Beyond muscle: could GLP-1 receptor agonists offset the tendon risk of intensive lipid-lowering therapy?

INVITED EDITORIAL

Beyond muscle: could GLP-1 receptor agonists offset the tendon risk of intensive lipid-lowering therapy?

Running head: GLP-1 receptor agonists, lipid lowering and tendon safety

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Dear editor:

Tendinopathy and tendon rupture occupy an odd position in cardiovascular (CV) medicine: formally recognised as adverse events of special interest (AESI) in contemporary lipid trials, and routinely adjudicated within them, yet almost never discussed at cardiology meetings. The systematic review and meta-analysis by Khayyat and Khayyat in the current 4/2026 issue of Archives of Medical Science [1] approaches the tendon from the opposite direction, asking whether glucagon-like peptide-1 receptor agonists (GLP-1RAs) promote its healing. Their answer is cautious, and appropriately so. The question their work opens is considerably larger, and it belongs to lipidology.

What the meta-analysis establishes, and where it stops

The authors screened 773 records and synthesized 41. Of six retrospective cohorts, only two - both in total shoulder arthroplasty - proved poolable, yielding an odds ratio for revision of 0.71 (95% CI: 0.59–0.85) with $I^2 = 0\%$ [1]. The estimate is statistically tidy and evidentially thin: two administrative database analyses, standing alongside a third cohort that reported increased perioperative complications and readmission, cannot demonstrate that GLP-1RAs protect tendon, and the authors rightly present the result as hypothesis-generating [1]. A second limitation deserves emphasis. Although the review is framed around tendon and ligament healing, and its eligibility criteria admitted ligament transection and rupture models alongside cruciate and collateral ligament injury in humans, virtually no ligament-specific outcome data were retrieved. Ligament is at present an extrapolation rather than a finding, and future work should describe it as such.

Biological plausibility and clinical relevance

The mechanistic case is nonetheless coherent. Exendin-4 (potent natural GLP-1 receptor agonist) induces tenogenic differentiation of human mesenchymal stem cells, upregulating scleraxis and mohawk together with collagen I, decorin, biglycan and tenascin-C [2]. In a rat model of rotator cuff repair, liraglutide reduced supraspinatus fatty infiltration and improved functional recovery without measurable muscle loss [1]. Clinically, preoperative semaglutide has been associated with fewer postoperative complications and a lower two-year re-tear rate after arthroscopic cuff repair in patients with type 2 diabetes [3]. Whether the operative mechanism is cytokine suppression, reduced matrix metalloproteinase (MMP) expression, improved glycaemic control with diminished accrual of advanced glycation end products, or mechanical unloading through weight reduction, the vector is consistently anti-catabolic. The clinical relevance is immediate: incretin therapy is now increasingly common among patients undergoing tendon surgery, and peri-operative interruption has become routine because delayed gastric emptying leaves residual gastric contents that raise the risk of aspiration during anaesthesia, and such decisions are currently taken without any consideration of their consequences for healing in either direction.

Could GLP-1RAs offset the tendon risk of intensive lipid lowering?

Most patients in whom these observations arise are concurrently receiving lipid-lowering therapy (LLT), and here the tendon literature runs in the opposite direction. French pharmacovigilance identified 96 statin-attributed tendon events, the majority within the first year of exposure and concentrated among patients with diabetes, hyperuricemia or heavy physical loading [4]. Eliasson and colleagues combined two

Swedish population-based cohorts with a three-dimensional human tenocyte construct model: current, though not former, statin use was associated with trigger finger (adjusted hazard ratio [aHR] 1.50 in men) and shoulder tendinopathy (1.43 in men), while simvastatin approximately halved construct failure force and stiffness, with a six-fold increase in MMP-1 release and no reduction in total collagen [5]. The lesion is one of matrix turnover rather than matrix deficiency. The evidence is not uniform: earlier cohorts confined to rupture endpoints were null [5], and because hypercholesterolemia itself alters tendon structure and pain, confounding by indication is substantial [6]. Bempedoic acid nonetheless carries a labelled tendon-rupture warning, although in CLEAR Outcomes tendinopathy-related events occurred in only 2% of patients in both arms [7].

This juxtaposition supports a hypothesis that we believe merits explicit statement. If intensive LLT may destabilize tendon by shifting the MMP–tissue inhibitor of metalloproteinases balance toward collagenolysis, and GLP-1RAs suppress the same collagenases and the cytokines that induce them, then concurrent incretin therapy might mitigate the tendon risk (even though it remains small) attributable to statins, to bempedoic acid, or to intensive combination lipid lowering more generally (**Figure 1**). We stress that no data address this: it is a hypothesis, and we advance it as one.

