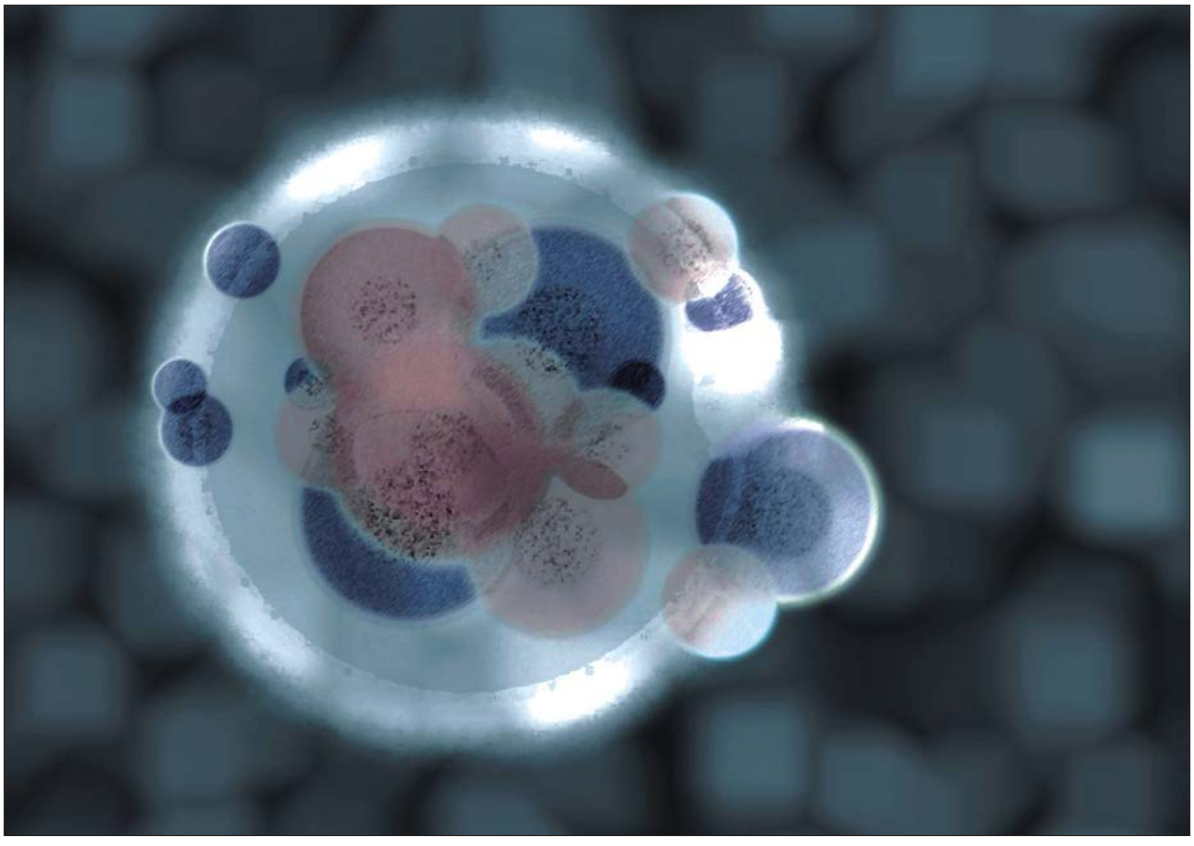

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A Review of Literature on Thyroid Hormone Disorders Originated from Extra Thyroidal Illness

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Abstract: The definition of non-thyroidal illness arises from the fact that thyroid hormones within blood circulation is reduced not due to the malfunction of thyroid organ, but it is mamifested from disorders of other organs. Clinical conditions such as cardiovascular diseases mainly myocardial infraction, sepsis, surgery and many other chronic and sever diseases are associated with thyroid hormones reduction. Serum T3 concentration is reduced during non-thyroidal illness, but serum T4 concentration is seemed to be raised in most of the cases, which is due to the inhibition of T4 conversion into T3 as result of reduced activity of deidoniase enzyme. It seems the reduction in the T3 concentration do not exhibit neither any negative side effects in metabolism nor any irreversible harm in patient involved. There is not any suggestion that hypothyroidism originated from non-thyroidal illness can be rapidly leads to fatal outcome but such low reduction in thyrod hormones and particularly T3 can be considered as a key factor for the initiating the medical attendance and the necessary steps to prevent further clinical complication.

Key words: Thyroid gland, thyroid hormone, hypothyroidism, non-thyroid illness

INTRODUCTION

Thyroid is among the largest endocrine gland in human, the two hormones produced by thyroid are the most crucial and important hormones interfering in various aspects of metabolism. Tetraidothyronine most is known as thyroxin (T4) and triidothyronine (T3) are the thyroid hormones although T3 is produced outside thyroid gland in peripheral tissues from deiodination of T4. Thyroid produce T4 and T3 internally which is triggered by Thyroid Stimulating Hormone (TSH) itself biosynthesized in pituitary gland as result of Thyrotropin Releasing Hormone (CRH).

Thyroid hormones dysfunctions due to variety of disorders related with the thyroid gland are well established, which comprised from many abnormalities in the thyroid gland itself leading into hypothyroidism and hyperthyroidism (Mansourian, 2010a, b).

The definition of non-thyroidal syndrome arises from the fact that thyroid hormones within blood circulation is reduced not due to the malfunction of thyroid organ. The apparent clinical manifestation of established hypothyroidism is not as a result of thyroid abnormality, but the suppressed serum levels of T3, T4 are belong to other peripheral and central diseases, which in practice nothing to do with thyroid gland. The non-thyroidal disease accompanied with the clinical manifestations which are occurred not only as result of hypothyroidism with no thyroid origin and is associated syndromes of other vital and key hormonal deficiencies (Murakami, 2012; Mebis *et al*., 2009; Suvarna and Fande, 2009; Warner and Beckett, 2010; Bello *et al*., 2010; Pappa *et al*., 2011; Luca *et al*., 2010).

