LOW TRIIODOTHYRONINE IN METABOLIC AND INFLAMMATORY STRESS: A CONTEXT-DEPENDENT MODEL OF THYROID ADAPTATION

Biletska O.M.[1], Golka G.G.[1], Danylchenko S.I.[1, 2], Arestova T.V.[3], Shevchenko A.S.[1, 4]

[1]Kharkiv National Medical University, Kharkiv, Ukraine
[2]Kherson State University, Kherson–Ivano-Frankivsk, Ukraine
[3]V.N. Karazin Kharkiv National University, Kharkiv, Ukraine
[4]Kharkiv Regional Institute of Public Health Services, Kharkiv, Ukraine

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ABSTRACT

Background. Low triiodothyronine status has been described in a wide range of physiological and pathological conditions, including energy restriction, critical illness, and systemic inflammation. In the literature, these alterations are commonly referred to as the low T_3 state. Traditionally, they have been interpreted within the framework of the Non-Thyroidal Illness Syndrome (NTIS). However, accumulating experimental and clinical evidence suggests that a similar biochemical phenotype may arise in different systemic contexts through distinct regulatory mechanisms. Thus, low triiodothyronine status may be considered a context-dependent phenotype of systemic adaptation that develops under diverse metabolic and immune conditions.

Aim. To summarize current pathophysiological concepts of low triiodothyronine status in systemic inflammatory and metabolic stress, to analyze their limitations, and to propose an integrative context-dependent model of thyroid adaptation.

Materials and Methods. The study is a literature review. A bibliographic analysis of scientific literature published between 2015 and 2025 was conducted using the PubMed, Scopus, ScienceDirect, Google Scholar, and MEDLINE databases. The following keywords were used: adaptive physiological processes, deiodinases, thyroid hormones, energy metabolism, cytokines, and allostatic load. Clinical, experimental, and review studies meeting contemporary evidence-based medicine standards were included in the analysis. The study was conducted as a private initiative of the authors, without grant support and state registration of the topic.

Research Ethics. This review was conducted using previously published studies performed in accordance with current bioethical standards.

Results. Analysis of the literature indicates that most current concepts interpret low T_3 either as an energy-saving adaptive response or as a marker of disease severity. At the same time, the role of the immune system as an active regulatory component of thyroid homeostasis remains insufficiently addressed. The present review proposes a context-dependent model of thyroid adaptation, according to which an identical biochemical phenotype of low T_3 may develop under different systemic conditions – energy deficit or systemic inflammation – through distinct regulatory mechanisms. Particular attention is given to the integration of neuroendocrine, metabolic, and immune signals, including the roles of cytokines, deiodinases, and the potential involvement of iodine-dependent mechanisms of innate immunity. A central element of the proposed model may be the functional interaction between the thyroid axis and phagocytic activity.

Conclusions. Low triiodothyronine status should be considered a context-dependent phenotype of systemic adaptation that emerges from interactions between metabolic, immune, and neuroendocrine regulatory processes. The proposed model expands current understanding of the mechanisms underlying low T_3 and provides a conceptual framework for future mechanistic and clinical studies.

Keywords: *endocrinology, literature review, deiodinases, thyroid hormones, energy metabolism, cytokines*.

Corresponding Author:
Biletska Olga M. – MD, DMedSc, Professor, Professor of the Department of sports, physical and rehabilitation medicine, physical therapy and occupational therapy of the Kharkiv National Medical University, Ukraine.
✉ 4, Nauky ave., Kharkiv, 61022, Ukraine.
E-mail: om.biletska@knmu.edu.ua

Introduction

Low circulating Triiodothyronine (T_3) levels are a common metabolic feature observed under conditions of systemic stress of various origins. This phenomenon has been well documented in severe infections, sepsis, trauma, and a range of chronic diseases [1–4]. At the same time, both experimental and clinical evidence, including early

observations during starvation [3; 5], suggests that a similar hormonal pattern may also develop in the absence of systemic inflammation. In this context, reduced serum T_3 can be viewed as part of a broader neuroendocrine-metabolic adaptation, mediated by different regulatory mechanisms depending on metabolic and immune conditions [1; 2].

