Thyroid Hormone Conversion, Deiodinase Activity, and Visceral Adiposity (VAT)

What Is Known, What Is Emerging, and What Remains Theoretical

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Executive Summary

Thyroid hormone action is determined not just by blood levels of FT4 and FT3, but by **local intracellular T3 availability**, which depends on tissue-specific deiodinase activity (D1, D2 and D3).

Strong scientific evidence shows that **obesity and visceral adipose tissue (VAT)** alter these enzymes in a way that may reduce intracellular T3, impair thermogenesis, and promote metabolic dysfunction — even when standard thyroid blood tests appear normal.

This paper distinguishes between:

1. **Well-supported conclusions**
2. **Emerging evidence**
3. **Plausible but unproven theories**

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1. Background — Thyroid Hormone Is Activated Locally, Not Systemically

The thyroid secretes mostly T4; tissues must convert T4 → T3 for metabolic activity. This conversion depends on **iodothyronine deiodinases**:

- **D1** – activates T4→T3 (liver, kidney, white fat)
- **D2** – activates T4→T3 (brown/beige fat, skeletal muscle, CNS)
- **D3** – inactivates T4 and T3 (producing reverse T3)

The fundamental principle of **local thyroid hormone regulation** is well-established.[1–3]

Blood tests cannot reliably indicate thyroid hormone action *inside* tissues.

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2. What Is Well Supported by Human Evidence

2.1 Obesity reduces D2 (activating enzyme) in adipose tissue

A key human study demonstrated that obese individuals have significantly **reduced D2 expression in adipose tissue**, particularly in visceral depots, associated with inflammatory markers.[4]
This reduction limits local T3 generation.

2.2 Inflammation increases D3 (inactivating enzyme)

Inflammatory cytokines—common in VAT-rich obesity—**upregulate D3**, increasing conversion of T4/T3 into **reverse T3 (rT3)**.[6]
This reduces intracellular T3 even when circulating FT4 is normal.

2.3 Thermogenesis in brown fat is T3-dependent

Brown and beige fat rely heavily on T3 (generated locally via D2) to activate mitochondrial thermogenesis.[8]
Reduced D2 therefore directly reduces calorie burning.

2.4 Human adults possess functional brown fat

This was confirmed in a landmark study showing cold-activated BAT in adults using PET-CT.[7]
BAT is metabolically potent and depends on D2-mediated T3 activation for heat production.

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3. Moderately Supported Concepts (Emerging Evidence)

3.1 Insulin resistance alters deiodinase behaviour

Scientific evidence suggests insulin resistance contributes to:

- ↓ **D2** activity
- ↑ **D3** activity
- ↓ Intracellular T3 in metabolic tissues

These findings are biologically plausible given that IR activates inflammatory pathways known to alter deiodinases.

3.2 VAT is more inflammatory than subcutaneous fat

VAT secretes more IL-6 and TNF-α, which are known suppressors of D2 and activators of D3.
It is therefore **likely** that VAT disproportionately reduces T3 availability compared with SC fat.

3.3 FT3/FT4 ratio reflects conversion efficiency (but imperfectly)

The FT3/FT4 ratio falls in obesity and inflammation, reflecting reduced conversion, but:

- It is **not** a surrogate for reverse T3
- It does **not** measure tissue thyroid action directly
- It is considered an **indirect** marker

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4. What Is Plausible but Still Theoretical

4.1 VAT may induce "local hypothyroidism" in fat and muscle

A widely discussed hypothesis is that VAT-driven inflammation and D3 activation create a **tissue-level hypothyroid state**—even when blood tests are normal.
This is consistent with biopsy findings and deiodinase biology, but **not yet proven** in longitudinal human studies.

4.2 rT3 may accumulate locally even when normal in serum

rT3 is rarely measured clinically, and its serum levels may not reflect tissue rT3 production.
Scientists **think** that VAT-driven D3 activity could increase rT3 in local tissues, blocking T3 receptor access.

4.3 Modern indoor warmth suppresses D2 chronically

Because cold exposure strongly increases D2 in brown fat, and modern life strongly reduces cold exposure, it is **proposed** that warm indoor environments may suppress brown-fat activation long-term — contributing to VAT gain.

