GLP–1 Receptor Agonists: The New Magic Bullet? Musculoskeletal Consequences and Countermeasures

The emergence of glucagon–like peptide–1 receptor agonists (GLP–1RAs) and other incretin pharmacotherapies, including semaglutide and tirzepatide, represents one of the most significant developments in obesity management. By producing weight losses previously achievable only through bariatric surgery, these agents have transformed the therapeutic landscape and stimulated considerable interest among clinicians, researchers, policymakers, and patients. Whilst the metabolic and cardiometabolic benefits of these medications are increasingly well established, considerably less attention has been directed towards their implications for musculoskeletal health. This is an important omission given that preservation of skeletal muscle, bone integrity, and physical function are essential determinants of long–term health outcomes, particularly in populations at risk of sarcopenia, frailty, and musculoskeletal disease. A key concern is that substantial pharmacologically induced weight loss is accompanied by reductions in fat–free mass. Evidence from randomised controlled trials indicates that a meaningful proportion of the weight loss achieved with these medications comprises lean tissue, although the magnitude of this loss could well vary according to age, baseline adiposity, degree of weight reduction, and the methodology used to assess body composition. Importantly, reductions in lean mass might occur in parallel with decreases in mechanical loading, creating a physiological milieu that may have implications for musculoskeletal adaptation. Whilst decreases in lean mass (often taken to imply muscle mass) are consistently reported, the functional significance of these changes remains incompletely understood, and emerging evidence suggests that alterations in muscle quality and performance may not necessarily mirror changes in muscle quantity. The skeletal consequences of incretin pharmacotherapies are perhaps even more uncertain. Weight loss is traditionally associated with increased bone turnover, reductions in bone mineral density, and, under some circumstances, elevated fracture risk. Although evidence does not yet demonstrate a consistent detrimental effect of these medications on skeletal health, the literature remains limited by relatively short intervention durations and a paucity of studies incorporating comprehensive assessments of bone outcomes. As the use of these agents expands among middle–aged and older adults, greater understanding of their effects on bone remodelling and bone strength is required. This presentation will critically evaluate the evidence concerning the effects of incretin pharmacotherapy induced weight loss on skeletal muscle mass, muscle function, bone health, and physical performance. The presentation will also examine the limitations of existing evidence, methodological challenges, and key areas where further research is required. The latter part of the presentation will focus upon evidence–informed strategies to preserve

musculoskeletal health during treatment. Resistance exercise has been suggested as the most effective intervention available for attenuating losses of skeletal muscle mass and strength, while optimisation of dietary intake may further support the maintenance of lean tissue. Consideration will also be given to the potential role of weight–bearing exercise, nutritional adequacy, and broader lifestyle interventions in mitigating adverse musculoskeletal consequences. Clearly, a comprehensive understanding of the musculoskeletal implications of these medications will be essential to maximise their clinical benefits while minimising unintended consequences.