physiological life and the active biochemical pathway of TBG either increase or decrease whether liver provoked by estrogen or androgen respectively (Doe *et al.*, 1967; Ain *et al.*, 1987; Ain and Refetoff, 1988; Federman *et al.*, 1958; Barbosa *et al.*, 1971; Braverman *et al.*, 1967; Refetoff *et al.*, 1972; Tahboub and Arafah, 2009).

In some pathological case the TBG serum level altered due to alteration of thyroxine bindings globuline biosynthesis or increase clearance from kidney (Rfetoff *et al.*, 1976; Bartalena and Robbins, 1992; Gilles *et al.*, 2008).

Some reports indicated the TBG level increased and decreased in hypothyroidism and hyperthyroidism respectively, it seems that in some metabolic disorder normal physiological process leading to the TBG disintegration modified and on the base of this modification the TBG serum level altered, causing some thyroid diseases which is not the direct result of thyroid abnormalities but it is the thyroid hormone transporter disorder which might happen due to some other non-thyroidal disease such as liver and kidney diseases (Gilles *et al.*, 2008; Qi *et al.*, 2011; Bartalena and Robbins, 1993; Bartalena and Robbins, 1992).

Other immunological abnormalities are responsible for adverse effect of thyroid hormones (Cavalieri *et al.*, 1975; Refetoff *et al.*, 1976; Bartalena *et al.*, 1996; Byfield *et al.*, 1983; Ferrari *et al.*, 1987). In some patient with progressed liver disorders shown that the produced TBG is chemically abnormally due to the reduction in the content of sialic acid which is an important constituent of TBG. In real condition such produced TBG with lower content of sialic acid exhibit a type of TBG which is not function properly and in fact the ratio of such malformed TBG to the proper from of TBG is increased. Such a condition are demonstrated in various non-thyroid disorders in addition to the liver and kidney diseases (Marshall *et al.*, 1972; Reilly and Wellby, 1983; Bartalena and Robbins, 1992). Also TBG is produced by the liver but the other signification condition facing TBG is the removal of serum TBG itself from blood circulation by the liver through the receptors complex glycol protein contained sialic acid of the liver itself (Refetoff *et al.*, 1975; Marshall *et al.*, 1974). There are also possibilities that due to some genetic abnormalities TBG can not be glycosylated and in such cases the produced TBG, can not properly function and will end eventually with adverse effect of thyroid hormones disorders which is not originated from thyroid gland or thyroid hormone metabolism. The latter condition accompanied with sever disorder of non-thyroidal illness (Macchia *et al.*, 1995; Jaeken *et al.*, 1991; Stibler *et al.*, 1991).

Thyroxine Binding Pre-Albumin (TBPA) or Transthyretin (TTR): This thyroid hormone transporter protein which is recently known also as Transthyretin (TTR). This transporter protein has a quaternary structure with four similar polypeptide chains of about 127 amino acids with no carbohydrate residue. Also TTR transport thyroxin but it can give complex with retinol binding protein and by doing that indirectly play an important role in the retinol and vitamin A metabolism which is why now this thyroid hormone transporter is defined as TTR (Ingbar, 1985; Kanai *et al.*, 1968; Peterson, 1971; Tsuzuki *et al.*, 1985).

TTR also can bind with one molecule of T4 but it can simultaneously give a complex with four molecules retinol binding protein without any interference with T4 binding to the transporter protein (Palha, 2002; Sousa *et al.*, 2005; Irace and Edelhoch, 1978; Van Jaarsveld *et al.*, 1973). Also the serum level of TTR is much higher than TBG, it only transports about 20% of thyroid hormones within the circulation and it can not substitute TBG in any physiological change with reduction of TBG. It is also subsequently demonstrated that also the TTR was removed from serum using proper technique; it can not

still alter the level of free thyroid hormone circulated within circulation (Woeber and Inbager, 1968). It is also reported that T4 is demonstrated to have higher affinity for TTR than T3 (Cody, 1980; Pages *et al.*, 1973).