This fits evolutionary physiology but lacks long-term human trials.

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5. Insulin Resistance as a Force Multiplier

Insulin resistance is thought to:

1. Increase cytokine activity (JNK/NF-κB pathways)
2. Reduce mitochondrial performance
3. Reduce cold-induced D2 activation
4. Increase D3-mediated T4/T3 inactivation

This produces a **double hit**:

- Less T3 being made (↓D2)
- More T3 being destroyed (↑D3)

Resulting in **reduced intracellular T3** despite normal blood tests.

This framework aligns with human biopsy data showing lower D2 and reduced conversion efficiency in obese adipose tissue.[4]

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6. Clinical Implications

1. **TSH, FT4 and FT3 cannot rule out tissue-specific T3 deficiency.**
2. **VAT-driven inflammation may impair thyroid hormone action inside metabolic tissues.**
3. **Reduced D2 and increased D3 may slow thermogenesis and metabolic rate.**
4. **Standard thyroid panels may appear normal even when intracellular T3 is reduced.**
5. This provides a mechanistic explanation for:

- Cold intolerance in obesity
- Reduced metabolic rate
- Difficulty losing VAT
- Fatigue with “normal” thyroid tests

6. This also supports therapeutic strategies that target **VAT reduction**, **muscle building**, **sleep**, **cold exposure**, and **anti-inflammatory diets**.

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7. Conclusion

There is:

- **Strong evidence** that obesity impairs deiodinase-mediated thyroid hormone activation
- **Strong evidence** that inflammation drives D3 upregulation and T3 inactivation
- **Strong evidence** that brown-fat thermogenesis is T3-dependent
- **Moderate evidence** linking insulin resistance to deiodinase disruption
- **Plausible but unproven** theories that VAT induces local hypothyroidism even with normal thyroid labs

Understanding these mechanisms helps explain why thyroid symptoms and metabolic slowdown can occur despite normal blood results, and why VAT reduction and metabolic rehabilitation require more than caloric restriction alone.

References

1. Obregón MJ. Adipose tissues and thyroid hormones. Front Physiol. 2014;5:479.
DOI: 10.3389/fphys.2014.00479
https://www.frontiersin.org/articles/10.3389/fphys.2014.00479

2. Petito G, et al. Adipose Tissue Remodeling in Obesity. Int J Mol Sci. 2023;24(8):7625.
doi: 10.3390/ph16040572 https://pmc.ncbi.nlm.nih.gov/articles/PMC10146771/

3. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry and molecular biology of iodothyronine deiodinases. Endocr Rev. 2002;23(1):38-89.2002 Feb;23(1):38-89. doi: 10.1210/edrv.23.1.0455. https://academic.oup.com/edrv/article/23/1/38/2424111

4. Ortega FJ, Moreno-Navarrete JM, Ribas V, et al. D2 expression is reduced in adipose tissue of obese individuals. Int J Obes (Lond). 2012;36:320-324.
DOI: 10.1038/ijo.2011.101
https://www.nature.com/articles/ijo2011101

5. Reinehr T, Andler W. Thyroid hormones before and after weight loss in obesity. Arch Dis Child. 2002;87(4):320-323.
DOI: 10.1136/adc.87.4.320
https://adc.bmj.com/content/87/4/320

6. Boelen A, et al. Induction of type 3 deiodinase activity in inflammatory cells of mice with chronic local inflammation Endocrinology. 2005;146(12):5120-5126.
doi: 10.1210/en.2005-0608 https://pubmed.ncbi.nlm.nih.gov/16150911/

7. Virtanen KA, et al. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360:1518-1525.
DOI: 10.1056/NEJMoa0808949
https://www.nejm.org/doi/full/10.1056/NEJMoa0808949

8. Silva JE. Thermogenic mechanisms and their hormonal regulation. Physiol Rev. 2006;86(2):435-464.
DOI: 10.1152/physrev.00009.2005
https://journals.physiology.org/doi/full/10.1152/physrev.00009.2005