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Chapter 8

Non-Thyroidal Illness: Physiopathology and Clinical Implications

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1. Introduction

In critical illness, several abnormalities in thyroid hormone (TH) secretion, metabolism and action have been described in patients without previous diagnosis of intrinsic thyroid disease and are collectively called "Non thyroidal syndrome" (NTIS) [1]; this term is now largely employed, in the place of "euthyroid sick syndrome" [2-4] or "low-T_3 syndrome", due to the most common abnormality, a decreased level of serum total triiodothyronine (T_3), which can be detected very early, within 2 hours after the onset of severe physical stress [5-7]. However, T_3 lowering is only one of the endocrine picture described is such a situation; therefore the term NTIS seems to be more appropriate, also strengthening its extrathyroidal source.

NTIS has been depicted in about 70% of hospitalized patients for different diseases [8-10]. Moreover, the severity of morbidity and outcome in patients studied in intensive care unit (ICU) has been correlated with the alteration in thyroid function [11,12]. The hormonal response exhibits different pattern in acute and chronic phase, since in the first phase the alteration predominate in peripheral metabolism of TH, while in the latter central mechanisms controlling thyroid secretion progressively arise [13,14].

Since there is no clear evidence of tissue hypothyroidism, such a condition seems to be an adaptative response, and thyroid replacement therapy is not usually required, but this topic is still debated, since indirect signs of true hypothyroidism at tissue levels have been showed [15]. The question is open and different reviews have been published on this topic [1, 16-20]; but, very recently different molecular mechanisms have been shown to gain insight the complex situation of NTIS. The role of intracellular oxidative stress (OS) has

been underlined. Therefore we present a review of these recent results and some personal data in patients affected by chronic obstructive pulmonary disease and patients studied after major cardiovascular surgery.

2. Clinical observations

A low T_3 state has been described in a variety of clinical situations, such as starvation [21], sepsis [22], surgery [23], trauma [24], myocardial infarction and heart failure [25,26], cardiopulmonary bypass [27], respiratory failure [28], bone marrow transplantation [29], other severe illness [30]. In a very recent paper in unselected ICU patients, free T_3 (fT_3) was the most powerful and the only independent predictor of ICU mortality, with a prognostic improving value when added to APACHE II score [31]. A retrospective study in a large group of patients treated with mechanical ventilation (MV) confirmed that NTIS represents a risk factor for prolonged MV [32].

Due to the importance of TH in **cardiac function**, it is not surprising that cardiac patients have been extensively studied under this profile. TH influence cardiac function with different mechanisms: inotropic and chronotropic positive effect via nuclear and non-nuclear pathways in cardiomyocytes, increase in cardiac contractility through augmented tissue oxygen delivery and consumption; decrease in systemic vascular resistance, through direct TH action on vascular smooth muscle cells; other endocrine effects are exerted on renin-angiotensin-aldosterone axis and on erythropoietin secretion [19, 33].

One of the early studies was performed in patients serially followed after acute myocardial infarction; a sustained and prolonged decrease of total T_3 (TT_3) and fT_3 was described, while TT_4 but not fT_4 showed a transient decrease; thyroxine binding globulin (TBG) levels remained unchanged, while thyroxine binding prealbumin (TBPA) and albumin exhibited a prolonged fall. TSH, despite low T_3, did not increase, remaining inappropriately low [34]. In this sense, the increase of TSH was shown to be correlated with a good prognosis [35].

It has been reported that patients with heart failure have low T_3 serum concentrations, which correlate with cardiac function [36]. In advanced heart failure, a low fT_3 index/reverse T_3 ratio was associated with higher right atrial pulmonary artery and pulmonary capillary wedge and lower ejection fraction [26].

Low T_3 syndrome has been considered a strong predictor of death and directly implicated in poor prognosis of cardiac patients in a large group of patients admitted in a cardiology department [37].

TH are implicated in metabolic function of myocardial cells; they have been shown to inversely correlate with Coenzyme Q_{10} (CoQ_{10}), a component of mitochondrial respiratory chain, also endowed with powerful antioxidant properties [38]. Preliminary data of our group in patients studied after major heart surgery showed low T_3 levels concurrently with signs of tissue hypothyroidism (elevated CoQ_{10} levels) [39]. In fact we found CoQ_{10} levels, evaluated by high

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performance liquid chromatography (HPLC), in the hypothyroid range, despite the fact cardiac diseases are well known to be associated with low CoQ_{10}.