There are also some reports, indicating that some chemical compound and drugs which are able competitively bind to TTR and cause the subsequent alteration in thyroid hormones which is the least outcome of such misplacements, with subsequent thyroid hormone metabolic disorder with healthy thyroid. It is also reported that thyroid hormones engage less than 1% of TTR present in blood (Lueprasitsakul *et al.*, 1990; Monzani *et al.*, 1993; Munro *et al.*, 1989) and therefore the fluctuation of TTR do not show to have any major effect on the T4 and T3 serum level (Woeber and Ingbar 1968; Braverman *et al.*, 1971). There are also many reports on the negative correlation between TBG and TTR serum level in one hand and age, gender, cortisol and estrogen on the other hand (Braverman *et al.*, 1966; Braverman *et al.*, 1967; Braverman and Ingbar, 1967; Oppenheimer *et al.*, 1966; Man *et al.*, 1969; Schreiber *et al.*, 1995; Yamauchi and Ishihara, 2009).

Albumin: It is synthesis within the liver it is a large protein of non-carbohydrate origin, with 585 amino acids (Peters, 1985). Albumin is a liver protein that binds to varieties of important substances such as hormones, fatty acids and some other hydrophobic components due to high hydrophobic region present within the albumin structure (Tabachnick and Giorgio, 1964; Hollander *et al.*, 1968).

Also there are few sites belong to the T4 and T3 within the albumin structure but it seems only one active site that can bind T4 and T3 with high affinity but as whole only 5% of all serum T4, T3 at one time can be transported by albumin in the circulation (Refetoff *et al.*, 1972; Hollander *et al.*, 1968) and in server from of liver disease leading to the albumin depletion, the latter scenario can not play any detectable role in the level of thyroid hormone within the circulation and consequently albumin deficiency within blood circulation do not show any disruption in the thyroid hormone functions in human metabolism (Pietrangelo *et al.*, 1992; Hollander *et al.*, 1968; Langsteger, 1996; Bartalena and Robbins, 1993; Bartalena and Robins, 1992).

Thyroid hormones alteration originating from thyroid hormones transporter protein: T4 and T3 following biosynthesis within thyroid gland can not reach the target tissues alone and they have to be transported by carrier proteins which are synthesis within the liver. Also it is not

decisively documented that any alteration of transporter protein can cause metabolic disorder but for sure it may cause an abnormalities on serum level of free thyroid hormones namely fT4, FT3 (Bartalena and Robbins, 1992; Bartalena *et al.*, 1996; Byfield *et al.*, 1983; Sorger *et al.*, 1992; Trainer and Howard, 1983; Domingues *et al.*, 2009; Nelson *et al.*, 2008; Albaar and Adam, 2009). Laboratory investigations of such subjects hint a disorder at thyroidal hormonal status which need further follow-up. The thyroid hormone transporter protein practically play an important role for the stabilization of thyroid hormone within blood circulation, still their fluctuation do not seems interfere drastically with thyroid hormones disorders. The dilemma facing the thyroid hormones following disruption in the amount of thyroid hormone transport protein originate from this fact that any alteration of these protein contribute to alteration into the serum level of total and free thyroid hormones, with subsequent either of thyroid hormone disorder or at least laboratory result miss understanding of thyroid function tests. The latter laboratory reports on thyroid hormones tests may eventually miss-lead the medical team in how the proposed thyroid patient should be follow-up and managed (Schussler, 2000; Langsteger, 1996; Van Deventer *et al.*, 2011; Stockigt and Lim, 2009; Nelson *et al.*, 2008; Sapin and Schlienger, 2003; Bartalena *et al.*, 1996; Byfield *et al.*, 1983; Ferrari *et al.*, 1987; Trainer and Howard, 1983; Sorger *et al.*, 1992). Other possibilities of thyroid hormones alteration can be due to genetically abnormalities which are present in some individuals and the reasons for that are well established (Bartalena and Robbins, 1992; Byfield *et al.*, 1983; Langsteger, 1996; Trainer and Howard, 1983). From laboratory point of view the least presentation can be accompanied with serum T4, T3 changes of euthyroid subjects either hyperthyroidism or hypothyroidism depends to the serum level of thyroid hormones without the clinical manifestation and if the laboratory results is to be taken as base for patient management serious miss-diagnosis eventually is encountered with possible serious averse effects (Beierwaltes and Robbins, 1959; Sunthornthepvarakul *et al.*, 1998; Refetoff, 1989; Trainer and Howard, 1983; Bartalena and Robbins, 1993; Bartalena and Robbins, 1992; Langsteger 1996; Surks and Sievert, 1995; Borst *et al.*, 1983; Hamblin *et al.*, 1986).

