Study of Serum Total T3 Level in Hepatitis C Related Cirrhosis and It is Relation to Severity of Liver Disease

Thesis
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Abstract

This study was aimed to determine the serum level of total T3, in patients with hepatitis C related cirrhosis and to correlate it with severity of liver disease and it is complication including hepatic encephalopathy.

This study included 45 patients divided into three groups:

Group I included 15 patients with Child Pugh classification A, **Group II** included 15 patients with Child Pugh classification B and **Group III** included 15 patients with Child Pugh classification C.

Patients were subjected to full medical history and clinical examination, Child Pugh classification & MELD scoring, abdominal ultrasonography, laboratory evaluation including CBC, liver and kidney function tests, serum electrolytes, ESR and tT3 ; and in case of any abnormalities, complete thyroid profile will be done for them .

Number of patients with low tT3 increased with severity of liver cirrhosis inclused in Child Pugh classification progress and MELD score. There were statistically high significant negative correlation between total T3 and Child Pugh score and with MELD score. The tT3 exhibited excellent ability to predict coma, prolonged INR $\geq$ 1.7 and good ability to predict the presence of ascites.

Key words:

Total T3.liver cirrhosis. Model for End-Stage Liver Disease. Child Pugh classification.

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List of Abbreviations

AITD	:	Autoimmune thyroid disease
Alb	:	Albumin
ALT	:	Alanine aminotransferase
ANA	:	Anti nuclear antibody.
anti HBc	:	Anti hepatitis B core
anti HCV Ab	:	Anti hepatitis C virus antibodies
anti-HBs	:	Anti hepatitis B surface
Anti-LKM Ab	:	Anti- liver-Kidney-muscle antibody
AST	:	Aspartate aminotransferase
Bil	:	Bilirubin
CTP	:	Child-Tuurcotte-Pugh
FT3	:	Free triiodothyronine
FT4	:	Free thyroxin
GD	:	Graves' disease
HBV	:	Hepatitis B Virus.
HCV	:	Hepatitis C virus.
HLA	:	Human leukocytic Antigen.
HPS	:	Hepatopulmonary syndrome
HT	:	Hashimoto's thyroiditis
IgG	:	Immunoglobulin G
LC	:	Liver Cirrhosis
MELD	:	Model of end stage liver disease
NAFLED	:	Non alcoholic fatty liver disease
NIS	:	Sodium iodide symporter
PBC	:	Primary biliary cirrhosis
PC%	:	Prothrombin concentration
PSC	:	Primary sclerosing cholangitis
TABs	:	Thyroid autoantibodies
Tg	:	Thyroglobulin
THs	:	Thyroid hormones
TPO	:	Thyroid peroxidase
TREs	:	Thyroid hormone response elements
TRH	:	Thyrotropin releasing hormone
TRs	:	Thyroid hormone receptor
TSH	:	Thyroid stimulating hormone
TSHr	:	Thyroid stimulating hormone receptor

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Introduction

The great majority of patients with acute hepatitis C develop chronic HCV infection. It can ultimately result in liver cirrhosis, hepatic failure (portal hypertension, ascites, and encephalopathy) or hepatocellular carcinoma **(Lee et al., 2012).**

Porto systemic encephalopathy is considered as a serious complication of chronic liver disease and is broadly defined as an alteration in mental status and cognitive function occurring the presence of liver failure **(Antaki et al., 2010)**.

Liver plays an important role in the metabolism of thyroid hormones, as it is the most important organ in the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) by type I iodinase resulting to 5 deiodination of T4. Moreover, it is involved in conjugation and circulation of thyroid hormones by synthesis of thyroid binding protein **(Sorvillo et al., 2003)**.

It was found that the decrease level of total T3 reflect severity of liver cell failure and hepatic encephalopathy **(Vezali et al., 2009)**.

Aim of The Work

Aim of this study will be to study level of total T3, in patients with hepatitis C related cirrhosis and to correlate it with severity of liver disease and it is complication including hepatic encephalopathy.

Chapter (1)