The studies in **pulmonary disorders** have not been so extensively investigated [40-42]. In the just cited paper, low T_3 state was again considered a predictor of outcome in respiratory failure [28]. Among chronic conditions, no conclusive data are reported on chronic obstructive pulmonary disease (COPD), as reported in a recent review [43]. No clear evidence of thyroid function alteration has been reported in such a condition [44], although in patients with severe hypoxemia a strong positive correlation between total T_3/total T_4 ratio (TT_3/TT_4) and PaO_2 has been described [45]. Increased fT_3 concentrations have been reported in stable COPD, with a positive association to $PaCO_2$ [46], while others reported lower total T_3, fT_3 and TT_3/TT_4 ratios in patients with severe hypoxemia [47]. Low Forced Expiratory Volume at 1st second (FEV_1) is associated with low basal and stimulated levels of thyroid stimulating hormone (TSH) [48]; however the impact of hypoxemia on TSH response to exogenous thyrotropin releasing hormone (TRH) is controversial [45,46].

We have recently studied patients with COPD, evaluating lung parameters and antioxidant parameters, due to a possible involvement of OS in NTIS (see below). COPD is a complex condition, which cannot be considered a lung-related disorder, but rather a systemic disease also associated to increased oxidative stress. We evaluated thyroid hormones and antioxidant systems, the lipophilic CoQ_{10} and total antioxidant capacity (TAC) in COPD patients to reveal the presence of a low-T_3 syndrome in COPD and investigate the correlation between thyroid hormones, lung function parameters and antioxidants. The evaluation of CoQ_{10} was particularly interesting, also for the energetic role of this molecule, which is a component of the mitochondrial respiratory chain, as above stated; its concentrations were also corrected for cholesterol, due to its lipophilic nature. We studied 32 COPD patients and 45 controls; CoQ_{10} was assayed by HPLC; TAC by the metmyoglobin-ABTS method and expressed as latency time (LAG) in radical species appearance. We found significantly lower LAG values, fT_3 and fT_4 levels and significantly higher TSH in COPD patients vs controls. LAG values significantly correlated with fT_3 concentration. Twelve out of 32 patients exhibited fT_3 levels lower than normal range. When dividing COPD patients in two groups on the basis of the fT_3 concentration (normal fT_3 COPD and low fT_3 COPD), we observed lower LAG values in normal fT_3-COPD, compared to healthy subjects, with a further significant reduction in low fT_3-COPD patients. Moreover higher TSH concentrations were present in normal fT_3-COPD, compared to healthy subjects, with a further significant increase in low fT_3-COPD patients. CoQ_{10}/cholesterol ratio was higher in low fT_3-COPD vs normal fT_3-COPD, with a nearly significant difference.These data seem to indicate an increased oxidative stress in low fT_3-COPD and a role of fT_3 in modulating antioxidant systems. However low fT_3 levels are joined to metabolic indexes of true hypothyroidism, suggesting that elevated CoQ_{10} expresses a reduced tissue utilization. Interestingly, there was no significant difference in lung parameters when comparing normal- or low-fT_3 COPD patients, according to the definition of COPD as a systemic disease, with respiratory parameters unable to define the severity of disease. In fact metabolic dysfunctions (i.e. osteoporosis, vascular and cardiac involvement, muscle impairment) play a role in the natural history of disease but were found poorly related to respiratory impairment,

underlying the need of indexes related to a real tissue condition; the pattern of fT_3 could indicate such a situation, as reinforced by the pattern of CoQ_{10} levels; decreased plasma antioxidant capacity and increased CoQ_{10} levels in low fT_3-COPD again suggested a possible condition of hypothyroidism at tissue levels [49].

The thyroid function has been investigated in patients with acute **kidney injury**. TSH levels inversely correlated with urea concentrations. 82.9% of patients exhibited alteration in thyroid function, especially low-T_3. This picture was ameliorated by improvement of renal function. No prognostic role was attributed to this dysfunction [50].

