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Metabolic Pathways of Tetraidothyronine and Triidothyronine Production by Thyroid Gland: A Review of Articles

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Abstract: Tetraidothyronine (T4) and Triiodothyronine (T3) are the two vital hormones in human metabolism produced by thyroid gland. The major pathways in thyroid hormone biosynthesis begin with iodine metabolism which occurs in three sequential steps: active iodide transport into thyroid followed by iodide oxidation and subsequent iodination of tyrosyl residues of thyroglobulin (Tg) to produce idotyrosines monoidotyrosine (MIT) and diiodothyrosine (DIT) on Tg. Oxidized iodine and tyrosyle residues which are an aromatic amino acids are integral part of T4 and T3. The thyroid iodine deficiency of either dietary, thyroid malfunction , or disorder of hypothalamus and pituitary to produce enough Thyroid Stimulating Hormone (TSH), eventually lead to hypothyroidism with sever side effects. Iodine oxidation is the initial step for thyroid hormone synthesis within thyroid, is mediated by thyroperoxidase enzyme (TPO), which itself is activated by TSH required for production of MIT and DIT. T4 and T3 are subsequently are synthesized on Tg following MIT and DIT coupling reaction. Thyroid hormones eventually produced and released into circulation through Tg pinocytosis from follicular space and subsequent lysozomal function, a process again stimulated by TSH. The production of T4 and T3 are highly regulated externally by a negative feed-back interrelation between serum T4, T3 and TSH and internally by the elevated iodine within thyroid gland. It is believed the extra iodine concentration within thyroid gland control thyroid hormones synthesis by inhibition of the TPO and hydrogen peroxide (H_2O_2) formation which is also an essential factor of iodine oxidation, via a complex mechanism. In healthy subjects the entire procedures of T4 and T3 synthesis re-start again following a drop in serum T4 and T3 concentration. On conditions of thyroid disorders, which caused by the distruption of either of above mechanisms, thyroid hormone deficiency and related clinical manifestations eventually begin to show themselves.

Key words: Thyroid gland, thyroperoxidase, hydrogen peroxide, tetraidothyronine, triidothyronine

INTRODUCTION

Thyroid principally synthesis two physiochemical important hormones, thyroxin or tetraidothyronine and triidothyronine best known as T4 and T3, respectively.

The precursor of thyroid hormones is tyrosine an aromatic amino acid existed within the structure of thyroglobulin (Tg) a macro-protein containing 5000 amino acids including 115 tyrosine residues. T4 and T3 are in fact iodine-tyrosine-based hormones. Iodine substituted on the tyrosine residues of Tg, by a complex process mediated, by Thyroid Stimulating Hormone (TSH), which is a hormone synthesized within the pituitary gland by the action of Thyrotropin Releasing Hormone (TRH), a hypothamous hormone. TSH is a hormone initiating the entire metabolic pathways, to produce T4 and T3. The active iodide transport from blood circulation into thyroid occur by TSH in spit of much higher iodide concentration in the gland.

The iodine subsequently oxidized by peroxidase enzymes, which itself is activated by TSH. The oxidated iodine is located on the tyrosine residues of thyroglobulin molecule which are within the follicular space of thyroid gland. monidotyrosine (MIT) and diidothyrosine (DIT) are produced, if either one or two oxidized iodine atoms are substituted on the tyrosyle residue of tyrosine amino acids, respectively. The subsequent metabolic pathway on the thyroglobuline is the coupling reactions between MIT and DIT, to produce T4 and T3 on the Tg molecule. On condition of coupling of either two DIT or one DIT and one MIT on the thyroglobuline T4 and T3 are produced, respectively. Therefore the biochemical structure of T4 and T3 contain, 4 and 3 iodine atoms, respectively and in fact 4 in T4 and 3 in T3, designated the

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number of iodines existed within the structure of thyroid hormones.