The stake is not orthopaedic. Statin intolerance affects approximately 9.1% of treated patients worldwide, and is more frequent with older age, female sex, obesity and type 2 diabetes [8] — precisely the profile of degenerative tendinopathy. Patients who become intolerant following myocardial infarction sustain more recurrent coronary events but no increase in all-cause mortality than those who remain adherent

[9]. Tendon is clinically silent until it fails, has no serum marker, and presents to orthopaedic rather than cardiovascular services; any tendon-derived component of what is recorded as musculoskeletal intolerance is therefore liable to be misattributed, managed as though it were myalgia, and permitted to drive discontinuation of therapy that prevents death. On the other hand, if it ruptures, urgent orthopaedic surgery is needed and is followed by a prolonged period of rehabilitation and immobilization, which - especially in post-event or elderly patients - can further elevate cardiovascular risk.

Testing the hypothesis

Three approaches can be carried out without launching a new clinical trial. First, because tendon AESIs are already adjudicated and concomitant glucose-lowering therapy already recorded, a formal interaction analysis within completed and ongoing lipid outcome programs demands no additional data collection. Second, target trial emulation in claims databases, using an active-comparator new-user design matched on body mass index, glycated hemoglobin and fluoroquinolone or corticosteroid exposure, would supply an independent estimate. Third, Third, the pre-clinical model that originally revealed the statin signal can simply be reused: tendon tissue is exposed to simvastatin with and without exendin-4, and matrix metalloproteinase release (MMP-1 and MMP-13) together with ultimate failure load are measured, allowing a single laboratory experiment to confirm or refute the proposed mechanism.

Caveats

Optimism would be premature. The effects of GLP-1RAs on the muscle–tendon unit are not uniformly favourable: a substantial share of the weight lost is lean tissue [10,11], and the enthesis is loaded by muscle rather than by drug, so a deconditioned muscle re-loaded onto a matrix conditioned by years of hyperglycemia is not self-evidently safer. Suppression of the early reparative inflammatory phase may not be desirable. Timing may matter more than exposure. And because weight loss itself reduces tendon load, part of the reported odds ratio may be biomechanical rather than biological.

What should follow

Tendon endpoints should be prospectively defined and harmonised rather than captured as free-text adverse events; where AESI adjudication already exists in lipid trials, its interaction with incretin exposure should be reported; GLP-1RA outcome programmes, which have randomised tens of thousands of patients from the highest-risk tendinopathy demographic, should adopt the tendon endpoints that lipid trials already collect; and musculoskeletal complaints arising during intensive LLT deserve explicit separation of myalgia from tendinopathy before therapy is down-titrated or withdrawn. Khayyat and Khayyat asked whether GLP-1RAs help tendons heal. The more consequential possibility raised by their work is that one class prescribed for the vasculature may modify the safety profile of another, in a tissue that neither literature has yet troubled to measure. In an era of numerous highly effective, innovative therapies—and patients who often present with multiple risk factors and comorbidities requiring polypharmacy—such a comprehensive approach can

optimize personalized treatment. It enhances not only drug efficacy but also safety, thereby improving overall clinical outcomes.