Primary hypothyroidism (non-autoimmune) is often observed in patients with chronic kidney disease (CKD); in particular the prevalence of subclinical hypothyroidism is related to GRF decline [51]. The earliest and the most common thyroid function abnormality in CKD patients is a low T_3 level (especially TT_3 than fT_3) [52]. The mechanisms for T_3 decrease in this condition are: fasting, chronic metabolic acidosis and chronic protein malnutrition, influencing T_4 deiodination, as well as protein binding of T_3. Moreover, inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 inhibit the expression of type 1 5′-deiodinase (see below), which is responsible for peripheral conversion of T_4 to T_3 [53]. Alteration of renal handling of iodine can increase serum iodine levels, causing a prolonged Wolff – Chaikoff effect [54]. A prognostic role has been attributed to the hormonal marker: the low fT_3 levels in CKD patients have been correlated with higher levels of markers of inflammation [highly sensitive C-reactive protein (hsCRP), IL-6, etc.], malnutrition (lower prealbumin, IGF-1), increased endothelial dysfunction, poorer cardiac function, poor survival, and higher all-cause as well as cardiovascular mortality in some studies [53, 55].

Little is known in TH alterations in acute **liver failure** (ALF) [56]. An animal model was investigated (pigs subjected to surgical liver devascularisation). In this case serum T_4 and T_3 levels were markedly decreased, but fT_3 and TSH did not change. The downregulation of T_4 and T_3 levels during ALF seems to correlate well with the severity of disease and was also related to alteration in parameters of inflammation, oxidative stress and myocardial thyroid receptors; thus the mechanisms in this case seem to be very complex. In humans acute liver failure (ALF) is accompanied by hormonal implications, as has been recently shown for the hepatoadrenal syndrome [57], since an unexpected incidence of adrenal failure was discovered in ALF and post-transplantation patients; a glucocorticoid treatment can influence outcome. Thyroid function alterations have been described during chronic liver failure [58-60]; a low T_4-variant of NTIS has been described in a subgroup of patients with cirrhosis at risk for decreased survival [58]; serum levels of fT_3 and TT_4 (but not TT_3 and fT_4) were significantly lower in patients with hepatic encephalopathy compared to decompensated cirrhotic patients without encephalopathy [60]. Much less clear data are available for ALF [61, 62]. In cirrhotic and also in acutely ill patients from various etiologies, derangements of thyroid hormones are common (up to 79% in the latter group, as reported from autoptic observations) [63].

Finally, during **starvation** (especially carbohydrate deprivation) deiodination of T_4 to T_3 is rapidly inhibited, causing the low-T_3 syndrome [1, 21, 64]. Interestingly, caloric deprivation can be also a major factor influencing TH in severe illness, as demonstrated in bacterial sepsis [65].

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A particular model is that of eating disorders, especially anorexia nervosa, in which low-T_3 is accompanied by a constellation of hormone alteration, index of hypothalamic derangement [66]. Other psychiatric models should be considered with caution when evaluating thyroid alterations, due to other interfering factors, such as the underlying psychiatric disorder, substance abuse or other medications [67].

On the basis of the reported studies and other reviews [68, 69] we can summarized the main variations in the pituitary-thyroid axis as reported in Fig. 1, according to the severity of NTIS.

