Introduction

During critical illness, changes in circulating hormones levels are common phenomenon. These alterations are correlated with the severity and outcome of patients in intensive care unit. Thyroid hormone plays a key role in the maintenance of the body growth, modulating metabolism and the immune system ***(Marx et al., 2003; Schuetz et al., 2009).***

Previous studies had found that thyroid dysfunction was associated with the mortality of the patients admitted to the ICU. These alterations of thyroid hormones referred to as the "sick euthyroid syndrome" or "non thyroidal illness syndrome (NTIS)" which is characterized as a low serum levels of free and total triiodothyroid (T3) and high levels of reverse T3 (rT3), accompanied by normal or low levels of thyroxine (T4) and normal or low levels of thyroid stimulating hormone ***(Docter et al., 1993).***

Subsequent studies confirmed the association between NTIS and adverse outcome in patients with sepsis, multiple trauma, acute respiratory distress syndrome, respiratory failure and mechanically ventilated patients, as well as in unselected ICU patients. However the performance of the thyroid hormones to predict adverse outcome in general ICU patients is unimpressive until now ***(Wang et al., 2012)***.

Some studies demonstrated the free triiodothyronine levels in non survivors was significantly lower as compared

with survivors while other studies shown that there was no association between FT3 levels and outcome of ICU patients ***(Ray et al., 2002).***

Conflicting results also existed in terms of other indicators, such as total triiodothyronine (TT3), total thyroxin (TT4) and TSH. Most of these studies were rather small and just evaluated the prognostic value of some but not the complete thyroid hormonal indicators. Until now, which one among the complete thyroid hormonal indicators is best for predicting ICU mortality has not been recommended. Limited studies detected the independent predictive ability of thyroid hormones or assessed additive ability of thyroid hormones to scoring system for predicting ICU mortality ***(Wang et al., 2012)***.

APACHE Π score and C-reactive protein (CPR) have been shown as independent predictors of ICU mortality. Whether thyroid hormonal indicators can predict ICU mortality independently of the both predictors is unclear. The performance of these variables to predict ICU mortality has not yet been compared ***(Wang et al., 2012).***

We will undertake a prospective, observational study in population of unselected ICU patients to detect the independent predictors of ICU mortality from the complete thyroid hormonal indicators (FT3, TT3, FT4, TT4 and TSH) and evaluate the ability of thyroid hormones additive to APACHE Π score to predict ICU mortality.

Aim of the Work

Thyroid hormone abnormalities are very common in critically ill patients, and this study should aim to clarify the role of the thyroid hormones abnormalities as predictors to the mortality outcome of ICU patients, confirming the association between the ability of thyroid hormones abnormalities additive to APACHE Π score to predict ICU patient's mortality.

Thyroid Gland Physiology

The thyroid gland weighs 10 to 20 grams in normal adults. Thyroid volume measured by ultrasonography (US) is slightly greater in men than women, increases with age and body weight, and decreases with increasing iodine intake ***(Hegedüs, 1990; Pankow et al., 1985).***

Synthesis and Secretion of the Thyroid Metabolic Hormones:

About 93 % of the metabolically active hormones secreted by the thyroid gland are thyroxin, and 7 % triiodothyronine. However, almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so that both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine ***(Hall, 2015).*** Thyroid hormones are reversibly bound to thyroid binding globulin (TBG) (0.04% thyroxine and 0.4% of triidothyronine is free form). Binding affinity of triidothyronine is 10 times greater than thyroxine.