Starvation and illness are the clinical conditions which suppressing the serum thyroid hormonal concentration. At initial stage of sickness the T3 concentration reduce slightly, but T3 and also T4 concentration in blood circulation drop further as the disease status getting worse and progressed. Although the serum concentration of T3, T4 are dropped, but this occur without the increase in the amount of TSH (Mebis *et al*., 2012; Liu *et al*., 2011; Ozen *et al*., 2011; Wajner and Maia, 2012).

In addition to starvation variety of diseases and adverse clinical conditions such as cardiovascular diseases mainly myocardial infraction, sepsis, surgery and many other chronic and sever diseases and sickness are associated with thyroid hormones reduction (Pereg *et al*., 2012; Li *et al*., 2011; Cini *et al*., 2009; Ranasinghe and Bonser, 2010; Meyer *et al*., 2011; Kowalczuk-Wieteska *et al*., 2011; Mansourian, 2012a, b, c; Mansourian, 2013a). The definition of euthyroid sick syndrome is a definition which is also given to the clinical manifestation of non-thyroidal

syndrome, which also elaborate the condition of a disease which can not be comprehended and elucidated properly (McIver and Gorman, 1997; DeGroot, 2003; Stathatos and Wartofsky, 2003; Hennemann *et al*., 1988; Phillips *et al*., 1984; Vardarli *et al*., 1987; Eber *et al*., 1995; Holland *et al*., 1991; Plikat *et al*., 2007; Vexiau *et al*., 1993).

Controversial dialogues have been carried out for quiet of long time in medical institutions in regards to the thyroid hormones fluctuations during some critical diseases in sever sickness and in fact some were in believe that the reduced serum T3, T4 concentration reported by the clinical laboratory either can be a mistaken report by the laboratory personal and the method of thyroid hormone measurements or otherwise if the thyroid hormones measurements is acceptable is not an indication of the real hypothyroidism. Some studies indicated that also in severe illness hypothyroidism is existed, but this occur to prevent the energy expenditure and preserve the energy for combating the present sever illness (Harris *et al*., 1978; Welle and Campbell, 1986; Gardner *et al*., 1979; Burman *et al*., 1979; Mebis *et al*., 2007; Girvent *et al*., 1998, Suvarna and Fande, 2009; Cengiz *et al*., 2008; Kaptein, 1997; Docter *et al*., 1993; Chopra *et al*., 1985a; Wartofsky and Burman, 1982; Mansourian, 2013c).

Under any arguments hypothyroidism manifested either due to central or peripheral abnormalities of thyroid hormones physiological function which cover wide spectrum of severe illness eventually end up with inadequate thyroid hormone supply to the target tissues of T4 and T3. There are some studies and report indicate that although serum concentration of T4, T3 are reduced but this scenario does not resemble the hypothyroidism clinical manifestation and the euthyroid sick syndrome is given to such medical presentation (Mebis and Van den Berghe, 2011; Thee *et al*., 2011; Ranasinghe and Bonser, 2011; Economidou *et al*., 2011; Jiao *et al*., 2011).

The big and confusing argument which still is going on in medical circles is whether to put the diagnosed hypothyroid patient of non-thyroidal syndrome on thyroid hormones substitution therapeutic regiment. The aim of this present review is to elaborate on the clinical manifestation and thyroid hormones alteration observed during non-thyroidal syndrome and the way this abnormality should be faced.

STATUS OF THYROID HORMONES DURING NON-THYROIDAL ILLNESS

Carbohydrate deprivation is considered as one of the significant characteristic behavior of human metabolism abnormality during starvation. As carbohydrate deprivation persist the conversion of thyroxin into triidothyronine which is mediated through deiodination of T4 by the deiodinase in the liver will be retarded but it seems the production of reverse T3 (rT3) not only inhibited but it is increased as result of other isomer of deiodinase responsible for the conversion of active T3 into non-active T3 which is rT3 soon after carbohydrate deprivation which can be resulted as by product cosequence of starvation (Kowalczuk-Wieteska *et al*., 2011; Harris *et al*., 1978).

The thyroid hormonal change of carbohydrate deprivation and starvation is the reduction and elevation in the serum T3 and rT3 respectively. The basic metabolic rate is reduced during starvation and there are studies indicated the reduction in the amount of T3 is natural reaction to preserve energy expenditure and proteins which is the ultimate response of reduced T3 in human metabolism (Welle and Campbell, 1986).

Experimental investigations highlight the importance of T3 in carbohydrate deprivation and starvation in enhancing the level of nitrogen loss and based on these findings many argues that thyroid hormones should be given as therapeutic regiments to the patients suffering from non-thyroidal illness.

The above finding is open to discussion and there are some studies indicating that the observed clinical manifestation related to hypothyroidism as result of non-thyroidal illness show itself in initial state of disease and not in prolonged time of disease onset.

These studies also emphasize although serum T3 concentration is reduced during non-thyroidal illness, but serum T4 concentration although is not altered but also there are some reports which indicate a rise in serum T4, which can be due to the inhibition on T4 into T3 as result of reduced activity of deidoniase enzyme responsible for the production of T3 from T4. In addition it seems the reduction in the T3 concentration do not exhibit neither any negative side effects in metabolism nor any irreversible harm in human (Castro *et al*., 2013; Gardner *et al*., 1979; Burman *et al*., 1979; Tognini *et al*., 2010; Goldsmit *et al*., 2011).

SERUM THYROXIN CONCENTRATION REDUCED DURING NON-THYROIDAL ILLNESS

It seems that as the trend of non-thyroidal illness is worsen which it is also accompanied with starvation, the serum T4 concentration is also reduced in addition to the T3 which is an predictable in no thyroidal diseases.

In spite of low thyroid hormone of T4, T3 the serum thyroid stimulating hormone is remain low or even at normal range of reference intervals, which according to

the negative feedback mechanism which is available in hypothalamus-pituitary is not normal (Mebis *et al*., 2007; Jiao *et al*., 2011; Mansourian *et al*., 2010a, b; Mansourian and Ahmadi, 2010; Mansourian and Veghari, 2011; Mansourian, 2010c, d, e).

As the non-thyroidal pattern of diseases is progressed further and in fact those patients hospitalized for the severity of diseases onset will be presented with reduced thyroid hormones.