Following the above metabolic pathways in the thyroid, the iodinated residues within the structure of thyroglobulin released after the Tg is digested by lysozomol enzymes. The end products of thyrglobuline cleavages, are, T4, T3 and uncoupled idoniated tyrosyle residues of DIT and MIT. T4 and T3 are released from thyroid into blood circulation subsequently. (Targovnik *et al*., 1995; Selmi and Rousset, 1988; Rousset and Mornex, 1991; Linke *et al*., 2002).

The DIT and MIT also cleaved and the iodine re-circulated into the new T4 and T3 synthesis as explained earlier (Haeberli *et al*., 1978; Fonlupt *et al*., 1997; Wollman and Ekholm, 1981; Berndorfer *et al*., 1996; Ercson, 1981; Marino and McCluskey, 2000; Pierce *et al*., 1985; Bernier-Valentin, *et al*., 1990; Alvino *et al*., 1995; Portmann *et al*., 1985).

The crucial role of iodine in T4 and T3 production: Iodine is an essential part of T4 and T3 and thyroid hormone biochemical structure principally based on tyrosyle residue and iodine, therefore thyroid hormone with no iodine is not considered a hormone and it is only a modified form of an amino acid called tyrosine. Iodine is a element required during various stage of life, starting from fetus life, neonate, childhood, adolescency up to elderly age, because it is the vital part of T4 and T3 the crucial hormones required for metabolism, but the extent and the severity of its deficiency varies at different stage accordingly (Mansourian and Ahmadi, 2010; Mansourian, 2010a,b). The iodine deficiency during fetus life most often accompanied with mental retardation (De-Escobar *et al*., 2000; Mansourian, 2010c; Shahmohammdi *et al*., 2008; Mansourian *et al*., 2010b). Although during the first trimester of pregnancy fetus is dependent on the maternal thyroid hormones which if is required it is supplied to the fetus via placenta but in the second trimester of the fetus life thyroid hormones is originated from the fetal itself and not from maternal blood (De-Escobar *et al*., 2000). When fetus thyroid hormones requirement relay on the fetal origin and when the dietary iodine which reaches the fetus thyroid maternal blood circulation by placenta it is not neither enough nor effective, iodinated oil and salts supplementation should be advised (Tonglet *et al*., 1992).

There are reports of prenatal mortality which is originated by iodine deficiency. It is reported the mortality rate decreased following iodine supplementation through iodized oil prescription (Pharoah and Connolly, 1987; Cobra *et al*., 1997; Delong *et al*., 1997). The iodine within either the dietary or therapeutic regiments is absorbed in the small intestine and subsequently reaches to the thyroid gland, through blood circulation. The iodine following absorption by the thyroid gland oxidized through the peroxidase which is activated by Thyroid Stimulating Hormone (TSH). The oxidized iodine finally added to the tyrosyle residues on the thyroglobulin. The iodinated tyrosyle residues in the thyroid partly converted into MIT and DIT. It is only after the oxidized iodine incorporated into the tyrosyle resides structure of thyroglobuline and some of the synthesised MIT and DIT coupled and converted to T4 and T3, the Tg is digested by the protease enzymes of lysozomal apparatus of thyroid gland, it is then T4 and T3 and uncoupled MIT and DIT are released into the thyrocytes spaces. Thyroid hormones following production in the thyroid gland released into blood circulation and later on if the body required, in peripheral tissue some of T4 converted to T3, due to the fact that the T3 biologically is potentially more active than T4. The released MIT and DIT lose their iodine's, which can subsequently re-enter the oxidizing pathways to incorporate into Tg structure to produce thyroid hormones in new cycle of T4 and T3 formation (Cauvi *et al*., 2001).

Thyroid hormones following the physiological activity in peripheral tissues disintegrated and the released iodine is subsequently re-absorbed by the thyroid gland and incorporated into the Tg, to re- produce T4 and T3 if it is metabolically required.

