ISSN 2181-

NEUROENDOCRINE RESPONSES OF THE THYROID AND PARATHYROID GLANDS DURING ACUTE CEREBRAL ISCHEMIA

Botirova Nigina Akram qizi, Ph.D
Tashkent State Medical University,Uzbekistan

Abstract

Acute cerebral ischemia (ischemic stroke) triggers systemic neuroendocrine responses that commonly alter thyroid and parathyroid physiology. The most consistent thyroid pattern is the “non-thyroidal illness syndrome” (NTIS, or low-T3 syndrome) characterized by reduced peripheral T3, variable T4, raised reverse T3 (rT3), and typically normal or low-normal TSH. These changes correlate with stroke severity and worse outcomes in many studies. Changes in parathyroid function and mineral metabolism—principally altered parathyroid hormone (PTH), vitamin D status, and calcium—have also been reported; elevated PTH and low 25-OH vitamin D associate with increased stroke risk and with particular stroke subtypes in some cohorts. This article reviews the physiology, proposed mechanisms, human and animal evidence, clinical significance, and potential implications for management and research.

Keywords: acute ischemic stroke, thyroid hormones, non-thyroidal illness syndrome (NTIS), parathyroid hormone (PTH), neuroendocrine, prognosis

Introduction

Stroke is not only a focal neurological event but also a systemic disorder that elicits complex endocrine and metabolic responses. Among those, the changes in thyroid and parathyroid axes are frequent and may influence prognosis, recovery, and secondary prevention strategies. Understanding these responses elucidates pathophysiology and may identify biomarkers or therapeutic targets. This review synthesizes experimental and clinical literature on thyroid- and parathyroid-related changes that occur during and after acute cerebral ischemia.

Thyroid axis: The thyroid axis acts via a classic feedback involving the brain and thyroid gland. It initiates in the hypothalamus, a small structure at the bottom of the brain, which produces thyrotropin-releasing hormone (TRH). TRH flows to the pituitary gland, which, in response, secretes thyroid-stimulating hormone (TSH) into the bloodstream.

TSH then acts on the thyroid gland to produce two important hormones, namely thyroxine (T4) and triiodothyronine (T3). The main product, however, is T4; it's largely inactive. Most of the biologically active T3 is generated outside the thyroid when enzymes called deiodinases remove an iodine atom from T4.

Type 1 and Type 2 deiodinases, D1 and D2, respectively, convert T4 into active T3. Active T3, in turn, regulates cellular metabolism, energy utilization, and temperature control. On the other hand, D3 deiodinates T4 into reverse T3 (rT3), an inactive form that dampens metabolic activity.

The body maintains balance via a negative feedback mechanism whereby high levels of T3 and T4 signal the hypothalamus and pituitary to reduce TRH and TSH release, respectively; this maintains hormone levels within a narrow range. During critical illness, peripheral deiodinase activity is shifted, serum binding is altered, and hypothalamic-pituitary regulation is changed, resulting in NTIS. (PMC)

During severe stress or critical illness, such as sepsis, trauma, or stroke, the thyroid axis undergoes profound changes—a phenomenon known as Nonthyroidal Illness Syndrome, or NTIS, also sometimes referred to as "euthyroid sick syndrome."

In this state:

- The conversion of T4 to T3 decreases because of the reduced activity of D1/D2, while the production of inactive rT3 increases owing to increased D3 activity.
- Circulating T3 levels decrease, while TSH and T4 can be normal or low.
- Inflammatory cytokines, such as IL-6 and TNF-α, further inhibit the release of TRH and TSH from the brain.

• Changes in protein binding decrease total but not free thyroid hormone levels.

These changes resemble hypothyroidism upon first glance, but NTIS is considered an adaptive and energy-conserving response to facilitate survival from severe illness by lowering metabolic demands. However, in prolonged or severe cases, persistent low T3 may worsen the outcome in critically ill or neurologically compromised patients.

Parathyroid axis: Whereas the thyroid axis represents metabolism, the parathyroid axis maintains the calcium level, which is crucial for nerve transmission, muscle contraction, and vascular tone.

The four small parathyroid glands behind the thyroid are constantly monitoring blood calcium levels via the calcium-sensing receptor (CaSR). When calcium levels drop, the release of PTH is triggered.

PTH acts on three major sites. Bone: It causes the release of calcium and phosphate by stimulating bone resorption. Kidneys: It increases calcium reabsorption while promoting phosphate excretion. PTH also activates the enzyme 1α-hydroxylase, which converts 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D (calcitriol), the active form of vitamin D. Intestine: PTH indirectly enhances the absorption of calcium and phosphate from the gut through calcitriol.

Once calcium levels return to normal, the secretion of PTH falls, completing the feedback loop. PTH and vitamin D also exert vascular and immunomodulatory effects relevant to cerebrovascular disease. (PMC)

In recent years, investigators have found that PTH and vitamin D do much more than just control calcium levels—they also affect the vascular system, the immune response, and even the brain. Vitamin D supports endothelial function, reduces inflammation, and helps regulate blood pressure.