There are some reports indicating that non thyroidal illness mostly is manifested among older patients, having acute operation difficulties accompanied with nutritional deficiency, neuronal over activity and complication pattern following operation (Jiao *et al*., 2011; Tognini *et al*., 2010; Girvent *et al*., 1998; Yaglova, 2011; Solter *et al*., 2012; Liu *et al*., 2013; Dickerman and Barnhill, 2012, De Marinis *et al*., 1985; Mansourian *et al*., 2007; Mansourian, 2011c).

The alteration in the serum concentration of T4 and T3 can be used as a index which is able to assume the risky scenario of children residing in the hospital intensive care unit those patient suffering from lung cancer and other resembling clinical conditions (Suvarna and Fande, 2009; Cengiz *et al*., 2008; Mansourian *et al*., 2010a, b; Mansourian and Ahmadi, 2010).

The fatal outcome of remarkable reduced serum thyroxin is reported with high incidence of mortality (Schilling *et al*., 1999).

The non thyroidal illness and mortality among patients having bone transplantation is occurred with high prevalence. Non thyroidal illness occurrence among older patients having acute operation is more prevalent (Schulte *et al*., 1998; Girvent *et al*., 1998).

There are many studies indicating on the vital role of thyroxin in metabolism and on the other hand the sever adverse consequence of thyroxin drop and the fatal incidence of T4 suppression (Schilling *et al*., 1999; Schulte *et al*., 1998; Girvent *et al*., 1998; Maldonado *et al*., 1992).

Although there is not an absolute suggestion that hypothyroidism originated from no thyroidal illness can be rapidly leads to fatal outcome but such low reduction in thyroxin can be considered as a key factor for the initiating the medical attendance and the necessary therapeutically steps to prevent later undesired clinical complication.

Also there are documented studies indicating thyroid hormones suppression during non thyroidal illness and accompanied clinical manifestation, but they argue that such drop in thyroid hormone as result of non thyroidal illness is a natural metabolic reaction for adapting with the new disease onset. In the absence of well documented reports one can not take this later suggestion for granted and leaving the sick patient unattended medically to recover from a sever and chronic illness because thyroid hormone suppression can be followed by fatal outcome (Wartofsky and Burman, 1982; Kaptein, 1997; Docter *et al*., 1993).

The main portion of studies indicate that the T3 in either in the form of free or total are low in non thyroidal illness, but studies in this area is controversial and are in believe that T3 concentration in no thyroidal illness can be low or at normal range of intervals.

There are also some reports indicating that the circulation thyroxin can be in normal or even above the mean of reference intervals. Majority of serum concentration of T3 come from conversion of T4 into T3 in the liver and only about the 1/4th of T3 produced in the thyroid gland which in the main time muscle can also contribute to this minor portion of T3. It is obvious that the advanced liver disease can have a profound adverse effect leading to reduction of serum T3 (Surks *et al*., 1988; Melmed *et al*., 1982; Kaptein *et al*., 1981a; Chopra *et al*., 1979; Bacci *et al*., 1982; Sapin *et al*., 1995; Chopra *et al*., 1996).

SERUM T3 AND FREE T3 IN NON THYROIDAL ILLNESS

Studies indicated that the serum concentration of T3 and also free T3 mainly reduced. The enzyme responsible for the conversion of T3 from T4 deiodinase-I which is mainly presented in the liver is reduced, therefore the biosynthesis of T3 from T4 is diminished accordingly. The majority of T4 in the circulation through the denomination of T4 in peripheral tissues and only about 1/4 of T3 in circulation come from thyroid gland itself. The production of T3 from T4 is dropped significantly during non thyroidal illness and liver disorder in particular (Surks *et al*., 1988; Melmed *et al*., 1982; Kaptein *et al*., 1981a; Chopra *et al*., 1979; Bacci *et al*., 1982; Sapin *et al*., 1995; Mebis *et al*., 2007; Mansourian, 2013b; Mansourian *et al*., 2011).

SERUM REVERSE T3 IN NON THYROIDAL ILLNESS

Reverse T3 can not be taken as an really important index for patient with non thyroidal illness although the serum concentration rT3 is significantly is increased during no thyroidal illness, although some reports indicate that rT3 serum concentration may be in between reference intervals. The other reports indicated that the

enzyme responsible for the production of rT3 from active hormones is inducted during non-thyroidal illness and the production of rT3 is increased as result. It is indicated that the activity of deiodinase-I enzyme which is responsible for T3 biosynthesis is decreased but on the same time the activity of deiodinase-III which can convert T3 into rT3 is increased as result the serum concentration of T3 and rT3 are reduced and increased respectively. Study indicated that the serum freeT3 with non thyroidal illness is lower than control subjects. It is worthy to mention that rT3 is reduced mainly due to the prevention of T4 entry into target tissues. As result of later manifestation T3 production and eventually the rT3 production is also limited as result of lower T3 (Peeters *et al*., 2003).

STATUS OF TOTAL SERUM T4

The thyroxin concentration is adversely reduced during non-thyroidal illness and it is dependent to disease condition and its severity and duration of disease onset. In case of acute diseases and trauma, starvation within a limited period thyroxin level is not altered. But as the severity of disease progressed and in some other cases such as infection the thyroxin reduced significantly and in some instance to the level which can be considered as risky factor specifically for newborns leading to fatal outcome which requiring urgent medical interventions (Gardner *et al*., 1979; Wartofsky and Burman, 1982; Kaptein, 1997; Docter *et al*., 1993; Chopra *et al*., 1987; Schilling *et al*., 1999; Schulte *et al*., 1998; Girvent *et al*., 1998; Maldonado *et al*., 1992; Surks *et al*., 1988; Melmed *et al*., 1982; Kaptein *et al*., 1981a; Klemperer *et al*., 1995; Osburne *et al*., 1983).