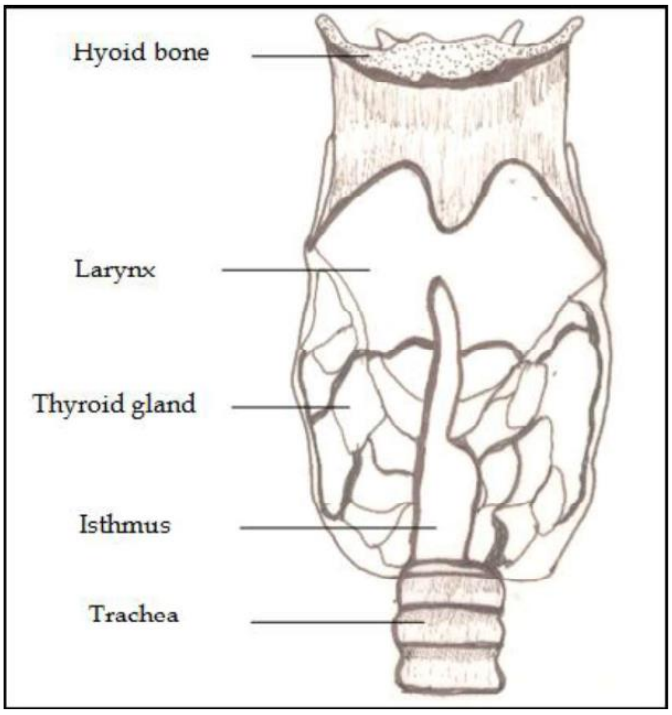

Figure (1): Showing anatomy of the thyroid gland ***(Ward, 2012)***.

Formation of thyroid hormones:

Biosynthesis of thyroid hormone is unique among endocrine glands because final assembly occurs extracellularly in the follicular lumen. The source of thyroid hormones (T4 and T3) is thyroglobulin (Tg), an iodo-protein produced by thyroid follicular cells. Thyroglobulin is the major portion of intraluminal colloid and is the most important protein of the thyroid gland ***(Kopp, 2005)***.

Iodide Pump (Iodide Trapping):

To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are

required each year, or about 1 mg/week. The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is called iodide trapping ***(Cooper, 2003; De La Vieja et al., 2000)***.

In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH ***(Bizhanoval and Kopp, 2009)***.

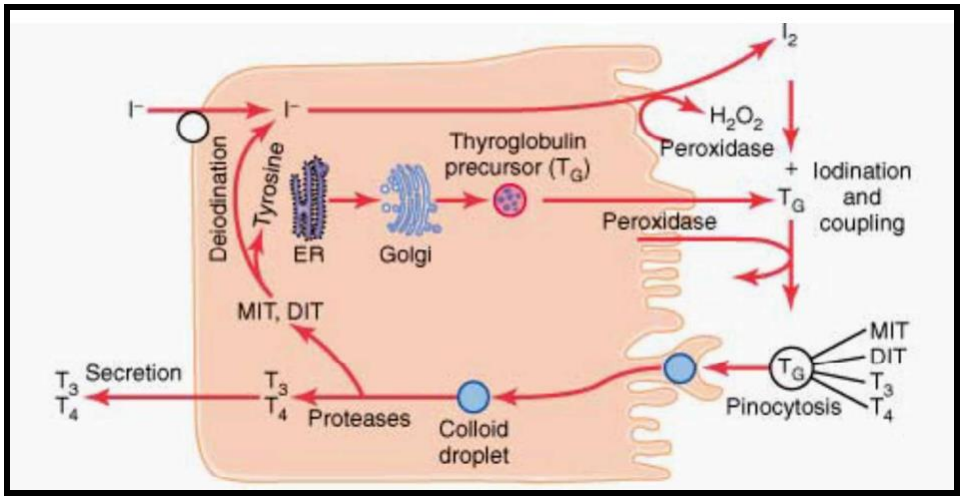

Figure (2): Showing Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood ***(Hall, 2015)***.

Formation and Secretion of Thyroglobulin by the Thyroid Cells:

The thyroid cells are typical protein-secreting glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin, with a molecular weight of about 335,000. Thyroglobulin is a 660 kilodalton (kd) glycoprotein composed of two identical noncovalently linked subunits. It is found mostly in the lumen of thyroid follicles ***(Arvan and Di Jeso, 2005).***

Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form within the thyroglobulin molecule. That is, the thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid ***(Hall, 2015).***

Iodination of Tyrosine and Formation of the Thyroid Hormones "organization" of thyroglobulin:

Iodide ions transported into the thyroid cells are oxidized before being used for iodinating tyrosyl residues present in the thyroglobulin molecule, a process called organification of the thyroglobulin ***(Principles and practice of endocrinology, 2001).***

Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become coupled with one another. The major hormonal product of the coupling reaction is the molecule thyroxine that remains part of the thyroglobulin molecule. Or one molecule of monoiodotyrosine couples with one molecule of diiodotyrosine to form triiodothyronine, which represents about one fifteenth of the final hormones ***(Hall, 2015)***.