PTH, continuously elevated—which happens in the case of hyperparathyroidism—can lead to vascular stiffness, hypertension, and endothelial dysfunction. Both hormones seem to interact with neural and immune pathways to

influence recovery and inflammation after such events as stroke or cerebrovascular injury.

Low vitamin D and elevated PTH levels have been linked with higher risks of stroke, poorer neurological recovery, and greater cardiovascular mortality, highlighting the broad systemic importance of this axis.

System	Key Hormones	Primary Function	Effect in Illness
Thyroid Axis	TRH → TSH → T4/T3	Controls metabolism and energy balance	NTIS: ↓ T3, ↑ rT3, suppressed TSH
Parathyroid Axis	PTH → $1,25(OH)_2D$	Regulates calcium, bone, and vitamin D	Dysregulation affects vascular tone, immune function, and stroke outcomes

The thyroid and parathyroid axes epitomize how intricately our hormonal systems interrelate with metabolic, vascular, and immune function. In health, these exist in a delicate balance. In disease, they shift—sometimes protectively and sometimes pathologically. Elucidation of these changes is integral to patient care in critical illness, endocrine dysfunction, and cerebrovascular disease.

The most consistent and widely reported finding is low total and free T3 (fT3) within hours to days following ischemic stroke, often with normal or low-normal TSH and variable fT4; rT3 is often elevated. This pattern is consistent with NTIS/low-T3 syndrome. Concentrations typically fall early (presentation to days 3–5) and improve in most patients during convalescence. (Nature)

Various observational studies and meta-analyses show that lower T3 levels, sometimes higher rT3 levels, are associated with larger infarct size, more severe neurological deficit, higher mortality, and worse functional outcome at follow-up.

Several cohorts report low T3 levels to be an independent predictor of poor outcome after adjustment for confounders.

NTIS may be an adaptive energy-saving response limiting metabolism during critical illness; alternatively, reduced active thyroid hormone at tissue level might impede neuronal recovery, neurogenesis, and repair. Animal experiments using models of ischemia have shown both protective and harmful effects of modulating TH signaling, with context dependence seemingly important (timing, dose, and expression of local deiodinases).

Mechanisms that link stroke with thyroid axis changes

1. Altered deiodinase activity — increased D3 (inactivating) and decreased D1/D2 reduce T3 and increase rT3 in peripheral tissues and possibly in brain.
2. Acute inflammation and cytokines — IL-6, TNF-α, and other mediators modify the expression of deiodinases and decrease peripheral conversion.
3. Hypothalamic-pituitary dysfunction — stroke with involvement of hypothalamic/pituitary regions or global stress-mediated suppression may decrease TRH/TSH drive in a subset of patients.
4. Nutritional and metabolic factors — fasting, catabolism, and altered binding proteins during critical illness alter the measured levels of hormones.
5. Medications and ICU therapies — dopamine, glucocorticoids, heparin, and amiodarone influence thyroid tests. (Consider when interpreting labs.)

Several studies report elevated PTH levels in patients with acute ischemic cerebrovascular events compared to controls, and associations between higher PTH (and low 25-OH vitamin D) with greater stroke risk or particular stroke subtypes (e.g., extracranial atherosclerotic disease) in some cohorts. Other groups report complex, sometimes contradictory, associations depending on comorbid renal disease, dialysis status, and population characteristics.

Vascular effects of PTH and vitamin D deficiency: PTH may promote endothelial dysfunction, vascular stiffness, and atherosclerosis; vitamin D deficiency is linked to inflammation, hypertension, and dyslipidemia—each a stroke risk factor.

Acute changes vs chronic state: Elevated PTH in acute stroke may reflect pre-existing secondary hyperparathyroidism (e.g., vitamin D deficiency or CKD) or an acute stress response; reverse causality is possible in observational designs.

Experimental ischemia models show thyroid hormone signaling modulates neuronal survival, excitotoxicity, and neuroinflammation; administration of T3/T4 or manipulation of deiodinases can alter infarct size and functional recovery in animals — direction depends on timing and dose in different studies. rT3 may also have biological effects modifying ischemic injury.

There are fewer mechanistic animal data on PTH in cerebral ischemia; however, PTH and vitamin D signaling influence vascular biology, inflammation, and neurovascular coupling in models relevant to stroke risk and recovery.

Low T3 at presentation is a reproducible prognostic marker for increased mortality and worse functional outcome after ischemic stroke in many cohorts and meta-analyses; rT3 may also predict mortality. However, heterogeneity in timing, assay methods, and adjustment for confounders limits uniform clinical adoption.

Elevated PTH and low 25-OH vitamin D levels are associated with higher stroke risk in observational studies and may add incremental risk information in some models; their independent predictive value remains under investigation.