The Thyroid Gland

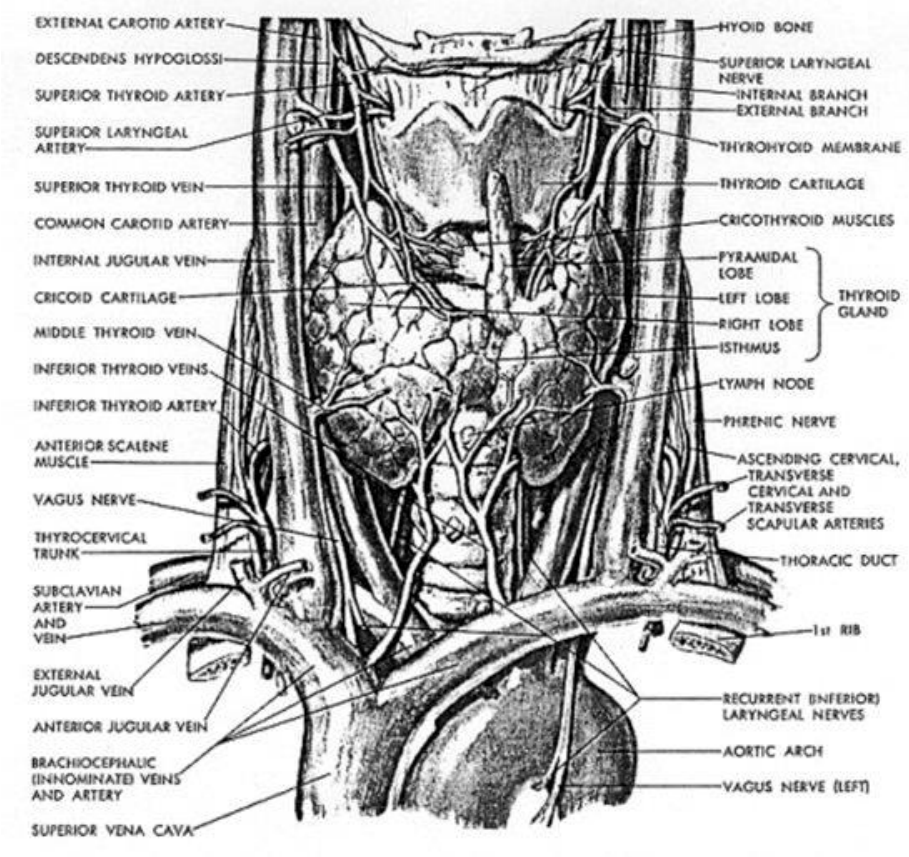

Fig. (1): Thyroid Anatomy ***(Felice & Lauro, 2004)***

Anatomy of thyroid:

The thyroid is a brownish-red and highly vascular gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic. The gland varies from an H to a U shape (with an average height of 12-15 mm) overlying the second to fourth tracheal rings (**Felice & Lauro, 2004)**.

Arterial supply:

From the superior and inferior thyroid arteries and, occasionally, the thyroidea ima artery **(Cummings et al., 1998)**.

Venous Drainage:

Pairs: superior, middle, inferior veins **(Cummings et al., 1998)**.

Lymphatic drainage:

To the periglandular nodes, to the prelaryngeal (Delphian), pretracheal, and paratracheal nodes **(Felice & Lauro, 2004)**.

Innervation:

Principal innervation of the thyroid gland derives from the autonomic nervous system. Parasympathetic fibers come from the vagus nerves, and sympathetic fibers are distributed from the superior, middle and inferior ganglia of the sympathetic trunk (**Felice & Lauro, 2004)**.

Histology:

The lobules are composed of follicles, enclosing a colloid-filled cavity, contains iodinated glycoprotein, iodothyroglobulin, a precursor of thyroid hormones **(Dumont et al., 2005).**

Principal cells (ie, follicular: and parafollicular cells (ie, C, clear, light cells: produce the hormone calcitonin **(Felice & Lauro, 2004)**.

