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HRT Not Working? How Senescent Cells and TPE Explain Ongoing Symptoms

Good labs but still fatigued, foggy, and aching on hormone therapy? Cellular senescence and the inflammation it drives may be the missing piece.

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TLDR: Hormone therapy restores your hormone levels, but it does not clear the senescent cells already accumulated in your tissues. These cells keep secreting inflammatory compounds (SASP) regardless of your labs, which can explain fatigue, brain fog, and joint pain that persist despite well-managed HRT. Supporting methylation and detoxification helps clear hormone metabolites and lower this inflammatory load, and for patients who have done that foundational work and are still stuck, therapeutic plasma exchange (TPE) is an option worth discussing, since it directly removes circulating SASP factors and has been linked in clinical studies to reduced senescence markers and biological age.

You started hormone therapy expecting to feel like yourself again. Your labs may even look good now. But the fatigue, brain fog, or joint pain never fully lifted. If this sounds familiar, the missing piece may not be your hormone levels at all. It may be cellular senescence.

HRT Restores Hormones. It Does Not Clear Senescent Cells.

Hormone therapy, whether pellets, creams, or oral bioidentical formulations, is designed to restore circulating estradiol, testosterone, and progesterone to healthier levels. This matters enormously, and I want to be clear that bioidentical hormones are not synthetic progestins. Bioidentical progesterone is molecularly identical to what your ovaries once produced. Pellet therapy such as EvexiPEL delivers estradiol and testosterone, not progesterone, which is why I pair it with bioidentical progesterone separately.

But restoring a hormone level is not the same as restoring how your tissues respond to that hormone. Estrogen has real, direct effects on cellular senescence: it decreases senescence in endothelial progenitor cells and helps protect bone from age-related decline (Faubion et al., 2020). A clinical trial

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found that hormone therapy lowered several circulating markers of senescence compared to placebo. But hormone therapy addressed the signal. It did not clear the senescent cells already accumulated in your tissues.

What Senescent Cells Are Doing While You Are on HRT

Senescent cells stop dividing but stay metabolically active, continuously secreting inflammatory cytokines and tissue-damaging enzymes, a pattern known as the senescence-associated secretory phenotype (SASP). This inflammatory background noise does not pause because your estrogen levels improved. It keeps circulating, contributing to the kind of low-grade, whole-body inflammation that can mimic or worsen hormone-related symptoms: fatigue, joint aches, poor sleep, and brain fog among them.

This is often why patients tell me their labs look perfect but they still do not feel right. The hormone level and the symptom are not always the same conversation. One is about supply. The other is about the inflammatory terrain your cells are operating in.

Where Detoxification and Methylation Fit

Before considering more advanced tools, it is worth asking whether the basics are optimized. A body carrying a heavy toxin burden or struggling with sluggish methylation has a harder time clearing estrogen metabolites and managing the inflammatory load that comes with cellular senescence. Supporting methylation with nutrients like methylated folate, B12, and B6 helps the liver clear hormone metabolites properly, and I often use formulations like our KHOSH Hepato Charge and Cycle Flow to support this pathway in patients on hormone therapy.

Therapeutic Plasma Exchange as a Deeper Layer

For patients who have optimized their hormone therapy, addressed nutrient and methylation support, and still are not feeling like themselves, I discuss therapeutic plasma exchange (TPE) as a more advanced option. TPE removes circulating SASP factors directly from the bloodstream rather than relying on the body to clear them on its own. A clinical study following patients through repeated rounds of TPE found reduced markers of cellular senescence alongside a measurable reduction in biological age (Kim et al., 2022). A more recent randomized, placebo-controlled trial confirmed shifts toward biological rejuvenation with TPE, particularly when combined with IVIG (Fuentealba et al., 2025).

At Holistique, therapeutic plasma exchange is provided by Circulate Health, with our team providing the supportive protocol around it.

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The logic here is straightforward. If SASP factors are part of what is keeping you from feeling well despite adequate hormone levels, a therapy that directly reduces that circulating inflammatory burden may succeed where hormone optimization alone has not. This is not a first step, and it is not for everyone. But for patients who have done the foundational work and are still stuck, it is worth a conversation.

The Bottom Line

If you are on HRT and still do not feel like yourself, your hormone levels may not be the whole story. Cellular senescence and the inflammation it drives can persist quietly underneath even well-managed hormone therapy. Addressing detoxification, methylation, and in select cases, senescence itself, may be what closes the gap between good labs and actually feeling well.

If you are on hormone therapy and still struggling with symptoms, our team at Holistique Medical Center can help you look beyond your hormone levels to find out what else may be holding you back.

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