Current understanding of thyroid hormone metabolism at the tissue level – including the role of deiodinases, cytokine signaling, and neuroendocrine regulation – indicates that changes in thyroid homeostasis are part of complex adaptive responses [4–8]. In this review, the term "low T_3 state" is used as a general concept describing reduced T_3 levels across different physiological and pathological settings. In the presence of systemic inflammation, this corresponds to Low T_3 Syndrome (LT3S) or Non-Thyroidal Illness Syndrome (NTIS) [1–3], whereas in conditions of energy deficiency it may represent an adaptive metabolic variant of the low T_3 state.

Thus, reduced T_3 levels can be viewed as a context-dependent adaptive phenotype shaped by metabolic and immune signals. In this review, we propose a model in which a similar hormonal profile may arise both in energy deficiency and in systemic inflammation through distinct regulatory mechanisms.

Aim and Objectives

The **aim** of this study was to summarize current pathophysiological concepts of the low triiodothyronine state in systemic inflammatory and metabolic stress conditions and to propose an integrative, context-dependent model of thyroid adaptation.

To achieve this aim, we addressed the following **objectives**:

1) to review experimental and clinical data on changes in thyroid homeostasis during systemic inflammation and critical illness;

2) to summarize the role of metabolic factors, particularly energy deficiency, in the development of the low T_3 state;

3) to examine regulatory mechanisms at the level of tissue thyroid hormone metabolism, including deiodinase activity, cytokine signaling, and neuroendocrine interactions;

4) to compare the characteristics of low T_3 in metabolic versus inflammatory stress;

5) to propose a conceptual model of context-dependent thyroid adaptation integrating metabolic, immune, and neuroendocrine mechanisms.

Materials and Methods

This study is based on a narrative review of the literature on thyroid homeostasis in systemic inflammatory and metabolic stress conditions. Literature search was performed using PubMed, Scopus, ScienceDirect, Google Scholar, and MEDLINE, covering the period from 2015 to 2025. The search included the following keywords and their combinations: adaptive physiology, deiodinases, thyroid hormones, energy metabolism, cytokines, and allostatic load.

We included clinical, experimental, and review studies addressing changes in thyroid hormone regulation in systemic inflammation, critical illness, energy deficiency, and related metabolic stress conditions. Preference was given to peer-reviewed publications indexed in major scientific databases. The selected studies were analyzed in the context of current understanding of tissue thyroid hormone metabolism, deiodinase activity, cytokine-mediated regulation, and neuroendocrine-metabolic interactions. Data were synthesized using a qualitative analytical approach.

Results

1. Evolution of concepts of thyroid homeostasis regulation under stress

Current understanding of the low triiodothyronine state in different stress contexts – particularly under conditions of energy restriction and systemic inflammation – has developed within broader concepts of internal regulation and adaptation. The foundations of these approaches were laid by Claude Bernard (1878) [11], who introduced the concept of the *milieu intérieur* as the relative stability of the internal environment required for cellular function. This idea was further developed by Walter B. Cannon (1932) [12], who formulated the concept of homeostasis and emphasized the role of feedback mechanisms as a universal principle of physiological regulation.

A major step forward came with the conceptualization of adaptation as a systemic response to stress within the framework of the general adaptation syndrome proposed by Hans Selye (1936; 1946) [13; 14]. In this model, the Hypothalamic–Pituitary–Adrenal (HPA) and Hypothalamic–Pituitary–Thyroid (HPT) axes were viewed as key components of neuroendocrine integration, coordinating metabolic and hormonal responses to various stressors.

Advances in integrative physiology have significantly expanded these concepts, showing that the regulation of thyroid homeostasis under stress

is a multi-level process involving interactions between neuroendocrine, metabolic, and immune signals (*Fig. 1*). In particular, activation of the HPA axis may be driven not only by classical neural mechanisms but also by mediators of the functional system that becomes dominant in a given physiological or pathological context [15; 16]. For example, during psycho-emotional stress, neurotransmitter-mediated regulation plays a central role, whereas in inflammatory conditions, cytokine-driven immune signaling pathways become the primary drivers [1; 17].

