# Glucagon-Like Peptide-1 Receptor Agonists Suppresses Adaptive Lymphocyte Responses in Total Joint Replacement Patients

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**INTRODUCTION:** Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide (Ozempic), have become cornerstone therapies for type 2 diabetes and obesity. Their expanding use has raised important questions about their implications in the perioperative setting, particularly in major surgeries like total joint replacement (TJR). Prior studies have highlighted the immunomodulatory potential of GLP-1RAs, including reduced systemic inflammation and lower rates of postoperative complications such as wound problems, hospital readmissions, and even periprosthetic joint infections (1). Mechanistically, GLP-1 receptors have been identified on T cells, where their activation exerts anti-inflammatory effects and shifts immune balance toward a more regulated state (2). Despite these insights, the direct influence of GLP-1RAs on adaptive immunity, specifically lymphocyte responses in the TJR population, remains poorly understood. Given the rapid rise in GLP-1RA prescriptions among TJR candidates, we pondered whether these agents alter lymphocyte responsiveness to potent mitogens, bacterial antigens, and metal haptens. We hypothesized that GLP-1RAs would exert anti-inflammatory effects on peripheral blood mononuclear cells (PBMCs) from TJR candidates. In a prospective cohort of primary and revision TJR candidates (n=67), we analyzed in vitro lymphocyte reactivity to phytohemagglutinin (PHA), Staphylococcus aureus peptidoglycan (PGN), and Nickel haptens using a lymphocyte transformation assay, comparing baseline responses with those observed under in vitro GLP-1RA treatment at the time of preoperative blood collection.

**METHODS***:* *Subject Groups*: Blinded de-identified pre-op bloodwork data was reviewed for primary (n=41) and revision (n=27) TJR candidates (19 males and 49 Females). In vitro lymphocyte responses to phytohemagglutinin (PHA), Staphylococcus aureus peptidoglycan (PGN), and Nickel haptens were reviewed under normal and GLP-1RA treated conditions. *Lymphocyte Transformation Testing*: Peripheral blood mononuclear cells (PBMCs) were collected from 30mL of peripheral blood by Ficoll gradient separation. PBMCs were cultured with either 10 ug/ml of PHA, 10 ug/ml of Staph A PGN and 1.0 mM Nickel Chloride in the presence or absence of 10 ug/ml of GLP-1 RA. 3H Thymidine was added at day 5 of culture and 3H thymidine incorporation was analyzed using a beta scintillation counter at day 6. A stimulation Index (SI) of reactivity was calculated by dividing scintillation counts per minute of PHA, StaphA PGN and Nickel treated cells over untreated controls in the presence or absence of GLP1-RA. *Statistical Analysis*: Statistical significance in lymphocyte SI comparing PHA, Staph PGN and Nickel in GLP-1RA treated vs. non-treated lymphocytes were calculated using a Non-parametric Mann-Whitney test.

**RESULTS**: *Basal Lymphocyte Reactivity to GLP-1RA:* GLP-1RA–treated PBMCs exhibited a statistically significant stimulatory effect in control PBMCs from TJR candidates, with median counts per minute (cpm) of 3,223 compared to 1,245 cpm in non–GLP-1RA–treated controls ($p < 0.0001$) (Fig. A). *GLP-1RA effect on Lymphocyte Stimulation to PHA, PGN and Nickel:* GLP-1RA exhibited an inhibitory effect on lymphocyte proliferation in TJR candidates in response to all mitogens, antigens, and haptens tested (Fig. B). GLP-1RA–treated lymphocytes exhibited a median stimulation index (SI) of 20.6 compared to a median SI of 40.3 in non–GLP-1RA–treated lymphocytes, representing a 50% decrease in reactivity ($p < 0.0001$). Similarly, Staphylococcus aureus PGN–treated lymphocytes exhibited a median SI of 5.8 in the presence of GLP-1RA compared to 11.04 in non–GLP-1RA–treated lymphocytes ($p < 0.0001$). Comparable inhibitory effects were observed in metal-sensitized TJR candidates, where nickel-induced lymphocyte proliferation showed a median SI of 7.6 compared to only 3.6 in GLP-1RA–treated lymphocytes.

**DISCUSSION:** Remarkably, the results of this study support our hypothesis that GLP-1RAs exert an immunomodulatory (anti-inflammatory) effect on lymphocyte proliferative responses to mitogenic (PHA), antigenic (PGN), and haptenic (nickel) stimuli in TJR candidates. To our knowledge, this is the first study to directly compare in vitro lymphocyte responses to diverse immunological stimuli in the presence or absence of GLP-1RA among TJR patients. Previous clinical studies have suggested that GLP-1RAs improve arthroplasty outcomes by lowering infection rates, decreasing hospital readmissions, and enhancing wound healing; however, some conflicting evidence highlights the need for larger multicenter, longitudinal investigations. Mechanistically, recent work has shown that GLP-1RA signaling functions as a negative costimulatory pathway in T lymphocytes. Our findings are consistent with these observations, demonstrating that GLP-1RA–treated lymphocytes exhibit a statistically significant reduction in proliferative responses. Notably, the decrease in lymphocyte reactivity observed to S. aureus PGN may have clinical relevance in the context of periprosthetic joint infection risk, particularly in TJR patients who may also be receiving additional anti-inflammatory therapies (e.g., biologics) pre- and postoperatively. Interestingly, the immunomodulatory effects of GLP-1RA may also confer unintended protective benefits in scenarios of exaggerated innate and adaptive immune activation in response to biomaterial degradation products, such as in cases of metal hypersensitivity. Supporting this, our data demonstrates that GLP-1RA treatment significantly reduces nickel-induced lymphocyte proliferation in metal-sensitive patients, suggesting a potential role in mitigating metal hypersensitivity immune responses in orthopedic patients. Several limitations must be considered when interpreting these findings. The 10 µg/mL concentration of GLP-1RA used in vitro provides proof of concept but may not reflect physiological GLP-1RA levels achieved in vivo, which vary considerably depending on the specific drug, dosage, half-life, and timing of administration. Moreover, it was not possible to confirm whether study participants were actively taking GLP-1RAs at the time of testing. Although GLP-1RAs are increasingly utilized as an effective preoperative weight-loss intervention, it remains imperative to better understand their long-term immunological impact on protective immunity in the TJR population. Additional studies are needed to define relevant thresholds at which chronic GLP-1RA exposure begins to attenuate adaptive immune responses in TJR candidates with adverse clinical consequences.

**SIGNIFICANCE/CLINICAL RELEVANCE**: The rapid rise of GLP-1RA therapies in the TJR population continues, but their long-term effects on immune function are not well understood. Our data provides preliminary evidence suggesting GLP-1RA can directly induce significant attenuation of adaptive immune responses to mitogens, metal haptens, and bacterial antigens in vitro, which raises the possibility of increased risk of infection and/or, alternatively, may be useful as a treatment for metal hypersensitivity responses in symptomatic orthopedic patients.

**REFERENCES**: 1- Lima et.al Journal of Arthroplasty 2025 2- Fiorina et.al Cell Metabolism 2024