Routine thyroid hormone replacement for NTIS is not established. NTIS is common in critical illness; trials of thyroid hormone supplementation in heterogeneous critical illnesses have produced mixed results, and robust randomized trials in stroke are lacking. Given the possibility that NTIS may be adaptive in some contexts, routine replacement is not currently recommended without clear primary hypothyroidism. Selected exploratory trials and animal data suggest potential for targeted therapy (timing/dose/patient selection), but more evidence is needed before clinical adoption.

Correcting severe vitamin D deficiency is reasonable for bone and general health, but there is no clear evidence that vitamin D or PTH-targeted therapies prevent stroke or improve acute stroke outcomes. Large randomized controlled trials addressing vitamin D supplementation and cardiovascular outcomes have been mixed. Clinical decisions should follow existing guidelines for vitamin D deficiency and secondary hyperparathyroidism, recognizing possible cerebrovascular associations.

Conclusion

Acute cerebral ischemia commonly provokes alterations in thyroid function consistent with NTIS (low T3, altered rT3) and is associated with worse clinical outcomes. Parathyroid hormone and vitamin D dysregulation are also associated with stroke risk and sometimes with acute cerebrovascular events, but the directionality and clinical implications remain incompletely defined. Current evidence supports using thyroid and mineral metabolism measures when clinically indicated and encourages research into whether targeted modulation of these axes can improve stroke outcomes. Routine hormone replacement for NTIS is not supported by current evidence. Clinicians should interpret endocrine changes in stroke within the broader context of critical illness, comorbidities, and patient-specific considerations.

References

1. Wajner SM, et al. *New insights toward the acute non-thyroidal illness syndrome.* (Review). — discusses NTIS mechanisms and peripheral deiodinase changes.

2. Jiang X, et al. *Prognostic value of thyroid hormones in acute ischemic stroke.* Sci Rep. 2017 — meta-analysis showing associations between low T3 and poorer stroke outcomes.

3. Huang S, et al. *Research progress on the role of hormones in ischemic stroke.* (Review) 2022 — overview linking multiple endocrine axes (including PTH/vitamin D) to stroke.

4. Çelik G, et al. *Parathyroid Hormone Levels in the Prediction of Ischemic Stroke.* 2017 — study examining PTH and 25(OH)D as predictors.

5. Rastogi L, et al. *Reverse triiodothyronine (rT3) attenuates ischemia ...* (experimental study) — explores rT3 effects in ischemic models.

6. Taroza S, et al. *Associations of Free and Reverse Triiodothyronine with outcomes* (2025) — recent cohort evidence on fT3/rT3 and mortality.

7. Squizzato A, et al. *Thyroid Diseases and Cerebrovascular Disease.* Stroke. 2005 — classic review linking thyroid dysfunction to stroke risk.

8. Onder H, et al. *The Association Between Hyperparathyroidism and Stroke.* Neuro Res. 2020 — association between PTH elevation and ischemic stroke subtypes.

9. АТЕРОКАЛЬЦИНОЗ РИВОЖЛАНИШИДА ЭНДОКРИН ТИЗИМ БУЗИЛИШЛАРИНИНГ РОЛИ

ММ Асадуллаев, ХТ Мирахмедова, НА Ботирова – 2024

10. ЭНДОКРИННАЯ СИСТЕМА И АТЕРОМАТОЗНЫЕ СТАДИИ АТЕРОСКЛЕРОЗА

НА Ботирова, НМ Вахабова, ХТ Мирахмедова… - 2024

11. ЗНАЧЕНИЕ ИЗМЕНЕНИЙ НАРУЖНОЙ СОННОЙ АРТЕРИИ И ЩИТОВИДНОЙ ЖЕЛЕЗЫ У ПАЦИЕНТОВ С РИСКОМ ИШЕМИЧЕСКОГО ИНСУЛЬТА

ММ Асадуллаев, НА Ботирова, НМ Вахабова - 2024

12. ЎТКИР ИШЕМИК ИНСУЛТ ЎТКАЗГАН БЕМОРЛАРДА УЙҚУ АРТЕРИЯСИНИНГ ЎТКАЗУВЧАНЛИК ХУСУСИЯТЛАРИ

ММ Асадуллаев, ДР Жуманазаров, НА Ботирова - Modern education and development, 2025

13. АНАЛИЗ ПРОХОДИМОСТИ СОННОЙ АРТЕРИИ У ПАЦИЕНТОВ С ОСТРЫМ ИШЕМИЧЕСКИМ ИНСУЛЬТОМ: ИССЛЕДОВАНИЕ АТЕРОСКЛЕРОТИЧЕСКИХ ИЗМЕНЕНИЙ И ГЕМОДИНАМИЧЕСКИХ ПАРАМЕТРОВ

ММ Асадуллаев, ДР Жуманазаров, НА Ботирова - Modern education and development, 2025

14. Vakhabova NM, Asadullaev MM, Raximbayeva GS. Botirova NA, & Shohruhbek Ulug'bek ug'li, A. Lipoproteins and Their Receptors Association in Cerebrovascular Disease Pathogenesis: A Comprehensive