In non-thyroidal illness the hypothalanus-pituitary-thyroid axis is modified to the level which eventually lead to reduced total serum concentration of T4. Thyrotrophin releasing hormone (TRH), Thyroid stimulating hormone (TSH) and Thyroxin production from hypothalamus-pituitary and thyroid glands respectively under a thinly control. In no thyroidal illness the TRH concentration can be reduced which eventually associated with T4 drop. The other scenario in this area of thyroid hormones disorders due to no thyroidal illness can be due to the reduction of Thyroxin Binding Globulins (TBG) as result of TBG destruction due to the TBG enzymatic catabolizing reaction. This TBG modification reduces the TBG capacity in binding T4. Data indicated that serum patient with sepsis showed to have TBG brake down residues. In a study done on patients with sepsis showed to have lower thyroid hormone serum concentrations. The reduction in TBG concentration as result of TBG enzymatic cleavage is the main reason behind low T4, T3 in non-thyroidal illness (Afandi *et al*., 2000; Jirasakuldech *et al*., 2000; Den Brinker *et al*., 2005; Mansourian, 2011a, b).

STATUS OF FREE T4 IN NON THYROIDAL ILLNESS

Free T4 can be considered as key hormones delivered to the tissues and the serum level of freeT4 can be manipulated by some index including the laboratory methods in its estimation and also some other agents within circulation can influence its serum concentration eventually. Drugs, the metabolic by products and in fact some nutrient within blood circulation such free fatty acids can interfere with T4 measurement with the laboratory methods. On the base of al uncertainty, but during non-thyroidal illness the studies do not give a precise information on the status of freeT4 (Surks *et al*., 1988; Melmed *et al*., 1982; Kaptein *et al*., 1981a; Chopra *et al*., 1979; Bacci *et al*., 1982; Uchimura *et al*., 1976; Nelson and Weiss, 1985; Wang *et al*., 2000; Mansourian, 2013c).

In severe kidney diseases and as result of renal dialysis some related chemical compound can probably have some adverse effect on freeT4 estimation also it is proved precisely that these substances can play an important role in freeT4 determination (Kaptein, 1996; Mansourian, 2012a). Free fatty acid at very high concentration may interfere with freeT4 determination, but it is doubtful the level of free fatty acids in the plasma reach to the level which can do modify free T4 estimation. Some other substances used in the laboratory such as heparin in theory can enhance the production of free fatty acids, during free T4 measurements, which can interfere with freeT4 assessments and should be taken into consideration when the thyroid hormones results is being considered for further investigation in patients management (Liewendahl *et al*., 1992; Mendel *et al*., 1986; Mansourian, 2013c).

Unfortunately different technique for the measurement of free thyroid hormones do not give homogenous results during non-thyroidal illness, but one can say in general freeT4 is mainly lower than reference interval during non thyroidal illness (Wang *et al*., 1985; Chopra *et al*., 1996; Surks *et al*., 1988; Mansourian, 2013c).

The interference of TBG in the estimation of freeT4 should carefully taken into consideration. The status of exact free T4 in non-thyroidal illness is a matter for further investigations and the decline in the amount of TBG during a sever critical illness, trauma surgery can be among reason of fluctuation in the state of free T4 during non-thyroidal illness.

As result of drop in the TBG concentration one should expect a gradual increase in the amount of freeT4, which can be at its reference interval as TBG serum level approaching its normal concentration, or free T4 can be reduced if the concentration of total T4 is reduced due to no thyroidal illness. As matter of interest freeT3 is not profoundly affected by the TBG alteration and in comprehending the status of T4, T3 it is the freeT4 which can be modified as result of TBG modifications. The reason for this later manifestation arise from the fact that Total T3 serum concentration during non-thyroidal illness drop but not comparable to the Total T4 and the other reason is that T4 is bounded strongly to TBG (Afandi *et al*., 2000; Mansourian, 2011a, b).

FACTORS AFFECTING THE BINDING OF T4 TO TBG

There are many controversial arguments in regards to the chemical agents which possibly can interact with freeT4 estimation. Some dialyzable substances present within serum might interfere with the way T4 binds to TBG (Mendel *et al*., 1991; Wang *et al*., 1998; Csako *et al*., 1987; Chopra *et al*., 1985b; Kaptein, 1996; Liewendahl *et al*., 1992). On the other hand there are some contradictory arguments indicating that inhibiting factors in the serum are not in the position to prevent the T4 attachment into TBG (Brent and Hershman, 1986).The general belief in thyroid hormone status during non-thyroidal illness arises from the fact that thyroid secret lower thyroid hormones and also the peripheral conversion of T4 into T3 is reduced also during no thyroidal illness. Therefore the low T4 and T3 during non-thyroidal illness is a direct consequences of the non thyroidal sickness and not due to some other suggestion such as inhibiting dialysis substances, which can inhibit binding of T4 into TBG, also the reduction of TBG in some cases by itself can affect the reduction of serum T4 seen in the non thyroidal illness (Brent and Hershman, 1986; Mansourian, 2011a, b, d).

SERUM THYROID STIMULATING HORMONE DURING NON THYROIDAL ILLNESS

Studies indicate that serum TSH level is either normal or reduced during non-thyroidal illness and clinical experimental study showed that TSH concentration return to its reference intervals if it has been already dropped, following patients substitute therapy (Brent and Hershman, 1986; Mebis *et al*., 2007; Surks *et al*., 1988; Melmed *et al*., 1982; Chopra *et al*., 1979, 1996; Docter *et al*., 1993; Chopra, 1996). Although serum TSH concentration can be at lower range of normal reference intervals, but some argue that this level of TSH is not correlated with the serum concentration of T4 and T3. The overall conclusion may be directed that TSH level can be low or low normal or even at normal concentration and also with low normal T4, T3 some argue that the patients during non-thyroidal illness remain at euthyroid condition.

Concentrating on the serum TSH status and at the time when TSH level is suppressed one can argue that how you can differentiate the possible hyperthyroidism which can be labeled with suppressed TSH and the suppressed TSH as result of non-thyroidal illness.

Although such clinical manifestation and medical confusion is rare, but the low TSH level during non thyroidal illness is due to the reduction of thyrotropin releasing hormone (TRH) secreted from hypothalamus, which is the stimulating hormone for pituitary to produce TSH.

It seems pituitary can also is adversely affected by non-thyroidal illness and the above clinical manifestation is the consequence effect and pituitary functional behavior return to normal following recovery from non thyroidal illness and as result TSH also return to its normal value. In some instance TSH level can even be elevated which can be considered as another sign for the recovery from hypothyroidism resulting from non-thyroidal illness (Brent and Hershman, 1986; Franklyn *et al*., 1994; Docter *et al*., 1993; Bacci *et al*., 1982; Shahmohammdi *et al*., 2008; Mansourian *et al*., 2010b; Mansourian and Veghari, 2011; Mansourian, 2010c).

