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Abstract

Semaglutide, a GLP-1 (glucagon-like peptide-1) receptor agonist, is widely prescribed for weight loss in non-diabetic populations. Given the link between obesity and overactive bladder (OAB), we explored whether GLP-1 use would improve urinary outcomes beyond its weight loss benefit for non-diabetic adults undergoing BOTOX treatment for OAB. Using the TriNetX database, we conducted a retrospective cohort study of non-diabetic OAB patients treated with BOTOX alone or with concurrent GLP-1 therapy. Propensity score matching (1:1) adjusted for age, race, ethnicity, hypertension, and BMI/obesity. After matching, 992 patients were included in each group. GLP-1 use was associated with a lower incidence of urinary retention (8.6% vs. 4.9%, risk difference 3.66%, $p = 0.0044$) and urinary tract infection (13.3% vs. 8.8%, risk difference 4.54%, $p = 0.00224$), with corresponding improved one-year retention-free and UTI-free survival on Kaplan Meier (KM) analysis. Antispasmodic initiation rates were similar (11.8% vs. 10.3%, risk difference 1.55%, $p = 0.6921$), and KM analysis showed no significant difference. These findings suggest that GLP-1 receptor agonist use may improve select urinary outcomes in non-diabetic adults undergoing BOTOX treatment for OAB and support further investigation into its potential adjunctive role in OAB management with longer follow-up.

Keywords: overactive bladder (OAB); GLP-1 receptor agonist; onabotulinumtoxin A (BOTOX); diabetes; semaglutide; weight loss; urinary retention

Key Contribution: This study demonstrates that GLP-1 receptor agonist therapy is associated with reduced risks of urinary retention and urinary tract infection in non-diabetic adults receiving BOTOX for overactive bladder; independent of weight loss. These findings highlight the potential of GLP-1 agents as adjunctive therapy in OAB management

1. Introduction

Overactive bladder syndrome (OAB) is defined as urinary urgency, often accompanied by urinary frequency and nocturia, with or without incontinence. This urinary urgency can significantly interrupt a patient's daily activities and sleep, profoundly diminishing their quality of life. The global prevalence of OAB is reported to be nearly 20%, with higher rates among female, elderly, overweight and obese populations [1]. With rates this high, several treatment strategies are offered to help patients manage their symptoms. Treatments vary in intensity, ranging from conservative measures to more advanced options. First-line often includes pelvic floor exercises to strengthen the pelvic floor muscles that suppress urgency, lifestyle therapies to mitigate the worsening effects of smoking and weight, and other less supported but more behavioral complement therapies such as hypnotherapy and acupuncture [2]. Pharmacological options, such as beta-3 adrenergic agonist drugs and anti-

muscarinic agents, are common adjuncts to these first-line treatments but may be associated with undesirable side effects, like cognitive impairment. With or without these agents, improvement from more conservative treatment plans may take up to 12 weeks to manifest. Minimally invasive procedures, like percutaneous tibial nerve stimulation or sacral neuromodulation, may substitute or replace medical therapy if not effective [3]. When all else fails and symptoms persist, surgical interventions like augmentation cystoplasty and urinary diversion may provide relief to these refractory patients, albeit with variable results and significant potential for complications.

Within 15 years, onabotulinumtoxinA (BOTOX) has emerged as an option for refractory OAB. BOTOX injections into detrusor muscle are an established treatment for refractory OAB, inhibiting neurotransmitter release and leading to reduced bladder overactivity [4]. Though a promising avenue, whether to include BOTOX in a patient's OAB treatment regimen, like all other treatment options, must depend on shared decision making between the patient and physician.

Ultimately, the management of overactive bladder, particularly in refractory cases, hinges on this nuanced and collaborative approach between patient and physician. Rather than adhering to a rigid stepwise progression, contemporary guidelines from the American Urological Association (AUA) and the European Association of Urology (EAU) now emphasize multi-dimensional, individualized care, recognizing that what works best clinically must also be acceptable and sustainable for the patient [5,6]. As such, the path to optimal symptom control is not a single trajectory but a dynamic, patient-centered dialogue that honors both medical expertise and lived experience. Factors to consider when planning treatment include a patient's ability to perform intermittent catheterization for BOTOX, their tolerance for minor surgery and implantation, their ability to commit to frequent visits, and general preferences and goals.

