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Editorial Comment

Menopause, Aged Fat Cells and Adipocyte Dysfunction

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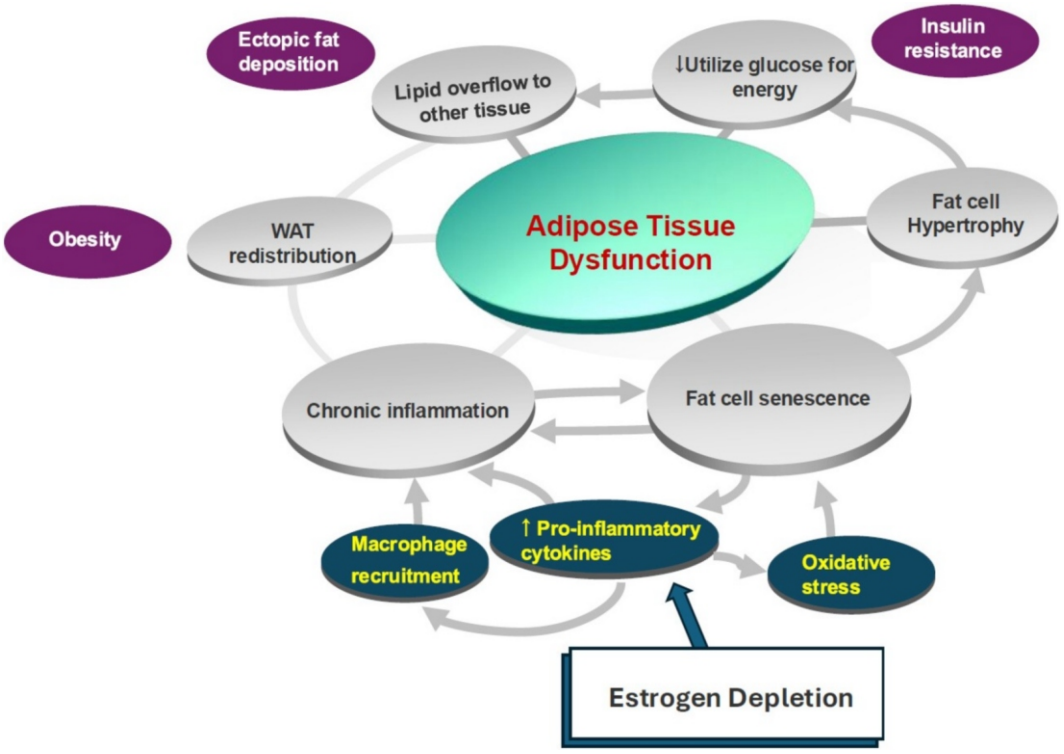

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Figure. White Adipose Tissue (WAT) dysfunction in estrogen depletion.
In the absence of estrogen, such as during menopause, pro-inflammatory cytokines like IL-6 and TNF increase, recruiting immune cells to adipose tissue and amplifying inflammation. This process elevates oxidative stress, leading to cellular senescence and the secretion of pro-inflammatory factors. Senescent adipocyte progenitors contribute to chronic inflammation, lose differentiation capacity, and cause adipocyte hypertrophy. Hypertrophic adipocytes become insulin-resistant, inefficiently utilize glucose, and, upon reaching storage limits, cause lipid overflow into other tissues (ectopic fat deposition). These changes impair calorie burning, promote energy imbalance, and contribute to weight gain.

Menopause marks a significant shift in women's metabolic health. While many factors influence weight, including ethnicity and lifestyle, a common experience is weight gain due to increased fat mass and decreased lean muscle mass.[1] This transition underscores the critical role of estrogen in maintaining healthy adipose tissue.

1. The Role of Estrogen Depletion in Adipocyte Dysfunction

Obesity has been identified as an important modifier of reproductive hormones. How does estrogen depletion contribute to adipocyte dysfunction? Most data on estrogen's role in obesity pathogenesis derive from preclinical studies involving cells or animals devoid of estrogen.[2] The most abundant estrogen receptor in adipose tissue is estrogen receptor alpha (ER). With depletion of ER in fat cells, several significant cellular consequences follow including altered adipocyte differentiation, impaired lipid metabolism, increased inflammation, increased oxidative stress and reduced insulin sensitivity. Disruption of ER signaling causes imbalances between lipogenesis, lipolysis, and fatty acid uptake and release, partly through the inhibition of peroxisome proliferator-activated receptor gamma (PPAR) coactivator recruitment.[3] In the absence of ER , inflammatory pathways become dysregulated, leading to increased production of pro-inflammatory cytokines such as IL-6 and TNF . The absence of Er signaling also increase cellular subsceptibility to oxidative damage such as stimulation from pro-inflammatory cytokines (e.g., TNF- , IL-6), which further amplify inflammatory status and contribute to cellular senescence. Senescent adipocytes secrete pro-inflammatory molecules such as chemokines and proteases, cre-