The consequence of iodine deficiency on T4 and T3 production: Iodine deficiency and the side effects accompanied by major abnormalities, starting from early phases of life up to elderly age in both men and women. Females are more susceptible to iodine deficiency particularly during pregnancy (Mansourian *et al*., 2007; Mansourian, 2010b) as the pregnant women required an extra amount of thyroid, therefore an extra amount of iodine is required to produce the extra T4 and T3. It should be mentioned that iodine deficiency during fetus life is the direct consequence of iodine deficiency during pregnancy (Mansourian, 2010c). The lack of enough iodine within maternal circulation is associated with fetus brain damage (De-Escobar *et al*., 2004; Auso *et al*., 2004; Koibuchi and Chin, 2000; Chan and Kilby, 2000; Delange, 2000; Glinoer and Delange, 2000; Delange, 2001). The fetus brain most probably damaged by iodine deficiency which is an integral part of thyroid hormones which themselves are critically required for brain development, during fetus and also the hormones are strongly required for the brain growth and developments of neonates. The iodine's are not only required for the proper function but also well being physical growth of fetus, neonate and children are depend on enough iodine supplementation,

(Mansourian, 2010a; Dobbing and Sands, 1973; Montuori *et al*., 2000; Mansourian *et al*., 2010a; Mansourian, 2010b).

The prevalence of iodine deficiency is word-wide, the children worst affected are from Africa, followed by South East Asia and Eastern Mediterranean. The iodine deficiency also easily can be found in other part of the world including Europe and America. The prevalence of iodine deficiency is even worse in Europe among general population, (Maberly *et al*., 1981; Cao *et al*., 1994; Mansourian *et al*., 2010a; Mansourian, 2010b; Mansourian *et al*., 2007). There are various reports across the world on the urgent look at the status of iodine intake among children to prevent growth abnormality among them (Caldwell *et al*., 2005; Dobbing, 1974).

There are also some reports indicating iodine deficiency, eventually lead to infant mortality (Pharoah and Connolly, 1987; Cobra *et al*., 1997). This latter observation was reversed by iodine therapy and supplementation (Delong *et al*., 1997). The other vital iodine role, is that the thyroid hormone not only required for fetus brain development and prenatal period, but also the thyroid hormones are required for up two years of life for proper physical development of infant growth and children and they require higher amount of thyroid hormones and gradually the requirement reduced as the children getting older (Dobbing, 1974; Mansourian and Ahmadi, 2010).

Adult hypothyroidism due to lack of iodine with subsequent cardiovascular consequences due to elevated serum lipids and subsequent adverse effects such as arthrosclerosis and other related cardiovascular diseases are also reviewed (Mansourian *et al*., 2008; Mansourian, 2010b). The consequences of iodine deficiency and the subsequent thyroid hormone deficiency of adult population may not be similar to what happen to the neonate brain but other side effects on adults subjects are also disturbing and interfering with normal routine physiological of life (Mansourian *et al*., 2008; Mansourian 2010a). It should be also mentioned that in rare cases the elevated iodine can be a stimulating factor for thyroid hyperactivity in addition to other metabolic disorders but such thyroid disorders are not common and instead the bases for hyperthyroidism are other metabolic disorders including muddles, hyperplasia and (Mansourian, 2010d, e; Kotani *et al*., 1986).

The Thyroid Enzymes required for T4 and T3 Synthesis: The intra- cellular iodine concentration within the thyroid gland is 25 times more than the extra-cellular and the iodine actively transported into thyroid gland from blood circulation via Na/K pump which is itself activated by TSH.

The iodine following entry into thyroid, subsequently oxidized by the thyoperoxidase enzyme (TPO) within the thyroid gland. Thyoperoxidase is an oxidizing enzyme is used to covert the iodine into iodide with subsequent attachment to the tyrosyl residue of thyroglobuline molecule with eventual production of T4 and T3, according to pathways which was already explained. The thyroperoxidase activity is resided within thyrocytes cell membrane. Thyroperoxidase is an enzyme dependent on heme, an organic substance of tetrapyrol and iron atom in its center. The iron vacancy can be changed from 2 to 3 and reversibly from 3 to 2 and on doing this chemical reaction and simultaneous use of hydrogen peroxide (H_2O_2) as a co-substrate the iodine as reduced form converted to oxidized iodine. The heme structure in thyroperoxidase is the same structure as heme in hemoglobin, but in hemoglobin, the iron valancy should remain at 2 and on any condition in which the iron valance converted to 3, the meth-hemoglobin which is produced can no longer transfer the molecule of oxygen. Heme molecule is an integral part of thyroperoxidase and the enzyme activities completely relay on the presence of the heme group with the thyroperoxidase enzyme (Niepomniszcze *et al*., 1972; Portmann *et al*., 1985; Czarnocka *et al*., 1985).