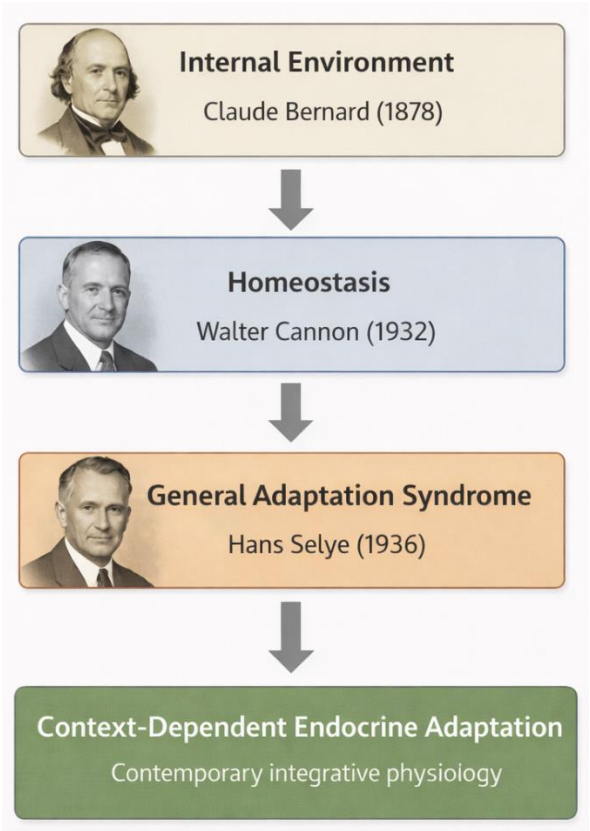

Fig. 1. Evolution of concepts of thyroid homeostasis regulation under stress

Within this framework, thyroid-related changes observed under stress conditions should not be viewed solely as isolated endocrine disturbances, but rather as part of broader adaptive processes in which the systemic metabolic or inflammatory context modulates both neuroendocrine regulation and tissue-level thyroid hormone metabolism.

Current concepts of the low T_3 state have evolved alongside general theories of physiological regulation – from the early idea of internal stability to modern models of context-dependent endocrine adaptation.

2. Metabolic-adaptive variant of low T_3 in energy deficiency

In this context, thyroid adaptation can be viewed as a variable, context-dependent process. Under conditions of reduced energy availability, decreased T_3 levels are primarily associated with adaptive energy conservation, driven by reduced triiodothyronine production with relatively preserved metabolic clearance of the hormone [18; 19].

This hormonal profile is generally interpreted as a manifestation of adaptive metabolic remodeling of thyroid regulation. Reduced circulating T_3 is accompanied by changes in peripheral thyroid hormone metabolism, contributing to a decrease in basal metabolic rate and overall energy expenditure. In this setting, low T_3 may act as a regulatory mechanism of energy conservation, aligning endocrine function with energy availability and supporting a reduction in total metabolic demands.

In quantitative terms, in healthy adults with caloric restriction, serum total T_3 levels typically decrease by [20–30]% within the first week of fasting, reaching values of [0.6–1.0] nmol/L compared to a reference range of [1.2–2.2] nmol/L, whereas in septic patients with low T_3 syndrome (NTIS), total T_3 levels may fall to [0.4–0.8] nmol/L despite similar absolute reductions, with concomitant elevation of reverse T_3 (rT_3) exceeding 0.6 nmol/L. These quantitative differences, together with distinct cytokine profiles (e.g., IL-6 > 50 pg/mL in sepsis vs. < 5 pg/mL in fasting), provide biochemical support for distinguishing the two phenotypes.

Such changes have been described, for example, in athletes with Relative Energy Deficiency in Sport (RED-S), where decreased T_3 levels are interpreted as part of a systemic adaptive response to chronic energy deficiency [20; 21]. In this context, the low T_3 phenotype reflects a predominantly energy-conserving mode of thyroid regulation aimed at optimizing the use of available metabolic resources.

In contrast to this metabolic-adaptive variant, reduced T_3 levels in systemic inflammation arise within a different regulatory framework, characterized by immune activation, cytokine signaling, and alterations in tissue-level thyroid hormone metabolism.