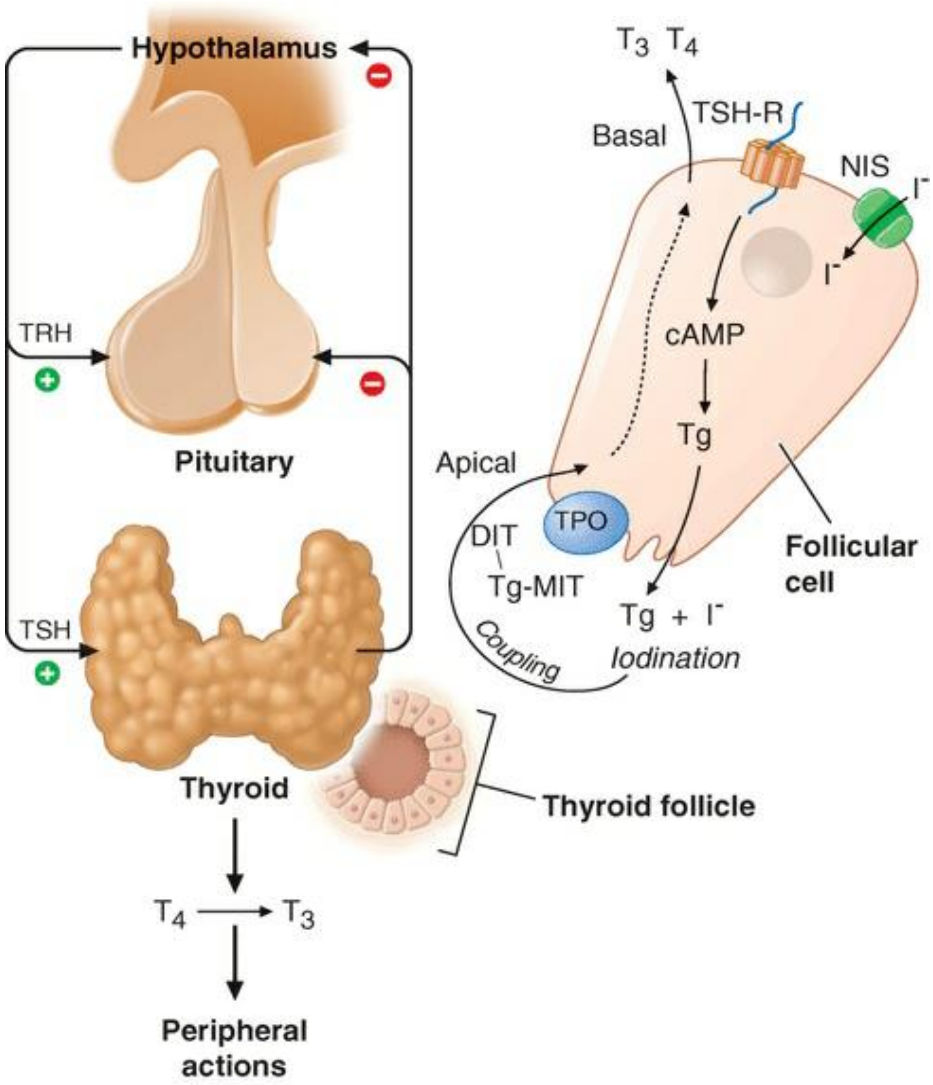

Fig. (2): Thyroid Axis (Fauci et al., 2008).

Left: Thyroid hormones T4 and T3 feed back to inhibit hypothalamic production of thyrotropin-releasing hormone (TRH) and pituitary production of thyroid-stimulating hormone (TSH). TSH stimulates thyroid gland production of T4 and T3. **Right**: Thyroid follicles are formed by thyroid epithelial cells surrounding proteinaceous colloid, which contains thyroglobulin. Follicular cells, which are polarized, synthesize thyroglobulin and carry out thyroid hormone biosynthesis (see text for details)**.** TSH-R, thyroid-stimulating hormone receptor; Tg, thyroglobulin; NIS, sodium iodide symporter; TPO, thyroid peroxidase; DIT, diiodotyrosine; MIT, monoiodotyrosine (**Fauci et al., 2008).**

The thyroid axis: is a classic example of an endocrine feedback loop. Hypothalamic TRH stimulates pituitary production of TSH, which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones, acting predominantly through thyroid hormone receptor 2 (TR 2), feed back to inhibit TRH and TSH production. The "set-point" in this axis is established by TSH (**Fauci et al., 2008)**

Organification, coupling, storage, release:

After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide. The reactive iodine atom is added to selected tyrosyl residues within Tg. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T4 or T3 can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines. After coupling, Tg is taken back into the thyroid cell, where it is processed in lysosomes to release T4 and T3. Uncoupled mono- and diiodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones (**Jameson et al., 2010).**

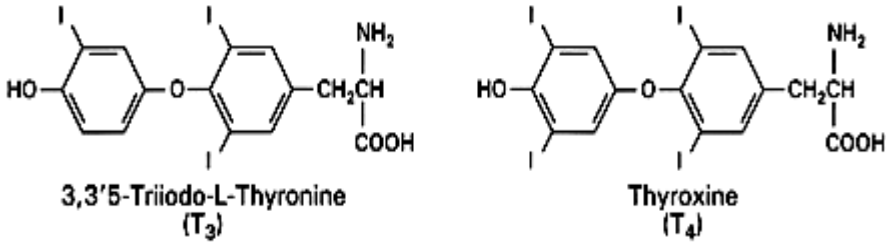

Fig. (3): Structure of the thyroid hormones **(Larry and Anthony, 2010).**

The majority of released TH is in the form of T4, as total serum T4 is 40-fold higher than serum T3 (90 vs. 2 nM). Only 0.03% of the total serum T4 is free (unbound), with the remainder bound to carrier proteins such as

thyroxine binding globulin (TBG), albumin, and thyroid binding prealbumin. Approximately 0.3% of the total serum T3 is free, with the remainder bound to TBG and albumin. It is the free TH that enters target cells and generates a biological response **(Jameson et al., 2010).**

The major pathway for the production of T3 is via 5'-deiodination of the outer ring of T4 by deiodinases and accounts for the majority of the circulating T3 **(Jameson et al., 2010).**

Other factors affect thyroid synthesis and release:

Although TSH is the dominant hormonal regulator of thyroid gland growth and function, a variety of growth factors, most produced locally in the thyroid gland, also influence thyroid hormone synthesis. These include insulin-like growth factor I (IGF-1), epidermal growth factor, transforming growth factor (TGF-), endothelins, and variouscytokines. Iodine deficiency increases thyroid blood flow and upregulates the NIS, stimulating more efficient iodine uptake. Excess iodide transiently inhibits thyroid iodide organification, a phenomenon known as the Wolff-Chaik off effect **(Boelaert, 2005).**

Thyroid hormone effects on target tissues:

A.Bone:

TH can affect the expression of various bone markers in serum, reflecting changes in both bone formation and resorption. TH increases alkaline phosphatase and osteocalcin in osteoblasts (**Oetting and Yen, 2007).**

B.Heart:

TH lowers systemic vascular resistance, increases blood volume and has inotropic and chronotropic effects on cardiac function **(Gregory, 2012).**