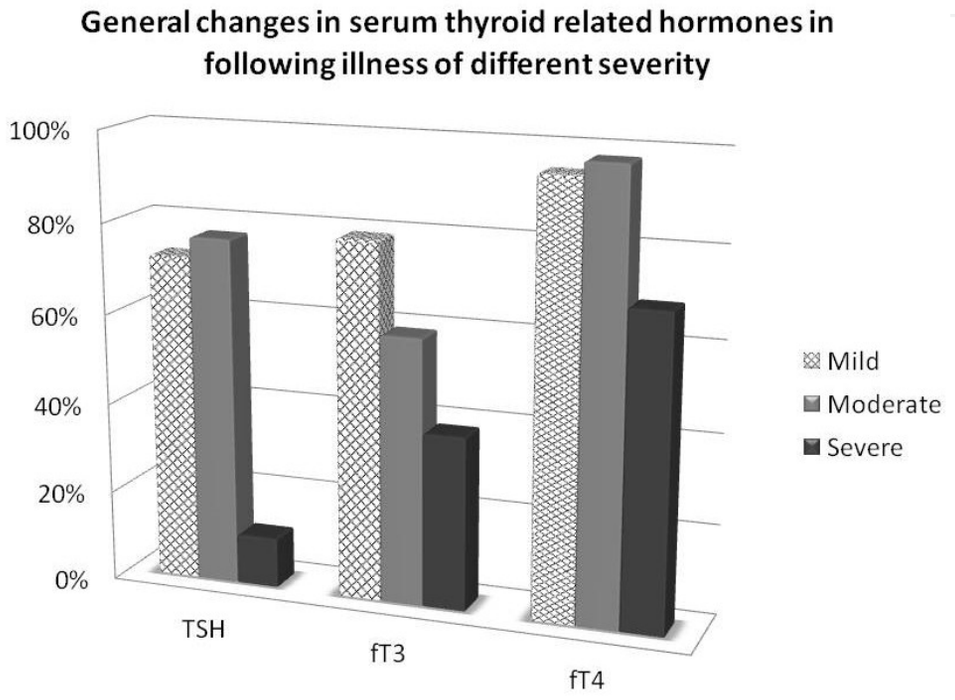

Figure 1.

3. Physiopathological mechanisms

Various mechanisms are responsible for the TH pattern observed in different situations, keeping in mind the difference between "acute" and "chronic" phases and possible differences related to the underlying diseases. They can summarize in four categories: central TSH regulation, TH blood transportation, peripheral metabolism by deiodinases, actions at receptorial and post-receptorial levels.

a. Central regulation of TSH

Basal TSH levels are usually normal or low, but not extremely inhibited [1, 70, 71]; in most cases they are inadequate in respect to thyroid hormone levels. The response to TRH is variable, ranging from blunted to normal response [72, 73]; the response to TRH, even in presence of

low basal level, can be interpreted as a sign of hypothalamic dysfunction, according to data concerning other hormones (gonadotropins, ACTH-cortisol axis) [13, 74]. Absence of circadian rhythm has been reported [75]. The variation of glicosilation is responsible for reduced bioactivity [76]. The finding that TH alterations are partially reversed by the combined infusion of TRH and GH secretagogues [77] reinforces the role of central component of NTIS.

b. Transportation

Also transportation of thyroid hormones is altered; Thyroxine binding globulin (TBG) has been shown to be reduced, probably for increased cleavage by proteases. The binding to transport protein is also negatively influenced by inhibitors (not only in serum, but also in tissues), therefore influencing the metabolism of TH [1]. Recently, decrease of TBG, determined by RIA or radioimmunodiffusion, albumin and transthyretin (TTR) have been described in septic patients [78]; therefore the total binding power of serum is low, in the view of authors, without the need to postulate the effects of additional factors, such as binding inhibitors or modification of binding affinity.

c. Deiodinase

A lot of studies concern the activity of deiodinases, the main group of enzymes, which by removal of iodine, catalyze activation or inactivation of TH. They are selenoproteins, members of the thioredoxin family, and require a thiol cofactor for their activity [20,79]. The activation of prohormone T_4 into the biologically active hormone T_3 is catalyzed by type 1 (D1, encoded by DIO1) and type 2 (D2, encoded by DIO2) via deiodination of the outer ring; on the contrary, the removal of inner ring iodine is catalyzed by type 3 (D3, encoded by DIO3), causing inactivation of both T_4 and T_3 [80]. In humans, 80% of circulating T_3 comes from deiodination by D1 and D2, while the other 20% comes directly from thyroid secretion. The most common alteration in NTIS patients is a decrease in T_3, caused by reduced conversion of T_4 to T_3 [81]. The Deiodinase 1 is down regulated, as demonstrated in liver, causing reduced T_3 generation [1]. Deiodinase 3 is instead increased, as observed in liver and muscle, especially in the case of low tissue perfusion, and the conversion of T_3 to reverse-T_3 (rT_3) is a mechanism reinforcing the low T_3 levels [80]. However, central and peripheral deiodinases are differently regulated; T_3 in the pituitary are normal since local deiodinaton is enhanced, thus the pituitary is actually euthyroid and therefore TSH circulating levels inappropriate to other tissue fT_3 levels [1]. The role of D3 has recently been reviewed [82]. Moreover more recent studies focused on modulation of deiodinases activity, rather than their levels (see below).