3. Immunometabolic phenotype of low T_3 in systemic inflammation

In contrast to the metabolic-adaptive variant observed during energy deficiency, the low T_3 state in systemic inflammation develops within

a fundamentally different regulatory context characterized by immune activation and profound metabolic reprogramming. In this setting, alterations in thyroid hormone homeostasis are largely driven by tissue-specific regulation of thyroid hormone signaling rather than by systemic endocrine changes alone.

A central feature of this process is the remodeling of intracellular thyroid hormone metabolism, mediated by changes in deiodinase activity, particularly increased type 3 deiodinase (D3)-dependent inactivation of T_3 and altered type 2 deiodinase (D2)-mediated local activation [7; 8; 17]. In parallel, inflammation-associated cytokine signaling modulates thyroid hormone transport and receptor expression in target tissues, including cells of the innate immune system, thereby reshaping local thyroid hormone action in a context-dependent manner [17].

Beyond classical endocrine pathways, emerging evidence suggests that components of the innate immune response directly interact with iodine-dependent biochemical systems. For instance, myeloperoxidase-mediated pathways in neutrophils utilize iodine-related substrates as part of antimicrobial defense mechanisms, further linking thyroid-related biochemical processes with immune function [22]. Although these pathways are not primary drivers of systemic thyroid hormone changes, they underscore the integration of thyroid-related mechanisms into host defense.

Collectively, these alterations in local thyroid hormone metabolism and signaling are consistent with the framework of NTIS, in which reduced circulating T_3 reflects increased tissue-level inactivation and redistribution of thyroid hormone action rather than primary thyroid dysfunction [23]. At the systemic level, this state is frequently associated with a shift toward catabolic metabolism, including enhanced substrate mobilization and the development of negative nitrogen balance, reflecting the broader metabolic demands of critical illness [1; 5; 24].

Taken together, the low T_3 phenotype in systemic inflammation represents an immunometabolic state in which endocrine, immune, and metabolic pathways converge to prioritize host defense and substrate redistribution. This phenotype is therefore mechanistically and functionally distinct from the energy-conserving low T_3 state observed in conditions of energy deficiency.

4. Two context-dependent phenotypes of low T_3

Available evidence suggests that the low triiodothyronine state does not represent a single pathophysiological syndrome, but rather reflects at least two distinct adaptive modes of thyroid regulation.

Under conditions of energy deficiency, reduced T_3 levels reflect a metabolically economical adaptation aimed at decreasing energy expenditure and optimizing the use of available metabolic resources. In this context, thyroid-related changes can be interpreted as part of a systemic metabolic adaptation that aligns endocrine regulation with energy availability.

In contrast, during systemic inflammation, low T_3 develops in the setting of immunometabolic activation and profound metabolic reprogramming. In this context, alterations in thyroid hormone status may be linked to the redistribution of metabolic resources toward effector mechanisms of innate immunity, including iodine-dependent halogenation processes in phagocytic cells, as well as to increased tissue metabolism and clearance of thyroid hormones [17; 22; 23]. This regulatory pattern is likely more energy-demanding and less stable from the perspective of systemic adaptation, which may partly explain the association between low T_3 levels and the severity of critical illness.

Within this framework, two principal variants of the low T_3 phenotype can be distinguished: firstly, an energy-deficit–associated, metabolically economical phenotype (low T_3 state; fasting/RED-S); and secondly, an inflammation-associated, immunometabolic phenotype (LT_3S, NTIS).

These variants differ in their underlying regulatory mechanisms, tissue-level thyroid hormone metabolism, and the contribution of local hormone clearance [7; 8; 23] (*Table*).

The following sources were used to compile the Table: for iodine-dependent immune mechanisms in phagocytes – Klebanoff S.J. (2005) [22]; for stability of adaptation – metabolically economical phenotype is relatively stable based on studies of prolonged caloric restriction (Spaulding S.W. et al. (1976) [18]; Chopra I.J. et al. (1975) [19]), while the immunometabolic phenotype is less stable and more closely linked to illness severity (Van den Berghe G. (2021) [23]; Fliers E. et al. (2015) [1]). Other rows are derived from the cited reviews [1; 4; 7; 8; 17; 23].

