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THE EFFECT OF ENDOPLASMIC RETICULUM STRESS-REDUCING AGENTS ON LEPTIN SENSITIVITY IN OBESE WOMEN

Isaqjonova Moxinur Nodirjon qizi
Endocrinologist, family polyclinic No. 4,
Fergana city, Fergana region

Annotation

Obesity-related leptin resistance in women involves endoplasmic reticulum (ER) stress as a key pathological mechanism. This study investigates how ER stress-reducing compounds-including taurine, resveratrol, quercetin, and curcumin-restore leptin sensitivity through modulation of cellular stress markers. By attenuating GRP78, XBP1, and CHOP expression, these bioactive agents improve leptin receptor signaling and metabolic outcomes, suggesting potential therapeutic applications for obesity management in women.

Keywords: leptin, obesity, stress, grp78, xbp1, chop, antioxidants, resistance, women, curcumin

Women with obesity frequently exhibit elevated leptin levels yet fail to respond appropriately to the hormone's satiety signals, a condition known as leptin resistance. This paradox stems partly from chronic endoplasmic reticulum stress in adipose tissue and hypothalamic neurons, where excessive protein misfolding overwhelms cellular quality control mechanisms. ER stress disrupts leptin receptor function and downstream signaling cascades, perpetuating weight gain and metabolic dysfunction. Emerging evidence suggests that certain natural compounds with antioxidant and anti-inflammatory properties can alleviate ER stress burden. Taurine stabilizes protein folding, resveratrol activates protective pathways, quercetin reduces oxidative damage, and curcumin suppresses inflammatory responses-all potentially restoring leptin sensitivity. Given sex-specific differences in adipose tissue biology and hormone metabolism, understanding how these agents work in women requires targeted investigation. The therapeutic potential lies in addressing the cellular stress that underlies leptin resistance rather than simply restricting caloric intake.

Endoplasmic reticulum stress triggers the unfolded protein response through three main pathways. GRP78 normally binds misfolded proteins but dissociates under stress conditions, activating downstream effectors. XBP1 undergoes splicing to promote adaptive responses, while CHOP accumulation signals severe, prolonged stress leading toward apoptosis. In obese women, adipocyte hypertrophy and inflammatory cytokine exposure chronically elevate these markers, impairing leptin receptor trafficking and signal transduction. Antioxidant compounds counteract this stress through multiple mechanisms. Curcumin directly inhibits IRE1α-XBP1 pathway activation, reducing inflammatory gene expression in adipocytes. Studies demonstrate that curcumin supplementation lowers spliced XBP1 levels in obese subjects, correlating with improved metabolic parameters. Resveratrol activates SIRT1, which deacetylates and stabilizes proteins, enhancing ER folding capacity and reducing GRP78 upregulation. Quercetin's antioxidant properties diminish reactive oxygen species that exacerbate ER stress, while taurine acts as a chemical chaperone, directly assisting protein folding and preventing aggregation. The restoration of leptin signaling occurs through several interconnected pathways. When ER stress markers decline, leptin receptors properly localize to cell membranes and maintain functional conformations. JAK2-STAT3 phosphorylation recovers, allowing leptin to effectively activate anorexigenic neurons in the hypothalamus. Additionally, reduced ER stress decreases JNK activation, which otherwise promotes serine phosphorylation of insulin receptor substrate proteins-a common mechanism linking leptin and insulin resistance. In female-specific contexts, these compounds may interact with estrogen signaling, as estrogen receptor activity influences both ER stress responses and leptin sensitivity. Clinical observations support these molecular findings. Women receiving resveratrol or curcumin supplementation show improved leptin-to-adiposity ratios and enhanced satiety responses compared to placebo groups. Animal studies reveal that taurine administration reduces hypothalamic CHOP expression while improving leptin-induced STAT3 phosphorylation specifically in female mice, suggesting sex-dependent benefits.

In cinclusion, endoplasmic reticulum stress-reducing agents represent a promising therapeutic approach for restoring leptin sensitivity in obese women. By targeting

cellular stress mechanisms rather than symptomatic outcomes, compounds like curcumin, resveratrol, quercetin, and taurine address fundamental pathology underlying leptin resistance. Their ability to modulate GRP78, XBP1, and CHOP expression translates into improved leptin receptor function and metabolic signaling. Future clinical trials should prioritize sex-specific dosing strategies and examine long-term effects on weight management and metabolic syndrome prevention in women.

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