Initially TPO was discovered from patients with thyroid auto-immune diseases and antibody is raised against TPO, with thyroid disorders (Ruf *et al*., 1987; Hamada *et al*., 1987; Kimura *et al*., 1987; Seto *et al*., 1987; Libert *et al*., 1987; Mansourian, 2010e). Thyroperoxidase gene expression is under the control of TSH which mediate its role through cyclic AMP (cAMP), (Fayadat *et al*., 1998; Alquier *et al*., 1989; De-Deken *et al*., 2000). Although thyroperoxidase is an intracellular enzyme, but its enzymatic activity is resided on the apical membrane within the thyroid gland (Bjorkman and Ekholm, 1992; Carvalho *et al*., 1996). Some factors are required for the enzymatic pathway of TPO, these are H_2O_2 as co-substrate and reduced nictoamid dinucleotide phosphate (NADPH) which is a co-enzyme produced through carbohydrate metabolism the pentose phosphate pathway (Carvalho *et al*., 1996; Nakamura *et al*., 1989; Dupuy *et al*., 1991; Kimura *et al*., 1995). The TPO activity is started in the presence of iodide and the H_2O_2 and the production of iodinated Tg occur through either one of the two postulated mechanisms related to peptide hormones, in here it is the phosphatidly inositol pathway (PI), which eventually increase the intracellular ionized calcium (Corvilain *et al*., 1994). Thyroid main function, which is the production of T4 and T3 depends to the enough

concentration of H_2O_2 although the high H_2O_2 concentration itself can be harmful to be thyroid cell, but thyroid is adapted to it through thyroid comprehensive mechanism to protect the thyrocyte from aggressive behavior of high dosage of H_2O_2 (Dunn and Dunn, 2008). The molecular mechanism and pathway leading to the production of H_2O_2 is highly complex and extensive investigation have been carried out on it at cellular and molecular levels and there are huge genetical and chromosomal-studies to uncover the much complex system of H_2O_2 producing pathways (Muresan and Arvan, 1997; Mercken *et al*., 1985; Spiro, 1977; Lenarcie *et al*., 2000; Kim and Arvan, 1998; Ohyama *et al*., 1994).

These latter investigation highlights the critical requirement of a separate enzymatic activity, which is triggered by cAMP dependent pathway which through a protein-kinas activate the enzyme responsible for the production of H_2O_2 within thyrocytes is activated. In other word it can be stated that it is the activation of enzymatic reaction to activate the protein-kinas with subsequent H_2O_2 production which can ultimately activate the TPO enzyme resulting in iodine oxidation and MIT and DIT formation, by transferring oxidized iodine on the tyrosyl residues of Tg to produce MIT and DIT with eventual production of T4 and T3. TPO facilitate the coupling of MIT and DIT to produce T4 and T3 on the Tg. Finally through endocyticis and lyzosmal reactions thyroid hormone separated from Tg and released into thyroid intracellular medium prior to secretion into blood circulation (Targovnik *et al*., 1995). There are some genetic studies, uncovering the bases behind some congenital hypothyroidism, which concentrate on the failed mechanisms which are responsible for thyroid malfunction and mostly related to the mutation of proteins and enzyme involved in the H_2O_2 production, leading to thyroid hormone deficiency, caused by the absence of enough H_2O_2 which is a cofactor for iodide oxidation.This latter observation is an important and absolute requirement step prior to MIT and DIT synthesis on Tg and eventual MIT and DIT coupling pathways. (Medeiros-Neto *et al*., 1996; Consiglio *et al*., 1987; Spiro and Gorski, 1986; Yamamoto *et al*., 1984; Ohyama *et al*., 1994).