PITUITARY-HYPOTHALAMUS STEM BEHAVIOR DURING NON-THYROIDAL ILLNESS

There are extensive studies in this area of research but with various data. TRH is the releasing hormone from hypothalamus and directly stimulate the pituitary to produce TSH and following secretion from the pituitary and ultimately reaching its sole target tissue which is the thyroid gland. TSH binds to its specific receptor and following production of cyclic AMP, the thyroid hormones T4 and T3 are produced, also T3 can be produced in peripheral tissues through the deidonation of T4.

During non thyroidal illness the pituitary react differently to TRH, majority of patients react with lower rate, while other show with a routine and normal reaction (Vierhapper *et al*., 1982; Faber *et al*., 1987).

It seems hypothalamus functional physiology is adversely affected and TRH production during non

thyroidal illness is reduced and therefore the biosynthesis of TSH is lowered with eventual reduction in the amount of serum T4, T3. The confirmation of latter statement come from clinical studies which based on prescription of TRH for those hospitalized patients in Intensive Care Units. Following TRH administration of TRH in such patients, the serum TSH level elevated and the serum level of T4 and T3 return to normal concentrations in the serum of involved patients (Arem and Deppe, 1990; Lee *et al*., 1987; Van den Berghe *et al*., 1998a).

The hypothalamus dysfunction not only is followed by thyroid hormone disorders, but also other hormonal abnormalities including sex related factors of follicle stimulating hormone, luteinizing hormone, testosterone are occurred which are due to reduction in the amount of gonadotropin releasing hormone produced in the hypothalamus which reaching the pituitary directly and stimulating the biosynthesis of sex hormones eventually. There are other hormonal dysfunction during critical illness, elevated serum cortisol, hypoadrenalism, are among such disorders (Spratt *et al*., 1992, 1993; Van den Berghe *et al*., 2001).

THYROID HORMONES DURING CRITICALLY ILLNESS

Various studies indicated that there are significant reduction of T4, T3 in the peripheral tissues, which in practice the target tissues of thyroid hormones are in hypothyroid condition, although again other studies are elaborating that thyroid hormones are in normal concentration during non thyroidal illness. On the other hand it should be elaborated again that in general the findings in this area are not homogenously reported. All of these controversial findings emphasize the need for further approach of thyroid hormones during non thyroidal critically illness (Kaptein *et al*., 1981b, 1982, 1987).

INTRACELLAR METABOLIC CORDINATION OF T4 AND T3

Although experimental studies indicated that the cellular thyroxin uptake is retarded by non thyroidal illness but also T4 and T3 are both are biosynthesized in thyroid but the main portion of T3 required for different organs are produced itrcellulerly from the conversion of T4 which is entered into the cells through active transport, into T3 by deiodination of T4 mediated by deiodinase-I enzyme. T3 is the main active thyroid hormone and it can be produced whenever the tissue need the higher potential of thyroid hormone. By the time T3 is not wanted any more, theT3 converted into rT3, which is non active form of T3. The enzyme responsible for T3 production is mainly is found in the liver, although the enzyme is also present in kidney, thyroid and pituitary. The deidodinase-I activity is lowered in hypothyroid condition and non-thyroidal illness, therefore the serum concentration of T3 is reduced, brain, pituitary and muscle tissues also can produce T3 from T4 by other isoform of deiodinase-II enzyme (Lim *et al*., 1993, 1994; Vos *et al*., 1995; Sarne and Refetoff, 1985; Mansourian, 2013a, b, c, d).

Many other studies focused on the possibility of reduction in the number of transports mechanism available for the entry of T4 into the target tissue cells during non thyroidal illness and the alteration found in the amount of T4 cellular entry is the natural consequence of hypothyroid state within target tissues. In addition to reduced cellular entry of T4, the deiodinase-I enzyme responsible for the production of T3 from T4 simultaneously retarded but the enzyme activity catalyzing the non active form of T3 increased as well as part of non thyroidal illness. Although intercellular T4 entry can manifest the higher serum concentration, but this is not clinically demonstrated in practice, but the conclusion drawn out of all these modification and alteration of T3 reduction and rT3 elevation leaving the cells at hypothyroid condition (Peeters *et al*., 2005; Rodriguez-Perez *et al*., 2008; Mebis *et al*., 2009; Mansourian, 2011a, b, d).

T4, T3 IN THE TISSUES AND THEIR RECEPTOR EXPRESSION

Data in thyroid research indicated that,there is a significant reduction of T3 within the tissue, but some reports demonstrated there are contradictory findings and proved skeletal muscle and cardiac tissues showed to have the elevated concentration of T3 intracellular.

Other study indicate that if the patient with reduced serum T3 left unattended it is followed by fatal outcome and probably eventual death.

There is a direct correlation between intracellular T3 and serum T3 and therefore lower serumT3 concentration during non-thyroidal illness can be directly correspond with the level of T3 inside the tissues which should be taken into consideration when dealing with the patients with non-thyroidal illness. The other findings indicate that the intracellular rT3 and also T3/rT3 index is directly related with the activity level of deiodinase enzymes (Peeters *et al*., 2005; Arem *et al*., 1993; Mansourian, 2011a).

THYROID HORMONE RECEPTOR EXPRESSION

Data in this area of research is sketchy and there are not enough actual results to elaborate on the true condition of thyroid hormone expression. Experimental study on animal model emphasis that thyroid hormone receptor expression during sickness and starvation positively correlated with its reduction. In one study the non-thyroidal illness was inducted on animal model which was followed by thyroid hormone receptor metabolic dysfunction (Rodriguez-Perez *et al*., 2008; D'Amati *et al*., 2001; Sanchez and Jolin, 1991; Mansourian, 2011a).

Correlation of non-thyroidal illness and hypothyroid manifestation: Various studies indicated that although during non-thyroidal illness there is a reduction of thyroid hormones particularly serum T3, but the hypothyroid index is not obvious but patients clinically manifest some degree of hypothyroidism.