ating a pro-inflammatory microenvironment which amplifies oxidative stress and inflammation, promotes further senescence in neighboring cells and contributes to insulin resistance, a major hallmark of metabolic dysfunction.[4] These senescence fat cells lose their ability to divide but still remain metabolically active and secreting harmful substances, collectively known as the senescence-associated secretory phenotype (SASP).

Senescent adipocyte progenitors also lose their ability to differentiate, reducing the turnover of healthy adipocytes and leading to the accumulation of hypertrophic adipocytes. These enlarged adipocytes exhibit reduced insulin sensitivity and increased lipid storage, exacerbating dysfunction and promoting metabolic complications such as insulin resistance[5] (Figure).

2. The Role of Estrogen in Body Fat Distribution

Menopause can significantly impact a woman's body shape from "Pear" to "Apple", which indicates to store more fat in their hips and thighs in premenopausal status to a tendency for fat to accumulate more around the abdomen after menopause. How does this happen ?

Estrogen plays a critical role in white adipose tissue (WAT) health through modulating adipocyte progenitor cell biology and adipogenesis in WAT.[6] WAT, composed of white adipocytes, is the most abundant adipose tissue in the body and is distributed as subcutaneous fat, visceral fat and bone marrow fat. Subcutaneous adipose tissue exhibits metabolically protective properties, while visceral fat is more closely linked to metabolic dysfunction. Adipocyte progenitors differ between subcutaneous and visceral fat tissues and respond differently to estrogen depletion. Estrogen depletion reduces the proliferative capacity and differentiation potential of subcutaneous progenitors. This disrupts the balance of anti-adipogenic and pro-adipogenic signals, leading to inefficient turnover of adipocytes.[7] In contrary, visceral progenitors are more sensitive to the pro-inflammatory effects of estrogen depletion. Under conditions of excess nutrients, the may exhibit enhanced differentiation into adipocytes contributing to visceral fat expansion.[6] Therefore, estrogen depletion alters the balance between subcutaneous and visceral fat, leading to an increase in visceral fat accumulation. Several studies have shown that an increase in visceral or central adiposity is associated with the most significant risk of mortality in women. Thus, weight control has become one of major women health's concerns.

3. Strategies to Mitigate Adipocyte Dysfunction

Several strategies have been proposed to disrupt the vicious cycle of oxidative stress, chronic inflammation, adipose tissue senescence, and metabolic derangements. These include lifestyle modifications, weight management, and, in some cases, hormone therapy. For instance, reducing overall calorie intake can decrease fat mass and enhance insulin sensitivity.[8] Adopting a Mediterranean diet — rich in fruits, vegetables, whole grains, lean proteins, and healthy fats — can improve insulin sensitivity and lower inflammation. Regular physical activity, including aerobic and strength training exercises, can also enhance insulin sensitivity, increase muscle mass, reduce inflammation, and promote fat loss.[9] Emerging therapies such as senolytics (drugs that target and eliminate senescent cells) and senomorphics (agents that modulate SASP) are being explored to mitigate the effects of senescent adipocytes, reduce inflammation, and improve overall adipose tissue health.[10] Additionally, GLP-1 receptor agonists (GLP-1 RAs) are widely utilized to enhance adipose tissue function and metabolic outcomes. By activating GLP-1 receptors, these therapies transiently increase circulating IL-6 levels, stimulate adipocyte lipolysis and thermogenesis, and promote adipocyte hyperplasia rather than hypertrophy. This shift supports increased energy expenditure and improved insulin sensitivity, making GLP-1 RAs a promising intervention for metabolic health.[11]

4. Conclusion

Menopause-induced estrogen depletion significantly impacts adipose tissue function, leading to cellular senescence, inflammation, and metabolic complications. While these changes are part of the natural aging process, they can be mitigated through dietary adjustments, physical activity, and emerging medical interventions. Consistent lifestyle changes remain crucial for long-term health improvements, while new therapies offer hope for addressing adipocyte dysfunction and reducing the risk of obesity-related diseases.

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