

## Non Thyroidal Illness Syndrome

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**Definition:** Non thyroidal illness syndrome, also called “low T3 syndrome, is a syndrome characterized by changes in serum thyroid hormone in the absence of hypothalamic-pituitary-thyroid primary dysfunction. Patients affected have low fT3, usually elevated rT3, normal or low TSH, normal T4 levels, and, if prolonged, low fT4. For the presence of normal levels of fT4 and TSH is known as “euthyroid sick syndrome”. It’s found in very ill patients, both acute and chronic illness, pulmonary, gastrointestinal, cardiac pathologies, in traumatized patients, sepsis, in old sarcopenic patients, in fact is present in 75% of hospitalized patients.

**Pathophysiology:** Normally the activation of the prohormone T4 into the biologically active hormone T3 is catalysed by type 1 (D1) and type 2 (D2) deiodinase. In contrast, type 3 deiodinase (D3), catalyses the inactivation of T3 into reverse T3 (rT3) and T3 into its form biologically inactive. So D3 contributes to thyroid hormone homeostasis, protecting tissue from excess of thyroid hormone. In this syndrome we can find a decrease D1 and D2 activity with a consequent reduction of T3’ production and an augmented D3 activity in liver and skeletal muscle of sick patients with a consequent increase in rT3 production. This is probably due to increase of inflammatory cytokines such as IL-6, IL-1 and TNF-alfa implicated in oxidative stress generation. These pro-inflammatory cytokines elicit an oxidative burst with the increase in superoxide radical O<sub>2</sub> production that disrupts deiodinase function. The reduction of T3 is associated with

low levels of TSH and TRH: this is probably due to an altered expression of hypothalamic iodothyronine deiodinase D2 and D3 with consequent increase of cerebral T3 that suppress TSH and TRH production and the physiological nocturnal surge of TSH; so in the acute phase of critical illness we can see low fT3 and high reverse T3 levels associated with normal levels of T4 and TSH; as the disease progresses T4 levels decrease, too, associated with normal or decreased TSH levels. In patients with low T3 levels the risk of mortality is about 23%; it increases until 80% if T4 levels fall down.

**Symptoms:** Symptoms are a specific and often similar to hypothyroidism, often due to underlying pathology, such as hypothermia, impaired ventilation, sensory disturbances, hydro electrolytic imbalances.

**Treatment:** Finally, treat or no treat? It is still a controversial matter. Some authors have advocated they would benefit from thyroid hormone replacement because intratissular hypothyroidism would lead to exacerbation of the pathology itself. In the contrast, the augmented thyroid hormone levels due to hormone replacement increase the metabolic activity of all the tissue: this lead to excessive amounts of ROS and superoxide radical. Thus, lowering thyroid hormone could decrease the energy expenditure and contribute to calorie-sparing economy, and the reduction of metabolic state protects cells against further increase of free radicals. For its protective role it is preferred not to treat thyroid decompensating but only underlying pathology.