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Letter to the editor

Beyond Benefits: The Unseen Risks of GLP-1 Receptor Agonists in Recent Trials

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1. Introduction

In recent years, GLP-1 receptor agonists (GLP-1RAs) have gained considerable attention in the medical community for their therapeutic potential. Currently approved for treating obesity and diabetes, these medications are also being investigated in numerous clinical trials for various new applications. Emerging indications include cardiovascular disorders, neurodegenerative diseases, metabolic liver disease, chronic kidney disease, and mental health conditions such as depression, further broadening their therapeutic scope [1,2]. While GLP-1RAs offer promising benefits, their use is not without risks. Established adverse effects commonly include gastrointestinal issues such as nausea, vomiting, diarrhea, constipation, reduced bowel motility, gallbladder disease, and acute kidney injury [3]. Recently, however, additional adverse effects have surfaced in various studies, raising concerns about the implications of widespread GLP-1RA use.

2. Muscle Mass Loss

One notable adverse effect of GLP-1 receptor agonists (GLP-1RAs) is the loss of lean body mass, including muscle. Research shows that muscle loss, assessed through decreases in fat-free mass, can account for 25% to 39% of total weight loss over 36 to 72 weeks [4]. Clinical trials reveal considerable variability in the impact of GLP-1-based therapies on lean mass: some studies report that reductions in lean mass constitute 40% to 60% of total weight lost, while others indicate losses of around 15% or less .[5]

This muscle loss appears to be more closely linked to the overall extent of weight reduction rather than a direct effect of GLP-1RAs themselves, although further research is necessary to validate this hypothesis. Notably, the annual muscle mass decline with GLP-1RAs is greater than the typical age-related loss of about 0.8% per year, or roughly 8% per decade for those aged 40 to 70.[6]

Some researchers suggest that the muscle-related changes associated with weight loss from GLP-1RAs may be adaptive, reflecting a physiological response that preserves or minimally impacts muscle health and function. Recent evidence, including studies utilizing magnetic resonance imaging, indicates that reductions in muscle volume during GLP-1RA treatment align with expected changes due to aging, disease status, and weight loss. Improvements in insulin sensitivity and reductions in muscle fat infiltration may contribute to this adaptive process, enhancing muscle quality and potentially reducing the risk of strength and functional loss [5,7]. However, factors such as advanced age and the severity of underlying conditions may affect the suitability of candidates for these therapies, particularly concerning the risk of sarcopenia. To promote better muscle health during weight loss, several pharmacological strategies aimed at maintaining or enhancing muscle mass in conjunction

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with GLP-1-based therapies are currently under development.

3. Increased Heart Rate

Another noted effect of GLP-1RAs is a slight increase in heart rate. While this increase has not yet been directly linked to cardiovascular events such as arrhythmias [8], the long-term implications remain uncertain. Due to this effect, it is suggested that GLP1-RA might not be beneficial in individuals with severe left ventricular dysfunction, reduced ejection fraction and/or a history of repeated hospitalization for heart failure [9]. The mechanism behind the heart rate increase induced by GLP-1RAs is not fully understood. However, a recent study suggests that GLP-1 may exert direct chronotropic effects on the heart, mediated by GLP-1 receptors located in the pacemaker cells of the sinus node. This interaction may lead to changes in action potential morphology and the primary pacemaking site through a calcium signaling response, characterized by protein kinase A-dependent phosphorylation of calcium cycling proteins involved in heart rhythm regulation [10].
Interestingly, it is speculated that the increase in heart rate associated with GLP-1RAs could potentially benefit patients with heart failure with preserved ejection fraction (HFpEF), where chronotropic incompetence is a common issue [11].

4. Conclusion

As GLP-1 receptor agonists continue to reshape treatment paradigms for various conditions, it is vital to remain vigilant regarding their side effects. The observed lean muscle mass loss and increased heart rate warrant further investigation to fully understand their implications for long-term patient health. Ongoing research will be crucial in determining the balance between the therapeutic benefits of GLP-1RAs and their potential adverse effects, ensuring that these medications can be used safely and effectively in clinical practice .

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