Daily Rate of Secretion of Thyroxine and Triiodothyronine:

About 100 mcg of thyroglobulin is released from the thyroid each day. This is a tiny fraction of the 25 mg that must be hydrolyzed to yield the 100 mcg (130 nmoles) of T4 that is secreted each day ***(Van Herle et al., 1979).***

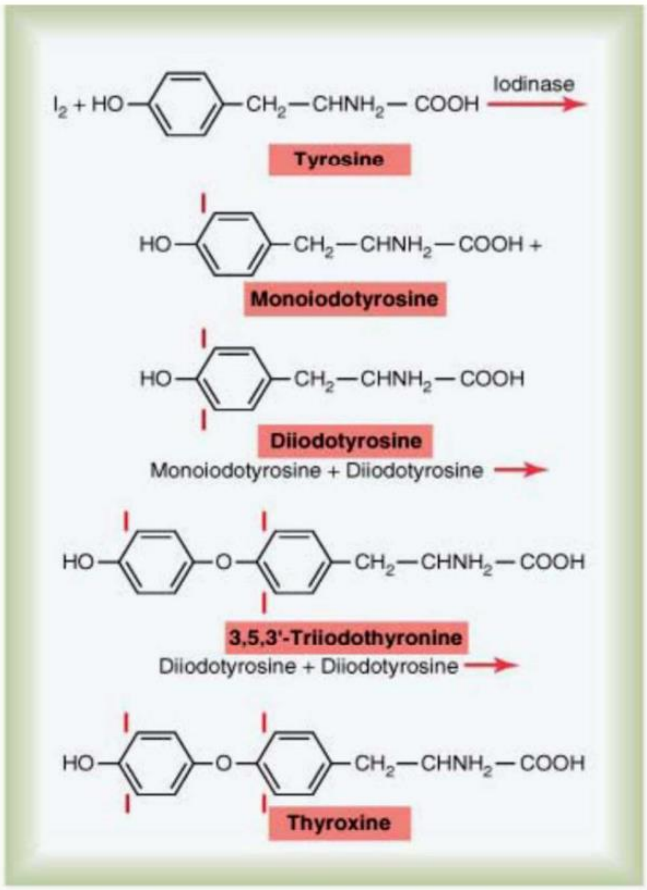

Figure (3): Showing the stages of thyroxine formation ***(Hall, 2015).***

The production rate of rT3 is 30 to 40 mcg (45 to 60 nmoles) daily, nearly all by extrathyroidal deiodination of T4. rT3 is degraded even more rapidly than is T3, mostly by deiodination ***(Engler and Burger, 1984).***

Transport of Thyroxine and Triiodothyronine to Tissues:

Thyroxine and Triiodothyronine Are Bound to Plasma Proteins, on entering the blood, over 99 % of the thyroxine and triiodothyronine combines immediately with several of the

plasma proteins, all of which are synthesized by the liver. They combine mainly with thyroxine-binding globulin and much less with thyroxine-binding prealbumin and albumin ***(Schussler, 2000).***

Thyroxine is bound to TBG in concentrations 10 to 20 times greater than T 3 and neither bound T 4 nor bound T 3 is directly available to tissues. Only unbound or "free" portions of T4 and T3 are metabolically available at the cellular level. The free portion of T 4 represents 0.02% to 0.05% of total serum T 4 and the free portion of T 3 represents 0.1% to 0.3% of total serum T3 ***(Benvenga, 2005).***

T3 is the biologically active form of thyroid hormone. Thyroxine's role in this process appears to be that of a prohormone, providing a readily accessible reservoir for conversion to T3 ***(Bianco and Larsen, 2005).***

At the cellular level, T3 is about twice as biologically active as T4, partly because T3 binds to thyroid receptors 10 to 15 times more than T4 ***(Yen, 2005).***

Physiologic Functions of the Thyroid Hormones:

Thyroid hormones (T4 and T3) regulate growth, development, and metabolism by affecting oxygen consumption and protein, carbohydrate, and vitamin metabolism. Around puberty, the effect on growth and development begin to wane, and in adults, thyroid hormones essentially affect only metabolism ***(Yen, 2005).***

Normal thyroid function, in terms of circulating levels of TT4, TT3, FT4, FT3, and the thyrotropin feedback system, appears to remain stable throughout life. Without intrinsic disease of the hypothalamic-pituitary-thyroid axis, age does not appear to have an adverse effect on the function of the thyroid gland or its component parts, in terms of serum concentration of T4 and T3 ***(Oiknine and Mooradian, 2006)***.