Figure

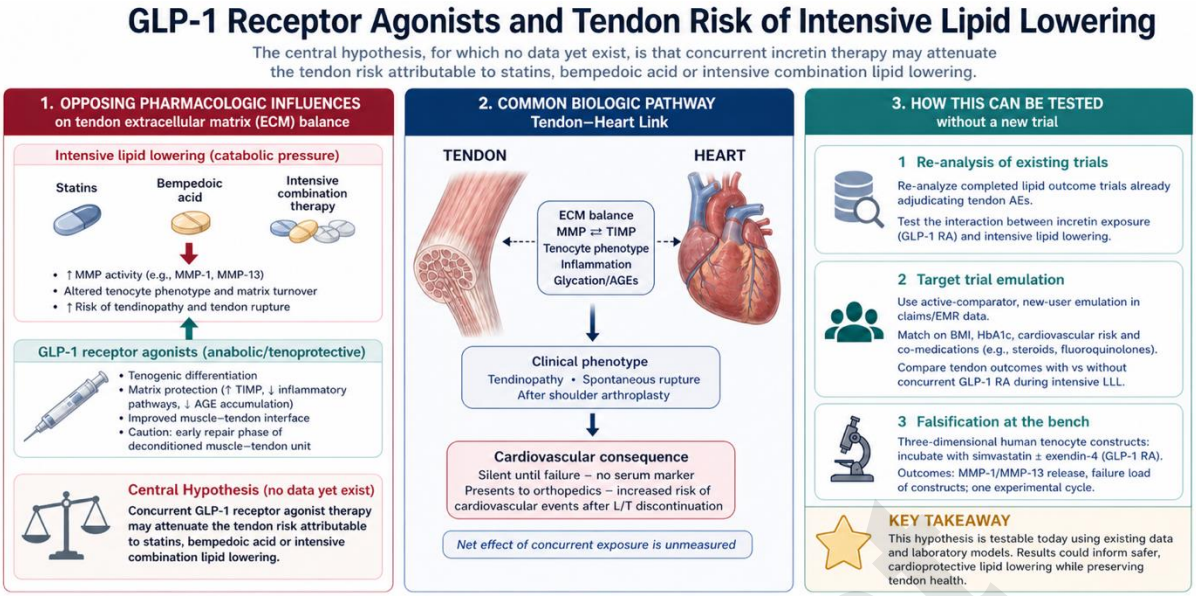

Figure 1. **Proposed conceptual framework linking GLP-1 receptor agonists with tendon risk during intensive lipid-lowering therapy.** *Intensive LLTsmay promote extracellular matrix (ECM) catabolism through increased matrix metalloproteinase (MMP) activity, altered tenocyte phenotype, and accelerated matrix turnover, thereby increasing the risk of tendinopathy and tendon rupture (left panel). In contrast, GLP-1 RAs may exert tenoprotective effects by promoting tenogenic differentiation, preserving ECM homeostasis through increased tissue inhibitors of metalloproteinases (TIMPs), reducing inflammation and advanced glycation end-product (AGE) accumulation, and improving the muscle–tendon interface. Based on these opposing biological influences, we hypothesize that concurrent GLP-1 RA therapy may attenuate potential tendon toxicity associated with intensive lipid lowering, although this hypothesis has not yet been directly tested. The central panel illustrates the proposed tendon–heart biological axis, in which shared mechanisms – including ECM remodeling, the MMP/TIMP balance, inflammation, glycation, and tenocyte phenotype – may influence both tendon integrity and CV health. Disruption of these pathways may manifest clinically as tendinopathy, spontaneous tendon rupture, or tendon failure following orthopaedic procedures, while also reflecting broader CV vulnerability. The net effect of concurrent exposure to GLP-1 RAs and intensive LLT on tendon outcomes remains unknown. The right panel outlines pragmatic approaches for testing this hypothesis without conducting a new randomized clinical trial. These include (1) re-analysis of completed CV outcome and lipid-lowering trials with adjudication of tendon adverse events and assessment of interaction by GLP-1 RA exposure; (2) target trial emulation using large electronic health record or administrative claims databases with active-comparator, new-user designs and adjustment for key confounders; and (3) mechanistic validation using three-dimensional human tenocyte models exposed to LLT with or without GLP-1RAs, assessing ECM remodeling, MMP/TIMP expression, and biomechanical failure. Together, these complementary strategies provide an immediately testable framework to determine whether GLP-1 receptor agonists can preserve tendon health while maintaining the CV benefits of intensive lipid lowering.*

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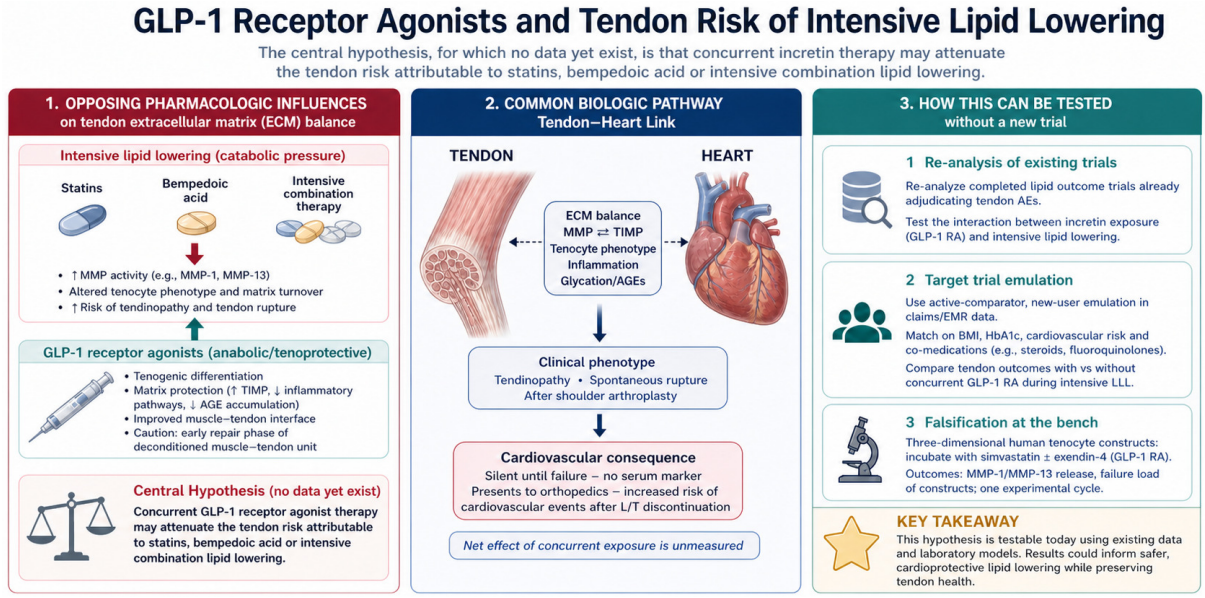

Proposed conceptual framework linking GLP-1 receptor agonists with tendon risk during intensive lipid-lowering therapy