The hypothyroid clinical manifestation such as febrile, edema, sepsis, sedative, cardio pulmonary abnormalities usually are accompanied with thyroid hormones disorders of non-thyroidal illness. Although clinical manifestation of hypothyroidism are not visible in the initial state non-thyroidal illness but it can be manifested in later stage of disease onset.

It should be stated that the clinical laboratory measurements such as lipid profile alteration, liver enzymes activity modification, basic metabolic rate changes are not clearly giving any documented clue to the presentation of hypothyroid state during non-thyroidal illness. Also some variation in some biochemical indices such as angiotensin converting enzyme, anti-thrombin, were seen in some experimental studies on animal models with inducted non-thyroidal illness and T3 administration can return some of those modification to reference standards, but the demonstration of hypothyroidism during non-thyroidal illness is not presented as clinical symptom (Brent *et al*., 1984; Seppel *et al*., 1996; Plikat *et al*., 2007).

Metabolic pathways behind serum thyroxin and triidothyronine alteration level during non-thyroidal illness: There is not a single reason for non-thyroidal illness and there are many reasons that can be conducted into non-thyroidal diseases in spite that the original cause of illness is not similar in every person. It should be mentioned that the liver and kidney dysfunctions demonstrate different form of clinical manifestation compared to other types of non-thyroidal diseases. As example the disorders in hypothalamus-pituitary physiological functions reduce the biosynthesis of TSH with subsequent suppression of total T4, leading to reduction of serum T3 concentration. In a experimental study on animal model with non thyroidal illness which caused by starvation accompanied by reduced T4 and leptin the biosynthesis of TRH from hypothalamus is induced by leptin an stimulator of hypothalamus which was followed by the elevation of serum T4 reaching to reference range of normal. In another experimental study which non-thyroidal illness was carried out on rat by inducing starvation the nuclear mechanism of TRH production is reduced with subsequent adverse effect on TSH biosynthesis. The reduced production of TSH leads to reduced T4 and ultimately T3 reduction (Blake *et al*., 1991; Fliers *et al*., 1997; Vierhapper *et al*., 1982; Faber *et al*., 1987; Mansourian, 2012a).

Clinical studies indicated that TRH prescription can be an vital inducer in correcting the serum T4 with subsequent elevation of T3 level through enhanced serum TSH concentration as result of TRH administration in patients suffering from non thyroidal illness. This later statement can be a crucial suggestion in the role of suppressed hypothalamus physiological function in causing non thyroidal illness (Van den Berghe *et al*., 1998a; Nicoloff *et al*., 1970).

Studies indicated that elevated concentration cortisol in adrenal cortex dysfunction can cause a reduction in the amount of TSH with subsequent suppression in the amount of thyroid hormone level. There are documented reports indicating elevated amount of cortisol and in general glucocorticoids can be an important barrier in pituitary for TRH to act on and produce TSH, as result of suppressed TSH, thyroid hormones of T4, T3 are reduced as well (Brabant *et al*., 1987; Benker *et al*., 1990; Bianco *et al*., 1987). Any stress stimulation in animal leading to elevated concentration of glucocorticoids causing suppression of TSH as result of diminished TRH with T4,T3 reduction eventually (Bianco *et al*., 1987).

The explanation behind suppressed biosynthesis of TSH in pituitary in spite of low T4, T3.

It seems that the pituitary intracellular conversion of T4 into T3 can be as reason for pituitary to remain at euthyroid clinical condition, but it is not true for the rest of human organs and they are in practice exhibit hypothyroid condition, although other study proved otherwise. Although there are other possibilities such as thyroxin by product for the above physiological function related to pituitary reaction during non thyroidal illness was presented, but there is not proper explanation in that why the pituitary alone should be in the euthyroid but other tissues in hypothyroid status (Lim *et al*., 1984; Mebis *et al*., 2006).

The scientific explanation which are acceptable in this area of research come from the fact that hypothalamus stimulation which can be occurred through many inducing factors such as starvation, stress, cortisol and glucocorticoids in general and cytokines are behind reasons for the pituitary to behave in manner explained above. The cortisol which can be secreted during stress can be an suppressing factor for pituitary to retard the production of TSH, in fact as result of depleted TRH which coming from hypothalamus. The other adverse side effect in the latest scenario, is the reduction of Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH), which are pituitary hormones also suppressed during non-thyroidal illness leading to reduction in the sex hormones mainly testosterone. All these changes most possibly originated from hypothalamus neuron modification as result some physiological changes such as stress, starvation, cytokines and glucocorticoids happen during serious illness. In some cases all these physiological alteration eventually lead to thyroid hormones suppression with eventual hypothyroidism.

Selenium is an element behave as Co-factor in the structure of iodothyronine deiodinase enzyme and selenium deficiency eventually lead to deiodinase dysfunction. This later enzyme is responsible for T3 production from T4 reverse T3 (rT3) retardation and mainly is found within liver (Kaplan, 1979). Some studies indicated that the reason for low T3 is not based on T4 slow cellular penetration and if it was the case the level of T4 should have been increased instead of suppression. Focusing on this later manifestation some are in believe that there is a possibility that the activity of deiodinase enzyme responsible for T4 conversion to T3 is diminished due selenium deficiency which is playing the co-factor role for the deiodinase and on the absence of such element the enzyme is not able to convert the T4 into T3 and therefore T4 concentration is increased while T3 is reduced, although there is controversy in this area as well (Van den Berghe *et al*., 1998b). During non-thyroidal illness T4, T3 catabolizing pathways is significantly decreased as the concentration of T4, T3 are reduced simultaneously. Some are in believe that the diminished thyroid hormones destruction can initially elevate the thyroid hormones concentrations and not the down-grading of thyroid hormones degradation. It should be mentioned that reduced degradation of thyroid hormones are as result of lower available thyroid hormones. Other study emphasize on the role of lower inactive form of Thyroxin Binding Globulin (TBG) during some critical illness (Afandi *et al*., 2000).