d. Thyroid receptors and Postreceptorial mechanisms

It has been shown that thyroid hormone receptors (TR) are down-regulated in skeletal muscle of patients with non-septic shock; in particular they showed lower expression of TR-β, TR-α_1 and their nuclear partner retinoid X receptor γ (RXRG) [83]. The RXRA gene expression was higher, even if its protein was lower, suggesting the existence of post-transcriptional mechanisms that down-regulate protein levels. Nuclear factor of kappa light chain enhancer of activated B cells (NkFB), a transcriptional factor involved in immune and inflammatory response, attenuates the induction of DIO1 by T_3 [84]; however NkFB1 activation was not

different in comparison to control subjects. However the results are not unequivocal, since there results were not reproducible in cultures of human smooth muscle cells (HSkMC) incubated with the patients' serum [83].

Molecular mechanisms of thyroid action in NTIS have been recently investigated in other models, studying, other than TR, also the transporters, which allow TH to be transported across the plasma membrane in order to be metabolized and interact with their receptors. Monocarboxylate transporter 8 (MCT8) has been shown to be a very active and specific transporter [85]. Moreover, other proteins modulate the transcription function of TR, acting as coactivators or corepressors; among the latter the silencing mediator of retinoid and TR (SMRT) via histone deacetylation [86]. In patients with septic shock, skeletal muscle expression of TR-β1, RXRG and D2 was lower than in control group and RXRA was higher. In subcutaneous adipose tissue, the authors found lower MCT8, TRHB1, THRA1, RXRG and SMRT and higher UCP3 expression, suggesting decreased thyroid hormone action [87].

Interestingly, the reduced expression of TH transporters has been considered a compensatory mechanism (rather than a cause of low-T_3), strongly suggesting a real hypothyroidism at tissue levels in such a condition [88].

4. The role of cytokines

The role of cytokines, as key molecules involved in coordinating the hormone, immune and inflammatory response to a variety of stressful stimuli, has been largely investigated [1].

In a series of septic patients studied shortly after admission to an ICU, TT_4, fT_4, TT_3 and TSH were depressed, and IL-1B, sIL-2R and TNFα were elevated [89] suggesting central suppression of TSH, even if the relationship with cytokines was not so clear. The hypothalamic-pituitary-adrenal axis was activated as expected. It has been shown that continuous infusion of IL-1 in rats cause suppression of TSH, T_3 and fT_4; higher doses of IL-1 were accompanied by a febrile reaction and suppression of food intake, with a cascade of events altering thyroid hormone economy [90], but IL-1 did not reproduce the decrease in hepatic 5'-deiodinase activity believed to be characteristic of NTIS.

TNF is another proinflammatory cytokine that is thought to be involved in many of the illnesses associated with NTI. Infusion of rTNF in man produced a decrease in serum T_3 and TSH and increase in r T_3 [91]. These studies suggest that TNF could be involved in the IL-6-mediated activation of hypothalamic-pituitary axis. Also in this case other data did not confirm the role of TNF, since the effects of endotoxin of TH in humans were not counteracted by the TNFα blockade by specific IgG fusion proteins [92]. TNFα was found during in vitro studies to activate NkFB [93], which in turn inhibits the T_3-induced expression of D1 as above reported.

On the contrary, an important role has been attributed to IL-6, which is often elevated in serum of NTIS patients [94] and its level is inversely related to T_3 levels [95]. Short term infusion of rIL-6 to human volunteers [96] caused a suppression of TSH, but daily injections over 42 days cause only a modest decrease in T_3 and a transient increase in r T_3 and in fT_4 concentrations.

More recent evidences on the role of IL-6 have been reported by studies in human cell lines: the effects of IL-6 on both endogenous cofactor-mediated and dithiotreitol-stimulated cell sonicate deiodinase activity have been studied [80]. In this model T_3 generation by D1 and D2 was suppressed by IL-6, despite an increase in sonicate dediodinases (and mRNAs): this inhibitory action was prevented by addition of N-acetyl-cysteine (NAC), an antioxidant that restores intracellular glutathione (GSH) concentrations. The interest of the paper is also the link of deiodinase activity and OS (see below).