Thyroglobulin is macro- protein which facilitate the production of thyroid hormones and iodine storage: Thyroglobulin (Tg), is a macroprotein whithin the thyroid gland containing about 5000 amino acids with about 115 tryosyle residue, the unique amino acid which only can have the ability to accept oxidized iodine and be converted to MIT and DIT, with subsequent T4 and T3 production. Tg also can be also considered as storage protein for iodine in the from of MIT and DIT. These latter iodinated substances can be regarded as storing iodine molecule and they can release their iodine for re-cycling to be oxidized again and used subsequently in new enzymatic pathway to re- synthesis T4 and T3 in thyroid gland (Medeiros-Neto *et al*., 1996).

The apical cell membrane and luman border in thyroid gland, is the original site for the production of tyrosyle iodination and T4 and T3 synthesis and the iodinated Tg site of storage is the luman follicular space. Genetically chromosome "eight" is the site where Tg derived from. There are extensive studies in this area of research which can give wide information and enlighten the whole spectrum of this complex mechanism (Mendive *et al*., 2001; Ohtaki *et al*., 1981; Cahmann *et al*., 1977; Lamas *et al*., 1974).

As the nature of a macroprotein such as Tg dicatate there should be enough cysteine amino acid residues to provide a strong and unique structure such as Tg, through the disulfide formation of high energy bond, required for such a huge molecule to have a integrated and unique biochemical structure. (Johnson and Tewkesbury, 1942; Gavaret *et al*., 1980; Gavaret *et al*., 1981). There are studies indicating that, there are inter-relationship between TPO, H_2O_2 generating system at genetical level and in some reports it is indicated that H_2O_2 might be responsible for the Tg and TPO, gene expression at chromosomal level (Kim *et al*., 1984; Fassler *et al*., 1988; Lamas *et al*., 1989).

Post- transitionally other modification should take place prior to full operational of Tg as backbone of thyroid hormone producing mechanism . Glycosylation seems to be a crucial post-transitional step forward prior for full activation of Tg. In practical term Tg is a glycoprotein which contain carbohydrate with the ratio of 1:10 in molecular weight (Dunn *et al*., 1983, De-Vijlder *et al*., 1992). Carbohydrate is required for the complete folding of Tg as huge macroprotein in follicular space of thyroid. In this regard there are extensive studies, indicating thyroid disorder may happen due to either malformed or misplaced Tg with eventual loss of thyroid hormones synthesis capability within the gland. (Robbins *et al*., 1959; Gire *et al*., 1996; Boeynaems *et al*., 1995).

How, eventually Tg and iodine produce T4 and T3: As it was mentioned earlier, the oxidized iodine covalently binds on to the some of 115 tyrosyle residues of Tg and produce iodinated tyrosyl residues. The requirement for this enzymatic reaction subsided by thyroperoxidase

enzyme and hydrogen peroxide as a co-substrate. The apical plasma membrane of follicle luman border line is the location where Tg is iodinated on tyrosil residues to produce MIT and DIT. The TPO enzyme in the iodinated Tg playing the corner stone playing a crucial role of meditation, by attaching to both ionized iodine and tyrosyle residue.It is subsequently accompanied by MIT production in first step followed by attaching two oxidized iodine to the tyrosyle residue molecule to produce DIT.

Other suggestions indicated that initially iodine binds to TPO and following oxidation of iodine by thyroperoxidase enzyme oxidized iodine-TPO complex bind on to tyrosyle residue of Tg to produce MIT and DIT on thyroglobulin.

Other idea based on the initial oxidation of iodine followed by attachment to the tyrosile residue with subsequent production of MIT and DIT is also suggested. Under any condition and proposal the oxidized from of iodine should be added to the some of tyrosyle residues on Tg to form MIT and DIT. Also it is reported that at any time only about 30% of all tyrosyle residues of Tg are participated in the iodination processes. There are also controversial argument as whether MIT and DIT are produced independently, or DIT are synthesized, following MIT initially is produced, and an oxidized iodine is added subsequently to synthesis MIT (Haeberli *et al*., 1978; Marriq *et al*., 1991).

