GLP-1 Receptor Agonists and Joint Health

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BACKGROUND AND AIMS

The primary objective of this research was to synthesise the current state of knowledge regarding the multi-faceted effects of glucagon-like peptide-1 (GLP-1) receptor agonists (RA) on the musculoskeletal system. By evaluating their impact on osteoarthritis (OA), osteoporosis, sarcopenia, intervertebral disc degeneration, and low back pain, this work highlights a therapeutic potential that extends far beyond metabolic regulation. GLP-1 receptors are not merely localised to the gut or brain; they are actively expressed within the synovial joint and in spinal tissues. When these receptors are activated, they initiate a cascade that reduces inflammatory signalling, mitigates oxidative stress, and suppresses the production of catabolic enzymes in chondrocytes and potentially other cell types in the joint. In preclinical models of OA, GLP-1 RAs have demonstrated the ability to attenuate cartilage degradation and preserve subchondral bone architecture.[1,2] Clinically, the weight reduction associated with these medications correlates strongly with decreased knee pain and enhanced joint function, though a notable gap persists in research that integrates advanced imaging with biochemical markers to confirm these structural benefits.

DISCUSSION

In bones, GLP-1 signalling plays a critical dual role by inhibiting the formation of bone-resorbing osteoclasts while simultaneously enhancing the activity of bone-forming osteoblasts. This biological synergy suggests that GLP-1 RAs may protect bone mineral density during periods of rapid weight reduction, which is accompanied by loss of bone. In skeletal muscle, while a reduction in lean mass often mirrors total weight loss, there is evidence that GLP-1 RAs may improve the 'quality' of the remaining muscle tissue, despite the loss of muscle mass. By enhancing mitochondrial function, improving insulin sensitivity, and reducing intramuscular lipid content, these agents may mitigate the typical sarcopenic decline associated with ageing and obesity.[3]

In the spine, adipokines are increasingly recognised for their pathogenic roles in driving degenerative spinal diseases,[4]

leading to profound immunometabolic alterations within disc cells.[5] Crucially, emerging preclinical models of intervertebral disc degeneration demonstrate that GLP-1 RAs exert potent anti-apoptotic, anti-inflammatory, and anti-fibrotic actions, suggesting they can actively slow the structural breakdown of the discs. Clinical observations have already pointed to significant improvements in the severity of low back pain. These improvements are likely mediated by a dual mechanism: the mitigating systemic effects of reduced adiposity and lower systemic inflammation, combined with a substantial decrease in the mechanical load placed on the spinal column.

CONCLUSION

The landscape of obesity pharmacotherapy is shifting rapidly from single-pathway agents like semaglutide to multi-hormone agonists. These next-generation co-agonists and tri-agonists aim to stimulate two or three metabolic pathways simultaneously, incorporating other incretin hormones such as glucose-dependent insulinotropic polypeptide along with GLP-1. For the treatment of obesity, these emerging combination therapies are designed to achieve greater weight loss and superior metabolic health, while avoiding the adverse side-effects commonly observed with monotherapy. While GLP-1 RAs demonstrate clear protective potential for cartilage, bone, skeletal muscle, and spinal tissues, more clinical evidence is required to establish their utility for the long-term management of specific musculoskeletal diseases. To fully realise this potential, well-designed, randomised, double-blind, placebo-controlled clinical trials are urgently needed. Such trials must prioritise objective imaging and biochemical biomarker endpoints to definitively determine whether these multi-hormone agents can function as true disease-modifying treatments capable of halting the progression of OA, low back pain, and other degenerative musculoskeletal conditions.[6]

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