As human arrive into short period of starvation and some other stress during critical diseases, the reduced concentration of T3 which in part is to diminished activity of deiodinase and retardation of T4 into T3 is a natural response to limit the basic metabolic rate and prevent energy loss and keep it for a forcible future during the sever diseases. Later in the course of illness the suppression of thyroid hormones and some other pituitary hormones and in fact many other metabolic alterations are clinically manifested which in fact are the physiological consequence of non-thyroidal illness.

The pathophysiological response during non-thyroidal illness is accompanied with insulin level abnormality, negative nitrogen balance, lipid accumulation on condition the supply of energy provided from some other sources. There are variety of other dysfunctions in the course of illness, neuron and heart disorders are among them. Studies in this field of research suggesting hormone-substituting replacement therapy in those hormones such as thyroid, growth and androgen hormones should be carried out to prevent the adverse effect of illness (Mebis *et al*., 2006; Van den Berghe *et al*., 1998b, 2001; Weekers *et al*., 2003; Mansourian, 2010d, e, 2011c, Mansourian *et al*., 2007, 2008; Mansourian, 2010d, e).

Some studies indicated that in non thyroidal illness such as sepsis it was shown that T4, T3 and TSH are reduced while interleukins are increased. It seems that glucocorticoids level is increased, but TSH concentration is reduced and further studies is demonstrated that interlukines can be preventive factor in the production of TSH, with ultimate T4, T3 reduction (Monig *et al*., 1999; Hermus *et al*., 1992).

As the dosage of some interleukins increased some clinical manifestation such as febrile, inadequate food intake are observed which can play a role in the reduction of thyroid hormone as natural consequences of non-thyroidal illness. Some interleukins showed to be a causative factor in the thyroid hormones biosynthesis in thyroid gland and this become even worse in various diseases originated from non thyroidal illness, but the role of interleukins in other studies have been contradicted. The interventional mechanism of cytokines in hypothalamus-pituitary axis is not fully understood but it most probable involved with disturbing of TRH-TSH axis and reducing TSH leading to reduction in thyroid hormones. Although the cytokines are manufactured by various dysfunctions such as various infections, inflammations, neoplastic illness. In spite all controversial which are existed in this area of no thyroidal illness, cytokines involvement during non thyroidal illness eventually lead to thyroid hormones dysfunctions (Cannon *et al*., 1990; Van der Poll *et al*., 1990, 1995, 1999; De Metz *et al*., 2000; Chopra *et al*., 1991;

Nagaya *et al*., 2000; Bartalena *et al*., 1994; Boelen *et al*., 1993, 1995, 1996, 1997; Abozenah *et al*., 2008; Stouthard *et al*., 1994; De Metz *et al*., 2000; Michalaki *et al*., 2001).

OTHER DISEASES ALTERING THYROID HORMONE CONCENTRATION

Hypoglycemia can also reduce TSH, free T4, freeT3 and it was also noticed that newborn suffering from hypoxia and related encephalopathy ischemia and oxygen suppression to the central nervous system can eventually enter into the dysfunction of hypothalamus-pituitary with subsequent thyroid hormonal abnormalities. Experimental studies in animal model indicated that inducing hyperglycemia as result of glucagon injection can cause thyroid hormone dysfunctions in other tissues most probably through the modification occur in the normal metabolic pathways in the cellular of thyroid hormones (Pereira *et al*., 2003; Custro *et al*., 1989).

Dopamine is a chemical compound which if is given in some diseases such as kidney and heart disorders, can prevent the biosynthesis of TSH with subsequent reduction thyroid hormones dramatically and if administration of dopamine is terminated the concentration of TSH is elevated and T4, T3 and rT3 are reduced and increased respectively. The whole scenario demonstrate that dopamine can eventually lead to hypothyroid during non-thyroidal illness which needs further attention (Van den Berghe *et al*., 1994; Fliers *et al*., 1997).

Starvation is a process manifested with low level of leptin a substance which can play a vital task in the physiology of thyroid hormones and their reduction during starvation which is facilitated by interventional pathways in the TRH-TSH stem. Leptin can stimulate TRH production and the mechanism is at nuclear level, with subsequent TSH biosynthesis. During starvation leptin concentration is dropped and therefore as result TSH concentration is also suppressed leading to thyroid hormone reduction, although this manifestation is an absolute requirement, for the energy conservation (Legradi *et al*., 1997, 1998; Flier *et al*., 2000).

Selenium and Atrial Natriuretic Peptide (ANP) are among other causative factors of non-thyroidal illness leading to thyroid hormones dysfunction, leading to reduced T4 and T3. It seems that selenium adverse effect through the inactivation of deiodinase and atrial natriuretic peptides acting on thyroid gland and not on hypothalamus-pituitary (Vesely *et al*., 2001; Berger *et al*., 1996).

In sever kidney disease non-thyroidal illness can be clinically manifested and T3 reduced significantly, but on the other hand rT3 is elevated (Lim *et al*., 1980, 1989; Liu *et al*., 2009).

Clinical laboratory assessment and patient management in non-thyroidal illness: The primary hypothyroidism can be diagnosed by elevated TSH and reduced T4 in general and T3 as well in some instances. In the absence of primary hypothyroidism and also pituitary dysfunction, the occurrence hypothyroidism in severe illness can be clinically manifested. The presences of auto immunity to the thyroid can be an stimulating factor in this concept of primary hypothyroidism. A low or normal TSH and low T4 and T3 are the unique feature of non thyroidal disease. The determination of cortisol can be an assistance in this regards. Hypoadrenalism in some rare cases can diagnostically be helpful because it can be happen in some type of severe illness. On condition of thyroid hormone replacement therapy serum cortisol level should be determined due the alteration which could happen in the amount of corticostroid binding globulin. FSH is another hormone which can be measured as an indicator of pituitary in menopause females to evaluate if there is anything wrong with pituitary itself. Some medicines can enhance the suppression of T4 which should be taken into consideration. Dopamine which is consumed as some sever diseases most probable stimulate an overt hypothyroidism a factor which should looked at it carefully when dealing with patient with severe illness. Also the suppressed TSH is the remarkable sign of hyperthyroidism, but this true in true in the presence of suppressed T4 and T3 which can easily be demonstrated by the clinical laboratory procedures and methods (Kidess *et al*., 1993; Merry *et al*., 1994; Lambert *et al*., 1997; Mansourian, 2013c).