CONCLUSION

The following discussion can be drawn out of the present review:

- T4 and T3 of thyroid are vital hormones essentially required for all the tissues within human body. In blood circulation they can be found as Free and Total hormones (fT4, fT3) and (Total T4, Total T3)

- Only a tiny amount of thyroid hormones are present as fT4 and fT3 and about 95-99% of T4 (thyroxine) and T3 (triidothyronine) are protein bounded, such protein are called thyroid hormones transporter proteins

- Thyroid hormones transporter proteins are synthesized within liver and they are Thyroxine Binding Globuline (TBG), Transthyritin (TTR), known as pre-Albumin and finally Albumin

- Although the precise role of thyroid hormone transporter are not well established but there are extensive reports indicating on the crucial role of thyroid hormones transporter protein as stabilizer and reservoir of T4 and T3 within blood circulation to prevent the damage which possibly occur due to sudden changes in the amount of free hormones

- Thyroid hormones transporter protein serum level can be altered either due to inherited or acquired diseases, examples of such disorders are defect on the gene responsible for biosynthesis of thyroid hormone transporter proteins and some metabolic disorder originating from liver and kidney diseases

- In some liver diseases it may eventually interfere with the biosynthesis of thyroid hormone transporter proteins and their deficiency occur but other hormones particularly estrogen stimulate the overproduction of thyroid hormone transporter proteins. In renal disorder and in case of proteinuria, the proteins are lost by the kidney and the amount thyroid hormones transporter protein depleted. In either of elevated or reduced concentration of thyroid hormone transporter protein, euthyroid hyperthyroidism or hypothyroidism may be followed, most probable without any major clinical manifestation of thyroid malfunctions

- It is also reported that some chemical substances and drugs may dissociate the thyroid hormones from thyroid hormone transporter protein and in fact in some cases replace substitute the thyroid hormones which can be considered as drugs adverse effect, with possible thyroid metabolic disorder

- Also any alteration in the amount of thyroid hormone transporter proteins may eventually alter total thyroid hormones within circulation but as far as the free thyroid hormone concentration is kept within the reference intervals, the involved person demonstrate euthyroid condition, with no major clinical complications

- The through out studies in this review emphasis on direct side effect of secondary diseases of liver, kidney and other hormonal disorder on the manipulation on the thyroid hormonal serum level with ultimate alteration on the thyroid hormone status assessments

- Thyroid hormone transporter protein deficiency and particularly TBG, can trigger the suppression of specifically total T4, although total T3 is may occur. The evaluation of a subject with healthy thyroid based on such laboratory findings without proper investigation on thyroid transporter protein will subsequently lead to serious misdiagnosis and prescribed unwanted thyroid hormonal therapeutic regiments with expected adverse-effects

- The present review highlight the importance of cooperation and understanding required between clinicians and laboratory findings as to what extend the laboratory investigations and clinical manifestation of thyroid patients should be matched to avoid the possible miss-diagnosis and miss-treatments of a person with healthy thyroid

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