Although changes in measurable levels of total serum T4 and T3 do result from changes in transport protein concentrations, FT4 and FT3 levels remain mostly constant ***(Hassani and Hershman, 2006)***.

1- Effect of Thyroid Hormone on Growth:

Thyroid hormone has both general and specific effects on growth. In humans, the effect of thyroid hormone on growth is manifest mainly in growing children. TH is critical for normal bone growth and development. In children, hypothyroidism can cause short stature and delayed closure of the epiphyses. Biochemical studies have shown that TH can affect the expression of various bone markers in serum, reflecting changes in both bone formation and resorption ***(Mosekilde et al., 1990; Allain and Mcgregor, 1993)***.

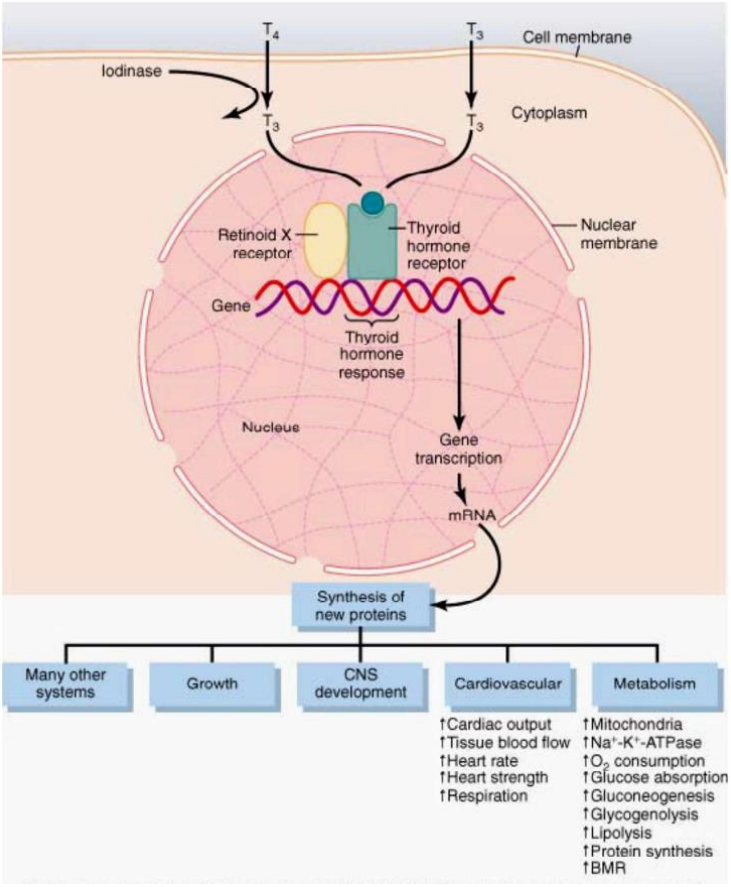

Figure (4): Thyroid hormone activation of target cells. Thyroxine (T4) and triiodothyronine (T3) readily diffuse through the cell membrane ***(Hall, 2015).***

2- Effects of Thyroid Hormone on Specific Bodily Mechanisms:

a) Stimulation of Carbohydrate Metabolism:

Thyroid hormone stimulates almost all aspects of carbohydrate metabolism, including rapid uptake of glucose by the cell enhanced glycolysis, enhanced gluconeogenesis, increased rate of absorption from the gastrointestinal tract, and

even increased insulin secretion with its resultant secondary effects on carbohydrate metabolism ***(Yen, 2001; Chidakel et al., 2005)***.

b) Stimulation of Fat Metabolism:

Essentially all aspects of fat metabolism are also enhanced under the influence of thyroid hormone. In particular, lipids are mobilized rapidly from the fat tissue, which decreases the fat stores of the body to a greater extent than almost any other tissue element. This also increases the free fatty acid concentration in the plasma and greatly accelerates the oxidation of free fatty acids by the cells ***(Hall, 2015).***

c) Effect on Plasma and Liver Fats:

Increased thyroid hormone decreases the concentrations of cholesterol, phospholipids, and triglycerides in the plasma, even though it increases the free fatty acids. Conversely, decreased thyroid secretion greatly increases the plasma concentrations of cholesterol, phospholipids, and triglycerides and almost always causes excessive deposition of fat in the liver as well. The large increase in circulating plasma cholesterol in prolonged hypothyroidism is often associated with severe atherosclerosis ***(Hall, 2015).***

d) Increased Basal Metabolic Rate:

Thyroid hormone regulates metabolic rate and is associated with modest change in body weight. Because thyroid

hormone increases metabolism in almost all cells of the body, excessive quantities of the hormone can occasionally increase the basal metabolic rate 60% to 100% above normal. Conversely, when no thyroid hormone is produced, the basal metabolic rate falls almost to one-half normal ***(Fox et al., 2008; Ortega et al., 2007)***.

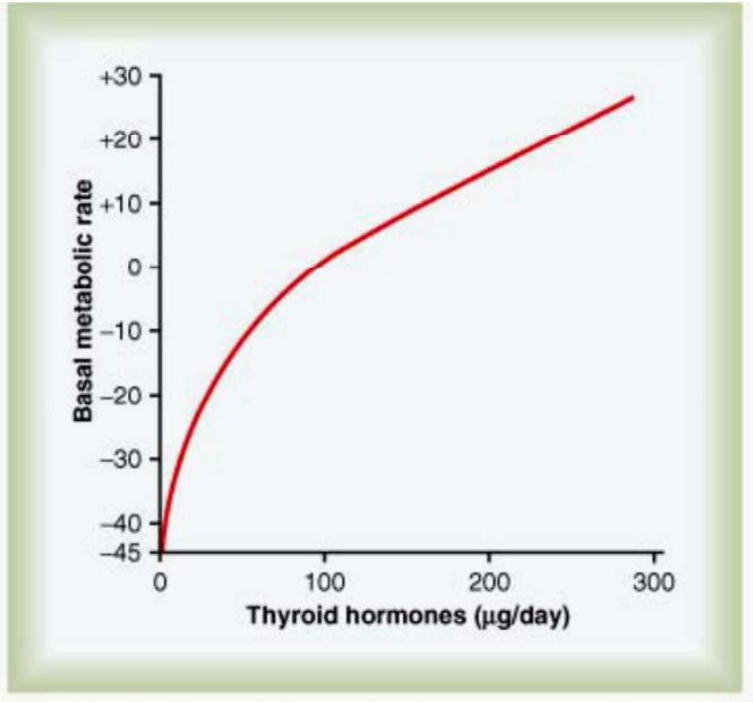

Figure (5): Showing approximate relation of daily rate of thyroid hormone (T4 and T3) secretion to the basal metabolic rate ***(Hall, 2015)***.

3- Effects of Thyroid Hormone on Heart:

TH lowers systemic vascular resistance, increases blood volume, and has inotropic and chronotropic effects on cardiac function ***(Kahaly and Killmann, 2005).***

The combination of these effects on both the circulation and the heart itself results in increased cardiac output. Hyperthyroid patients have a high output circulation state, whereas hypothyroid patients have low cardiac output, decreased stroke volume, decreased vascular volume, and increased systemic vascular resistance ***(Klein and Ojamaa, 1998).***

4- Effects of Thyroid Hormone on Respiration:

The increased rate of metabolism increases the utilization of oxygen and formation of carbon dioxide; these effects activate all the mechanisms that increase the rate and depth of respiration ***(Hall, 2015)***.

5- Effects of Thyroid Hormone on Central nervous system:

Thyroid hormone increases the rapidity of cerebration; conversely, lack of thyroid hormone decreases this function. The hyperthyroid individual is likely to have extreme nervousness and many psychoneurotic tendencies, such as anxiety complexes, extreme worry, and paranoia ***(Williams, 2008)***.

Regulation of Thyroid Hormone Secretion:

The thyroid participates with the hypothalamus and pituitary in a classic feedback control loop. In addition, there is an inverse relationship between the iodine level in the thyroid and the fractional rate of hormone formation. To maintain