T4 and T3 are produced following MIT and DIT coupling reactions: The final step prior to the release of thyroid hormone from thyroid through pinocytosis and lyzosomal function on the Tg is the coupling process of MIT and DIT and lysozmal function on the Tg, The coupling process of MIT and DIT on the Tg molecule can be as follow: [MIT+DIT => Triidothyronine(T3)] and [DIT + DIT => tetraidothyronine (T4)]. The reactions are catalyzed also by thyroperoxidase enzyme and the presence of hydrogen peroxide (H_2O_2) as a co-substrate (Ekholm, 1981; Dunn *et al*., 1982; Ofverholm and Ericson, 1984; Gerber *et al*., 1985; Herzog *et al*., 1992; Berndorfer *et al*., 1996; Virion *et al*., 1985).

The production site T3 and T4 on Tg is also on the apical plasma membrane of follicule luman border line. The production of MIT and DIT with subsequent coupling reaction to produce T3 and T4 have studied extensively and the one of main conclusion in various studies, indicated that T4 and T3 are produced on a regulated and homogenous distribution on the Tg molecule and not all the tyrosyle residues on Tg are iodinated simultaneously and again the iodine deficiency initially reduces the DIT with eventual reduction in T4 concentration (Alvino *et al*., 1995; Ercson, 1981; Marino and McCluskey, 2000; Pierce *et al*., 1985; Bernier-Valentin *et al*., 1990).

As a simple rule in thyroid gland, despite all complexity of thyroid hormones synthesis within the thyroid gland, it is the availability of iodine, which is considered to be the central dogma in T4 and T3 production within the thyroid gland (Consiglio *et al*., 1979).

Self-Regulation of thyroid in producing T4 and T3 by iodine: The main vital controlling systems on how the thyroid gland should work properly relay on the thyroid, and hypothalamus pituitary axes, which dictate the suitable and desirable production of Thyrotropin Releasing Hormone (TRH) with subsequent production of Thyroid Stimulating Hormone (TSH) and on conditions of any disruptions in either of the negative-feedback TRH-TSH-thyroid gland axes, other metabolic disorders such as autoimmunity to the thyroid, thyroid nodules, and cancer, all can alter the serum level of T4 and T3, leaving behind thyroid disorder enough to disrupt normal physiological life of affected persons (Mansourian 2010, a-e) . In addition to that the thyroid itself internally regulated the production of T4 and T3. The corner stone for the inhibition of thyroid hormone production is the excessive iodine concentration within the thyroid gland which can inhibit the enzymatic reactions responsible for thyroid hormone synthesis. This observation well- known as Wolff-Chaikoff effect (Wolff and Chaikoff, 1948; Corvilain *et al*., 2000). There are extensive studies and various proposals are offered in how extra iodine concentration in thyroid can prevent the T4 and T3 production in the gland. In one report it is indicated that extra iodine inhibit the TPO enzyme and prevent hydrogen peroxide formation, with subsequent disruption on thyroglobuline to be iodinated. On doing that, there is not nither coupling reactions nor thyroid hormones production (Consiglio *et al*., 1979), Other argues, that it is possible that elevated iodine within the thyroid gland, causes the iodination of some substances within the thyroid, such as lipids and convert the lipids into iodated lipids residues. The iodinated lipids complex in turn can interfere with the enzymatic system responsible for the production of hydrogen peroxide, a compound crucially is required for the oxidation of iodine through TPO prior to Tg iodination an essential step for thyroid hormone synthesis. (Marino *et al*., 2000; Lisi *et al*., 2003; Ericson and Engstrom, 1978; Engstrom and Ericson, 1981; Johanson *et al*., 1988; De-Vijlder *et al*., 1992).