Table. Context-dependent phenotypes of low T_3

Characteristic	Metabolically economical phenotype (low T_3)	Immunometabolic phenotype (LT_3S (NTIS)
Systemic context	Energy deficiency	Systemic inflammation and critical illness
Typical clinical settings	Fasting, caloric restriction, RED-S, prolonged exercise	Infections, sepsis, trauma, critical illness
Functional orientation	Metabolic energy conservation and optimization of energy utilization	Immunometabolic reprogramming and support of inflammatory responses
Key regulatory signals	Reduced energy availability; alterations in leptin, insulin, and metabolic signals	Cytokines (IL-6, TNF-α) and other inflammatory mediators
Neuroendocrine integration	Modulation of the HPT axis according to energy availability	Interaction between HPT and HPA axes; cytokine-mediated regulation
Systemic metabolic effects	Decreased basal metabolic rate and energy expenditure	Redistribution of metabolic resources toward immune effector mechanisms
Tissue thyroid hormone metabolism	Predominantly reduced T_3 production with relatively preserved clearance	Enhanced tissue-level regulation and increased thyroid hormone clearance
Cellular mechanisms	Energy-conserving metabolic adaptation	Activation of innate immune cells and alterations in thyroid hormone signaling
Iodine-dependent immune mechanisms	Not a primary feature	Possible involvement of iodine-dependent halogenation processes in phagocytic cells
Stability of adaptation	Relatively stable adaptive metabolic state	More demanding and potentially unstable regulatory state
Clinical significance	Adaptive metabolic response	May be associated with the severity of critical illness

Notes: RED-S – relative energy deficiency in sport; LT_3S – low T_3 syndrome; NTIS – non-thyroidal illness syndrome; HPT axis – hypothalamic–pituitary–thyroid axis; HPA axis – hypothalamic–pituitary–adrenal axis; IL-6 – interleukin-6; TNF-α – tumor necrosis factor alpha.

Context-dependent variants of the low T_3 state define distinct adaptive modes of thyroid regulation under energy deficiency and systemic inflammation. Thus, the low T_3 state can be interpreted as a context-dependent phenotype of systemic adaptation, arising from the interplay between metabolic, immune, and neuroendocrine regulatory mechanisms (*Fig. 2*).

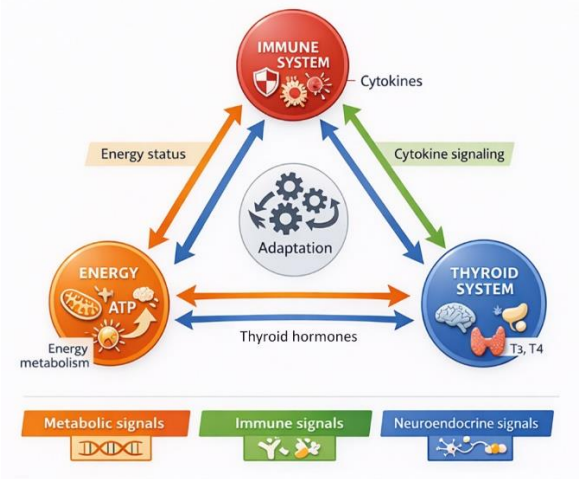

Fig. 2. Context-dependent integration of metabolic, immune, and thyroid regulation

Notes: T_3 – triiodothyronine; T_4 – thyroxine; ATP – adenosine triphosphate.

Energy metabolism, immune activity, and thyroid regulation constitute an integrated adaptive network. Metabolic, immune, and neuroendocrine signals collectively maintain internal equilibrium across a continuum ranging from homeostasis to allostatic adaptation and, under sustained stress, to exhaustion. This coordinated interplay governs the integration of energy expenditure, immune function, and endocrine regulation.

Integrated interactions between metabolic, immune, thyroid, and iodine-dependent pathways shape context-dependent adaptation, resulting in distinct energy-conserving and immunometabolic low T_3 phenotypes under conditions of energy deficiency and systemic inflammation.

In clinical practice, energy deficiency and systemic inflammation may co-exist, for example, in critically ill patients with prolonged fasting or in malnourished individuals with sepsis. Under such mixed conditions, the low T_3 phenotype likely reflects overlapping features of both adaptive modes, with cytokine-driven immune activation dominating early while an additional energy-conserving component may emerge during prolonged catabolism. The relative contribution of each mechanism may depend on the predominant systemic stressor and its duration, a concept that requires further experimental investigation.