Finally, the potential interaction between the complex network of cytokines and the hypothalamic pituitary thyroid axis, even if is not possible to build a simplistic model, probably plays a pathogenetic role in NTIS [1]. The role of cytokines in eating disorders and related TH alterations has also been reviewed [97].

5. Oxidative stress in NTIS

Previous studies have shown that both hyperthyroidism and hypothyroidism are associated with enhanced oxidative stress involving enzymatic and non-enzymatic antioxidants [98]. Besides, some complications of hyperthyroidism are due just to the oxidative stress in target tissues [99]. Thyroid hormones *per se* can act as oxidants and produce DNA-damage (contrasted by catalase), probably through the phenolic group, similar to that of steroidal estrogens [100]. Many other mechanisms, reviewed by Venditti & Di Meo [101], can be involved, with a specificity in tissue response. We recently reviewed the relationships between thyroid hormone, OS and reproduction [102].

At a systemic level, also in humans, hyperthyroidism has been associated with reduced circulating levels of alpha-tocopherol [103, 104] and Coenzyme Q_{10} [38, 104]. Coenzyme Q_{10} showed a trend to increase in hypothyroidism [38]; it appeared to be a sensitive index of tissue effect of thyroid hormones, in situations in which drug interference, such as amiodarone [105] or systemic illness inducing a low-T_3 conditions [106] complicate the interpretation of thyroid hormone levels. However, data on hypothyroidism in humans are conflicting [102]. Baskol et al showed in a group of 33 patients with primary hypothyroidism elevated malondialdehyde (MDA) and nitric oxide (NO) levels and low paraoxonase (PON1) activity, while superoxide dismutase (SOD) was not different from controls. Interestingly, thyroid treatment decreased MDA and increased PON1, without reaching levels observed in controls [107]. They concluded that a prooxidant environment in hypothyroidism could play a role in the pathogenesis of atherosclerosis in such patients. Elevated MDA levels were also shown in subclinical hypothyroidism [108]; the increased in OX was attributed to lack of antioxidants but also to altered lipid metabolism, since MDA showed a correlation with LDL-cholesterol, total cholesterol and triglycerides. Total antioxidant status (TAS) was similar in overt hypothyroidism, subclinical hypothyroidism and controls.

Another study [109] showed increased levels of thiobarbituric acid reactive substances (TBARS), but also of antioxidants, such as SOD, catalase (CAT) and Vitamin E. All these parameters correlated with T_3; moreover the correlation between T_3 and CAT remained

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significant also when corrected with total cholesterol. This datum was not confirmed by other authors [110, 111]. We showed low Total Antioxidant Capacity (TAC) levels in hypothyroid patients and increased CoQ_{10} levels also in secondary hypothyroidism (mainly due to its metabolic role in mitochondrial respiratory chain and therefore underutilized in hypothyroid tissue). In the last case, hypothyroidism has a predominant effect on the possible decreasing effect of OS [112].

Different conditions with NTIS are associated to OS, due to augmented production of radical oxygen species (ROS) or nitrogen species [113]; since thyroid hormones, as above stated, can increase ROS generation, OS could be viewed as a compensatory mechanism since, decreasing metabolic rate, could protect against further radical generation. A reducing environment is maintained in the cytosol by intracellular thiols, especially GSH and Thioredoxin (TRX), which, as we have seen, are cofactors for deiodinases. Therefore their depletion, due to buffering effect against radical propagation, could interfere with the conversion of T_4 to T_3 [79]. Moreover, another reported mechanism is the nuclear sequestration of the SECIS binding protein 2 (SPB2), which reduces incorporation of selenocysteine residues in the selenoproteins [114]. IL-6 is known to induce OS, therefore an unifying hypothesis is cytokine-induced OS and a secondary alteration of expression and activity of deiodinases [79]. However further studies can clarify these complex interaction and especially the potential role of antioxidant in protecting against OS in NTIS.

On the basis of the physiopathological studies above reported, we can conclude that the alterations of pituitary-thyroid axes do not only depend from the severity of the disease, but also from the nutritional status of the patients and their inflammatory response, also related to oxidative stress (see fig. 2).