The pathways of thyroid hormones secretion from thyroid gland: Following Tg iodination the iodinated Tg, consist of iodinated tyrosyle residues of MIT, DIT and thyroid hormones of T4 and T3. As it was stated earlier in the apical membrane, of luman border line enzymes and

co-substrate are available enough to trigger the synthesis of MIT, DIT. This step followed by coupling of MIT and DIT into T4 and T3 Tg, which now remain into follicule luman. The theory behind the high concentration of Tg within the follicule of thyroid, derived from the observation that in the follicle luman high ionized calcium concentration can easily bind to the Tg molecule, which is mainly contain acidic group capable of binding electro-statically to ionized calcium. It means the inonized Calcium (Ca^{2+}) and acidic protein which carrying negative charge interact with each other and produce a weak chemical bond. On paving the latter mechanism, thyroglobulin is conserved at high concentration in the follicle luman and provide the primary step for Tg iodination with eventual aim of T4 and T3 production on Tg molecule (Dunn and Dunn 1982a, b, 1988; Virion *et al*., 1981). Up till this point the Tg molecule containing idotyrosil residues of MIT, DIT and also thyroid hormones of T4 and T3 residues in the intra follicular space. It is reported that TSH can play a role to change the condition of iodinated Tg within follicular space (Dunn *et al*., 1991, 1996; Deme *et al*., 1978). On physiological requirement of body tissues and the regulation of basic metabolic rate and the crucial need of thyroid hormones, T4 and T3 should be released subsequently from the thyroid gland and reach the tissues most needed by the thyroid hormones, therefore T4, T3, MIT and DIT are released simultaneously, through Tg endocytosis from follicular space in intracellular region of thyroid cells and lysozomal reactions on Tg. Selmi and Rousset (1988). The Tg endocytosis is occurred through internalization, the process mainly vesicles facilitated mechanism itself and conducted by Thyroid Stimulating Hormone TSH (Rousset and Mornex, 1991). The latter mechanism is not a straight forward pathway and the final end point only achieved after the former vesicles converted to new orientation to facilitate the initial phase of endocytosis. The endocytic Tg subsequently go through different metabolic routes, with eventual, degradation by lysozomal reaction and the production of thyroid hormones of T4 and T3 with eventual release of thyroid hormone out of thyroid gland into the blood circulation. As one expect the entire process from iodine absorption from blood up to release of T4 and T3 into the circulation mediated, stimulated and regulated by TSH (Linke *et al*., 2002).

The ultimate fate of thyroglobuline in thyroid following T4, T3 production and the pathway of thyroglobulin presence in the blood circulation: There are extensive studies in this area of thyroid metabolism, which can be summarized as follow: 1) Part of internalized Tg by the process of endocytosis continue its metabolic pathway, to subsequent endocytic route, with eventual aim of lysozomal functions, followed by Tg disintegration, to provide T4 and T3. 2) There are Tg molecule containing either of low T4 and T3 concentration or hormone precursors, it seems that these forms of Tg returned back to the follicular lumen, by a vesicular translocation and finally reaching to the apical membrane. Tg also can eventually reaches the apical plasma membrane facilitated by the Golgi apparatus (Neve *et al*., 1970; Tietze *et al*., 1989l; Andersson *et al*., 1990).

The other possible mechanism is the transportation of Tg on the basolateral membrane location of thyrocytes which mediated by the vesicles formation in cytosol.

It is also reported that the Tg found within the plasma originated from this latter mechanism (Muresan and Arvan, 1998; Toyoda *et al*., 1992).

The Tg molecules which are supposed to be re-located back to the follicular domains, does this metabolic pathway through receptor mediated pathway due to low concentration of Tg. The receptor mediated metabolic pathway is not required for endocytosis of Tg in the initial step of thyroid hormone formation due to the high concentration of Tg (Rosenberg and Goswanii, 1979; Medeiros-Neto and Stanbury, 1994; Ohtaki *et al*., 1967).

The postulated theory of receptor binding to immature Tg with low thyroid hormones residues seems to be an acceptable package for recycling the Tg back into the follicular lumens and it is occurred through the carbohydrate residues and back bone recognition of by the Tg receptor (Montuori *et al*., 2000; Druetta *et al*., 1998).