5. Potential role of iodine in thyroid-immune system interactions

An important aspect is the role of iodine as a shared biochemical substrate linking thyroid hormone synthesis and effector mechanisms of innate immunity. In the thyroid gland, iodide is transported via the sodium-iodide symporter and incorporated into thyroid hormones through organification mediated by thyroid peroxidase. In parallel, in cells of the innate immune system, particularly neutrophils, the myeloperoxidase system utilizes halides, including iodide, to generate reactive halogen species involved in microbicidal activity [22].

At the level of tissue thyroid hormone metabolism, systemic inflammation is associated with alterations in deiodinase activity, thyroid hormone transport, and receptor signaling, leading to a redistribution of thyroid hormone action across tissues [7; 8; 17; 23]. In this context, a functional redistribution of the systemic iodine pool between the thyroid and immune systems may occur, driven by increased demand of immune cells for halide-dependent reactions [24–26]. Such redistribution, together with enhanced local inactivation of T_3 and changes in tissue-level thyroid hormone clearance, may reflect an allostatic reconfiguration of thyroid hormone homeostasis during systemic inflammation [15; 23].

Thus, iodine should be considered not only as a substrate for thyroid hormone synthesis but also as a potential mediator of immunoendocrine integration, contributing to context-dependent modulation of thyroid regulation.

6. Context-dependent model of low T_3 formation

Synthesis of current evidence indicates that alterations in thyroid hormone status across different stress conditions should not be interpreted as manifestations of a single pathophysiological syndrome, but rather as context-dependent adaptive mechanisms shaped by dominant metabolic or immune signals [2; 17; 23].

Available experimental and clinical data support the distinction of at least two major variants of low T_3: firstly, a metabolically economical phenotype associated with reduced energy availability; and secondly, an immunometabolic phenotype linked to systemic inflammation [1; 17; 23].

Within this framework, thyroid homeostasis can be viewed as part of a broader immune-neuroendocrine-metabolic adaptive network integrating signals of energy balance, immune activation, and stress responses [2; 15; 17]. Based on this concept, a context-dependent model of low triiodothyronine formation is proposed (*Fig. 3*). Reduced T_3 levels arise from multilevel regulatory remodeling: systemic stress contexts (e.g., energy deficiency or inflammation) act as initiating signals; neuroendocrine integration is mediated by interactions between hypothalamic-pituitary axes, cytokine signaling, and metabolic regulators; and tissue-level changes involve reprogramming of thyroid hormone metabolism, including alterations in deiodinase activity, transport, and cellular responsiveness [4; 7; 8].

Discussion

Reduced T_3 levels may develop under different systemic conditions. In states of energy deficiency, low T_3 reflects a metabolically economical adaptive mode aimed at reducing overall energy expenditure. In contrast, during systemic inflammation, an immunometabolic phenotype (NTIS) emerges, characterized by cytokine-mediated immune activation, redistribution of metabolic resources, and enhanced tissue-level metabolism of thyroid hormones. With prolonged inflammatory stress, this phenotype may be accompanied by exhaustion of the adaptive capacity of the thyroid system.