Thyroid hormone replacement therapy: There are many reports indicating that reduction in the amount of produced T3 during a severe illness is natural response of human physiology at the time when the body need to prevent an extra energy and keep it for combating the new pathophysiological condition and thyroid hormone replacement therapy can disrupt this physiological response during non-thyroidal illness.

Some studies carried out in this area of research indicate controversial findings, but it seems there are data that explain thyroid hormone replacement therapy can not be in any use at the time of non-thyroidal illness, but the findings indicate that there is not a sever adverse effect on thyroid hormone administration during hypothyroid state of non-thyroidal illness.

Studies on the role of thyroid hormone administration during kidney diseases prove to be in no benefit for a patient with severe kidney disease. In other various sever diseases such as burns, sepsis, cardiovascular diseases, hemorrhage, the thyroid hormone replacement therapy are mainly found that do not play a clear advantages, also some experimental studies talk about usefulness of T3 administration (Becker *et al*., 1982; Acker *et al*., 2000, 2002; Brent and Hershman, 1986).

In addition to thyroid hormonal dysfunction in sever prolonged illness variety of other abnormalities are manifested. Neurological, protein waste, abnormal lipid storage, blood glucose elevation leading to hyperglycemia and other biochemical alteration including reduced serum protein, elevated serum calcium, reduced serum potassium and elevation in serum triglyceride. In addition to earlier disturbances, reduction in the serum level of FSH, LH, testosterone and growth hormone are noticed, while serum level of cortisol is increased. Various hormonal therapy for those which seems to be abnormal have been suggested and in some instance even hypothalamus releasing hormone such as thyrotrophin releasing hormone, growth hormone releasing hormone, gonadotropin releasing hormone are recommended to overcome the pituitary hormonal deficiency such TSH, FSH, LH, GH and eventual correction of thyroid hormones, testosterone and growth factors which are observed in critically ill and non-thyroidal illness patients (Seppel *et al*., 1996; Van den Berghe *et al*., 1998a, 2001, 2002, 2005; Mebis *et al*., 2006; Herndon *et al*., 2001; Hamrahian *et al*., 2004; Takala *et al*., 1999; Mesotten *et al*., 2004).

Key points:

- Thyroid is the largest endocrine gland in human, the two hormones produced by thyroid T4 and T3 are the most crucial and vital hormones interfering in various aspects of metabolism
- Tetraidothyronine mostly is known as thyroxin (T4) and triidothyronine (T3) are the thyroid hormones produced inside the gland, although T3 is produced outside thyroid in peripheral tissues from deiodination of T4
- The disorders in thyroid hormones biosynthesis within thyroid gland due to many abnormalities is leading into hypothyroidism are well documented
- The definition of non-thyroidal illness arises from the fact that thyroid hormones mainly T3 is reduced not due to the malfunction of thyroid, but it is originated from disorders of other organs in human body
- Hypothyroidism due to either central or peripheral cover wide spectrum of severe illness eventually lead to inadequate thyroid hormone supply to the target tissues
- Cardiovascular diseases mainly myocardial infraction, sepsis, surgery and many other chronic and sever diseases are associated with thyroid hormones reduction leading to hypothyroidism not due to thyroid gland dysfunction itself
- Serum T3 concentration is reduced during non-thyroidal illness, but not serum T4 in fact there may be a rise in serum T4, which can be due to the inhibition on T4 into T3 as result of reduced activity of deidoniase enzyme responsible for the production of T3 from T4
- The enzyme responsible for the conversion of T3 from T4 deiodinase-I which is foun in the non thyroidal organs but mainly in the liver and kidney is reduced, therefore the biosynthesis of T3 from T4 is diminished accordingly
- It seems the reduction in the T3 concentration do not exhibit neither any negative side effects in metabolism nor any irreversible harm in human
- There are many reports indicating that reduction in the amount of produced T3 during a severe illness is natural response of human physiology at the time when the body need to prevent an extra energy expenditure
- In spite of low thyroid hormone the serum thyroid stimulating hormone (TSH) is remain low or at normal range of reference intervals, which according to the negative feed-back mechanism which is available in hypothalamus-pituitary is not fully comprehended
- Non -thyroidal illness mostly is manifested among older patients, having acute operation difficulties accompanied with nutritional deficiency, neuronal over activity and complication following operation
- It seems hypothalamus functional physiology is adversely affected and TRH production during non thyroidal illness is reduced and therefore the biosynthesis of TSH is lowered with eventual reduction in the amount of serum T4, T3
- Although clinical manifestation of hypothyroidism are not visible in the initial state non-thyroidal illness but it can be manifested in later stage of disease onset
- The hypothyroid clinical manifestation such as febrile, edema, sepsis, sedative, cardio -pulmonary abnormalities usually are accompanied with thyroid hormones disorders of non-thyroidal illness
- There is not a single reason for non-thyroidal illness and there are many factors which can be conducted into non-thyroidal diseases in spite that the original cause of illness is not similar in every person

- It should be mentioned that the liver and kidney dysfunctions are presented with different clinical manifestation compared to other organs non-thyroidal diseases
- The possibility of reduction in the number of transports mechanism available for the entry of T4 into the target tissue cells during non thyroidal illness and the alteration found in the amount of T4 cellular entry is the natural consequence of hypothyroid state within target tissues
- In addition to thyroid hormonal dysfunction in sever prolonged illness others pathological condition such as, neurological, protein loss, abnormal lipid storage, blood glucose elevation leading to hyperglycemia and other biochemical alteration including reduced serum protein, elevated serum calcium, reduced serum potassium and elevation in serum triglyceride are subsequently manifested in non thyroidal illness
- In addition to thyroid hormones suppression, other hormonal dysfunctions including reduction in the serum level of FSH, LH, testosterone and growth hormone are presented, while serum level of cortisol is increased in non thyroidal diseases
- The major and confusing argument in medical circles is whether to put the diagnosed hypothyroid patient of non-thyroidal illness on thyroid hormones substitution therapeutic regiment
- Thyroid hormone replacement therapy can not be in any use at the time of non-thyroidal illness, but the findings indicate that there is not a sever adverse effect on thyroid hormone administration during hypothyroid state of non-thyroidal illness

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