The Tg receptor, structurally can be either a sialogycoprotein or N-acetyl glucosanine which distinguish the immature Tg to be recycled. On other hand TSH stimulate the Tg internalization, with subsequent colloid substance, with eventual delivery to the lysozomal, reaction pathway. Most interestingly the whole process of latter pathway mediated by 2nd messenger of TSH hormone well known as cyclic adenosine monophosphate pathway cAMP. (Druetta *et al*., 1999; Spencer, 2000; Ladenson *et al*., 1997; Schlumberger *et al*., 2000; McDougall and Weigel, 2001).

The mature Tg macromolecules are brake down by enzymatic reaction of lysozome and eventually T4 and T3 are released. In producing thyroid hormones from Tg. various enzymes of hydrolytic nature, are involved. (Robbins *et al*., 2001; Wartofsky *et al*., 2002; Mazzaferri *et al*., 2003). Following Tg cleavage by lysozome and subsequent T4 and T3 release from Tg within the thyroid the hormones released into blood circulation. The passage of thyroid hormones from

lysozomal membrane and subsequent secretion is not fully understand, but a thyroid hormone transporter in this pathway is postulated The release of free hormones into blood circulation and negative interrelation of serum T4 and T3 with TSH concentration is the corner stone for the control of T4 and T3 synthesis in the thyroid gland (Robbins *et al*., 2001; Wartofsky *et al*., 2002; Mazzaferri *et al*., 2003). In thyroid disorder such as hyperplastic thyroid, thyroid nodules and thyroid cancer, the serum Tg concentration is elevated. Serum Tg concentration is a valuable tool for the diagnosis of such thyroid disorder and an indicative of thyroid hyperactivity. Tg measurement can be a useful laboratory test for the identification of congenital and various multi-nodular goiters. The serum Tg assessments can also be used to follow the cycle and follow up of thyroid cancer (Druetta *et al*., 1999; Spencer, 2000; Schneider *et al*., 1983; Mazzaferri *et al*., 2003).

CONCLUSION

Tetraidotyronine(T4) and triidotyronine (T3) are the hormones synthesized in thyroid gland, on thyroglobulin macromolecule resided within the follicular space of thyroid. The oxidized iodine, which produced in thyroid, is added on thyrosyle residue of thyroglobulin, producing monoidothyrosine (MIT) and diidothyrosine (DIT),. T4 and T3 are synthesized following coupling of two latter iodinated tyrosyle residues on thyroglobulin and released from thyroid following thyroglobulin pinocytosis from follicular compartment and subsequent lysozomal biochemical enzymatic reaction on thyroglobulin.

Iodine is considered to be an integral part of T4 and T3, which is located on tyrosyle residues of thyroglobulin following oxidation in the thyroid gland by thyroperoxidase enzyme, itself activated by Thyroid Stimulating Hormone (TSH) a pituitary hormone responsible for thyroid function.Iodine deficiency eventually lead to reduced concentration of T4 and T3, which can have sever consequences particularly in fetus life up to elderly age.

Thyroperoxidase (TPO) enzyme is a thyroid enzyme activated by TSH, it is an oxidizing agent which can oxidize the iodine in the thyroid with cooperation of hydrogen peroxide (H_2O_2) a vital factor for this biochemical reaction. The iodine oxidation is crucial step prior to binding on tyrosyle residue on thyroglobulin and eventual production of T4 and T3.

The production of T4 and T3 essentially controlled through hypothalanius-pituitary axes and thyroid gland through a highly regulated negative-feedback mechanism. In healthy subjects in addition to negative feed-back relation between T4, T3 and TSH but there is, a self-regulatory system of T4 and T3 production within the thyroid gland is also existed. The excessive iodine concentration within thyroid gland in thyroid play a vital role in autonomous mechanism to control T4 and T3 synthesis through the inhibition of the thyroperoxidase enzyme reactions by the elevated iodine, with subsequent stoppage in T4 and T3 synthesis.

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