PMCHS RESEARCH NOTE · LIPEDEMA

Lipedema: why diets don't work,

and what mast cells have to do with it

A misunderstood condition

Lipedema affects approximately 11% of women worldwide. It is characterised by abnormal subcutaneous adipose tissue accumulation — predominantly in the legs and hips — that resists diets, exercise, and worsens systematically at hormonal transitions: puberty, pregnancy, menopause. For decades, these women were told they lacked willpower. The reality is entirely different.

The self-sustaining cycle — how lipedema progresses

Recent work (Bonetti et al., 2023) has histologically confirmed the presence of activated mast cells in lipedema adipose tissue — with significantly elevated histamine and mediator levels compared to controls, and a notable reduction after sodium cromoglycate treatment. This is not ordinary inflammation: it is a self-sustaining cycle.

Here is how it works: activated mast cells release histamine that makes lymphatic vessels hyperpermeable — fluid and inflammatory mediators accumulate in the tissue. Mast cell tryptase degrades pericellular collagen, creating mechanical instability that re-activates mast cells. Progressive fibrosis generates chronic pain that triggers CRH and substance P — two direct mast cell activators. And oestrogens amplify every step via ERalpha/GPR30 receptors.

“ Lipedema does not progress because you eat too much. It progresses because a mast cell inflammatory cycle self-sustains in your adipose tissue — independently of your diet. ”

The hormonal axis: why it worsens at transitions

Progesterone naturally inhibits mast cell degranulation. In perimenopause, progesterone drops before oestrogens — removing the brake on mast cells before the fuel (oestrogens) diminishes. This imbalance explains the typical worsening of lipedema in perimenopause. Caution with phytoestrogens: they may paradoxically accelerate progression via GPR30 activation in PMCHS profiles.

The hypothalamic axis: why diets fail

Recent research (ANR THALATEL programme, Geli et al.) provides a neurobiological explanation for diet resistance in lipedema. TERT — an enzyme normally known for its role in telomeres — plays in hypothalamic neurons a protective role against oxidative stress, independently of telomeres. When TERT is depleted by chronic oxidative stress (such as that generated by prolonged mast cell inflammation), satiety neurons malfunction — producing hyperphagia of neurological, not behavioural, origin.

In plain terms: in long-standing lipedema with PMCHS terrain, the brain no longer correctly receives the satiety signal — not from lack of willpower, but because the neurons transmitting this signal are structurally weakened by years of inflammation.

What this means in practice

- **Mast cell stabilisation** (cromoglycate, quercetin, luteolin) as a disease-modifying intervention — targeting the cycle at its source.
- **Hormonal management**: bioidentical progesterone in perimenopause may slow progression by restoring the natural brake on mast cells.
- **Antioxidant strategies** (NAC, omega-3, melatonin) to protect the hypothalamic axis in resistant cases.
- **24-hour urinary histamine measurement**: rarely prescribed, often revealing of the level of systemic mast cell activation.