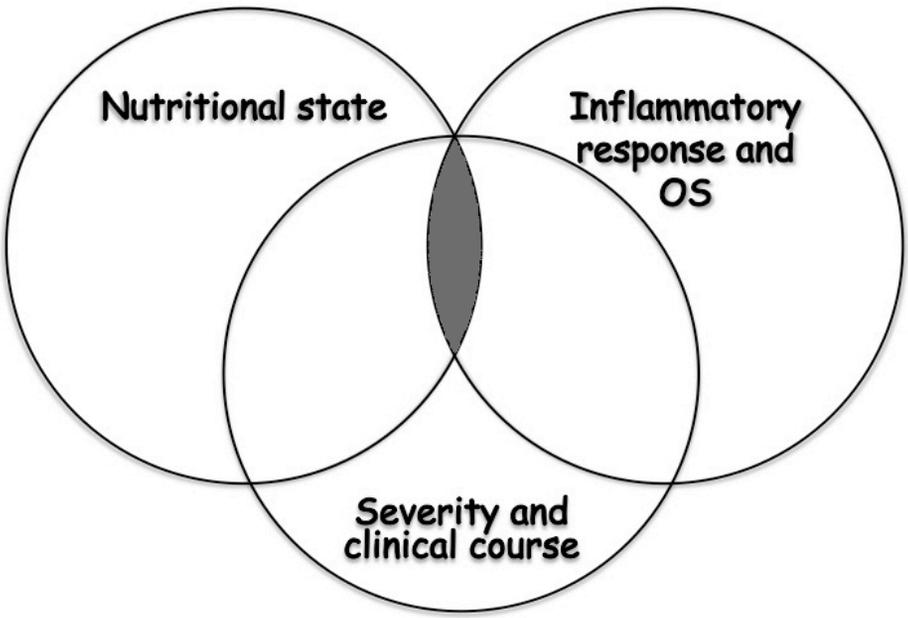

Figure 2. Interaction of factors influencing pituitary-thyroid axis

6. Treatment

Controversial results have been reported on the topic of replacement therapy. The replacement therapy with 1.5 μg/Kg BW L-thyroxine iv was able to restore normal T_4 levels, but not T_3 levels, without effect on mortality, which remained at 80% both in treated patients and control groups [115]. Similarly, another study in burns, using 200 μg T_3/daily, did not show significant benefits [116].

Despite studies in animals were in favour of a positive effect in experimental renal failure [1], in humans an increased mortality was showed in a group of acute renal failure treated with L-thyroxine and no beneficial effect of T_3 was observed in transplanted patients [117,118].

Studies in humans showed a slight cardiovascular benefit in patients with shock, respiratory disease, coronary artery bypass draft, premature infants [1, 119].

The discrepancies in the reported study, however, can be attributed to different severity of low-T_3, different schedule of treatment, clinical situations with very different physiopathology, so that it is difficult to obtain a definitive conclusion.

Other interventional studies are reviewed by Bello et al. [19], showing in their complex a beneficial effects on cardiovascular parameters, but not unequivocal benefit of patients' outcome. In fact, in patients with dilated cardiomyopathy, the administration of TH significantly increased left ventricular end-diastolic volume and stroke volume while decreased heart rate [120]. In patients studied after coronary artery bypass surgery, the administration of intravenous T_3 or placebo produced an increase in cardiac output and lowered systemic vascular resistance, without influencing the patients' outcome and therapeutic schedules [121]. In contrast, another study [122] performed after elective coronary artery bypass grafting showed a beneficial effect of intravenous T_3 administration on incidence of postoperative myocardial ischemia and on need for pacemakers or mechanical cardiac support devices. It must be reminded that the administration of TH can directly influence myocardial oxygen supply and demand, causing myocardial ischemic events, even in the absence of coronary artery stenosis or spasms, as reported in some cases [123].

Similar conclusions, biochemical rather than clinical advantage, were drawn in a group of patients after acute burn injuries [124].

7. Conclusion

In conclusion, we cannot answer the dilemma, just poned by eminent authors [125,126], about the treatment of low T_3 in NTIS. Some data argue in favour of a real hypothyroidism at tissue level in NTIS; therefore this condition cannot be simply considered an adaptive response. Probably, a full understanding of molecular mechanisms, which cause or are a consequence of low T_3 levels, will allow choosing patients who can really have a benefit from replacement therapy and the appropriate schedule of treatment.

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