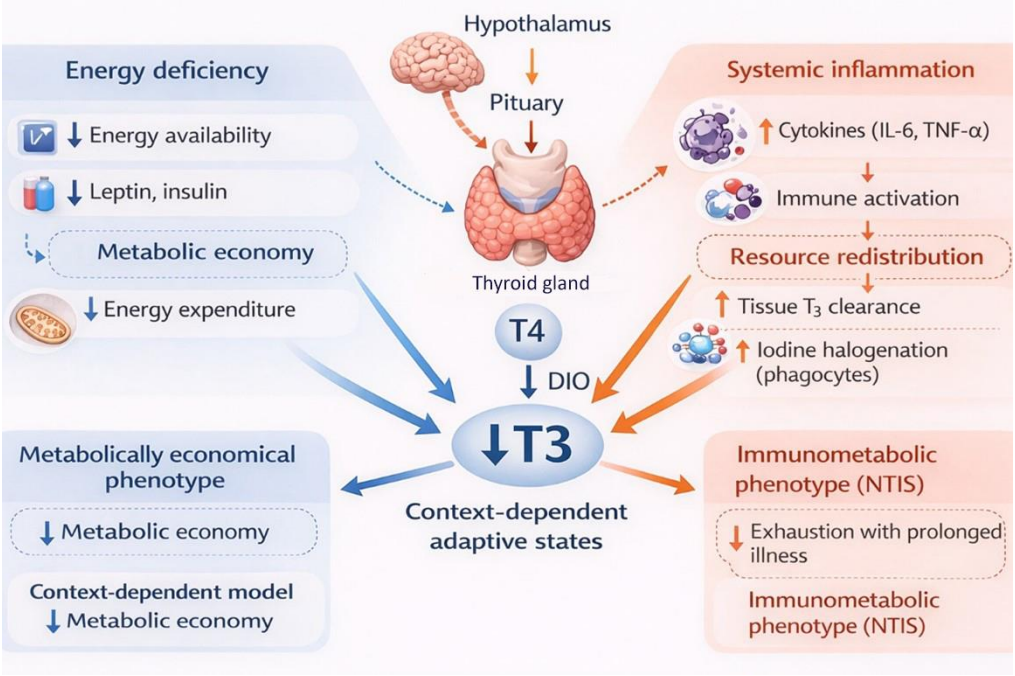

Fig. 3. Context-dependent model of low triiodothyronine formation

Notes: T_3 – triiodothyronine; T_4 – thyroxine; IL-6 – interleukin-6; TNF-α – tumor necrosis factor alpha; NTIS – non-thyroidal illness syndrome; DIO – deiodinase (iodothyronine deiodinase).

This results in a context-dependent low T_3 phenotype whose functional significance varies with the systemic metabolic or immune environment. Accordingly, the low triiodothyronine state should be interpreted not as a single pathophysiological entity, but as an adaptive endocrine phenotype arising from the interaction of metabolic, immune, and neuroendocrine regulatory mechanisms. In summary, this model links metabolism, immunity, and thyroid function.

Conclusions

1. The low triiodothyronine state represents a context-dependent phenotype of systemic adaptation rather than a unitary endocrine syndrome, emerging from the interplay of metabolic, immune, and neuroendocrine regulation.

2. In energy deficiency, reduced T_3 reflects a metabolically economical adaptation that conserves energy and aligns thyroid function with energy availability, whereas in systemic inflammation it arises within an immunometabolic context characterized by tissue-specific remodeling of thyroid hormone metabolism.

3. Low T_3 may serve as an integrative marker of systemic adaptation, reflecting the balance between energy demand, immune activation, and neuroendocrine control.

4. The proposed model provides a conceptual framework linking thyroid regulation with metabolic and inflammatory processes and may guide future research into distinct low T_3 phenotypes.

5. The proposed model is intended both as a framework for interpreting existing experimental and clinical data and as a source of testable predictions. First, the two low T_3 phenotypes should be distinguishable by specific biomarker profiles as proposed above. Second, experimental induction of energy deficiency in healthy volunteers will produce a T_3 reduction without significant elevation of inflammatory cytokines or reverse T_3. Third, blockade of inflammatory cytokines such as IL-6 or TNF-α antagonists in septic animal models will attenuate the decline in T_3 independently of nutritional status. These predictions provide a basis for future mechanistic and clinical studies to validate the model.

Prospects for Further Research

Further studies should elucidate context-dependent mechanisms of low T_3 regulation, with particular focus on tissue-level thyroid hormone metabolism and thyroid-immune interactions. This may improve the clinical interpretation of thyroid alterations across diverse systemic conditions.

Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Biletska O.M.	+	+	+	+	+	+
Golka G.G.	+		+			+
Danylchenko S.I.				+		+
Arestova T.V.				+		+
Shevchenko A.S.	+	+	+	+	+	+

Notes: A – concept; B – design; C – data collection;
D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

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Declarations

Conflict of interest is absent.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors. Figures were created using GPT-5.3 artificial intelligence tools based on language descriptions of models.

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