Despite all the possible avenues available for treatment, there are still significant limitations. Though effective, BOTOX is associated with an increased risk of elevated post-void residual volume and urinary tract infection [7–9]. When compared against neuromodulation treatments like sacral nerve neuromodulation and percutaneous tibial nerve stimulation in a meta-analysis, BOTOX was still associated with more complications of urinary retention and UTI [10]. Thus, these adverse effects can necessitate intermittent catheterization for patients and may diminish the overall benefits of the treatment [11]. Especially for those populations who are at higher risk for UTIs like elderly and obese patients, BOTOX injection benefits may not outweigh the potential complications [12,13].

The association between being overweight and OAB severity is well-documented [14–16]. Though the pathophysiology is not yet fully understood, many proposed mechanisms have been investigated. One mechanism describes how larger waist circumference, and BMI may cause excess abdominal pressure, elevating bladder pressure and urethral mobility, further exacerbating OAB [17]. Another proposed mechanism ascribes the weakened pelvic floor brought about by obesity as the culprit [18]. Additionally, weight loss has been shown to reduce the severity of OAB symptoms, supporting obesity's role as a modifiable risk factor in its pathogenesis [19].

GLP-1 receptor agonists (e.g, semaglutide, liraglutide) (GLP-1 RA) were first approved by the FDA in 2005 for the treatment of Type 2 Diabetes but have only recently revolutionized the market as a weight loss drug for the non-diabetic patient. Importantly, GLP-1 RA have shown to significantly reduce weight with an acceptable safety for obese or overweight patients without diabetes [19]. By mimicking the effects of endogenous GLP-1, these drugs stimulate insulin release from the pancreas, regulate appetite and satiety in the brain, and slow down gastric emptying [20].

With this in mind, we wanted to explore if the benefits of GLP-1 RA reach beyond simply weight loss. In diabetic patients, these drugs have shown to reduce albuminuria in chronic kidney disease, reduce all-cause mortality in cardiovascular disease, reduce blood pressure and dyslipidemia, and decrease metabolic complications in PCOS [21]. In non-diabetic patients, there is less direct, though intriguing support for its renoprotective, cardiovascular, and fertility effects [21–24]. Other research highlights a potential anti-inflammatory effect, reducing circulating inflammatory cytokines like TNF-a and IL-6, and highly sensitive C-reactive protein, in both mice and human models [25–28]. As

inflammation, autonomic tone, and detrusor overactivity all contribute to OAB, we speculate that GLP-1 RA could additionally influence bladder function.

So far, no studies have evaluated urinary outcomes of GLP-1 RAin non-diabetic OAB patients on BOTOX. This retrospective cohort study aims to explore the potential impact of GLP-1 receptor agonist use on urinary outcomes in non-diabetic patients with refractory OAB undergoing onabotulinumtoxinA treatment, addressing a critical gap in the current literature. Using the TriNetX database, we conduct a large-scale analysis highlighting any discrepancies in outcomes between GLP-1 RA users and control cohorts.

We hypothesized that GLP-1 RA are associated with improved urinary outcomes in non-diabetic female patients with OAB receiving BOTOX beyond weight loss benefits. Primary outcomes evaluated incidence of urinary tract infection (UTI), urinary retention, and urinary antispasmodic use following BOTOX treatment.

2. Results

A total of 19,907 OAB patients who received BOTOX alone and 992 OAB patients who received both BOTOX and a GLP-1 receptor agonist (GLP-1 RA) were identified before matching. After 1:1 propensity score matching, 992 matched pairs were included for analysis.

The median follow-up duration was 365 days for the BOTOX-only cohort (IQR: 77.5 days) and 365 days for the combination cohort receiving BOTOX plus a GLP-1 receptor agonist (IQR: 163.5 days). The mean age was nearly identical (59.3 vs. 59.4 years; $SMD = 0.011$; $p = 0.8073$), and the proportion of female patients was also similar (92.0% vs. 91.1%; $SMD = 0.033$; $p = 0.4668$). The prevalence of cystitis was marginally higher in the GLP-1 group (30.1% vs. 34.2%; $SMD = 0.086$; $p = 0.0545$), though this did not reach statistical significance. (Table 1)

Medication utilization after matching revealed higher use of antimicrobials in the GLP-1 group (93.5% vs. 98.4%; $SMD = 0.248$; $p < 0.0001$), as well as increased use of antiemetics (75.1% vs. 83.9%; $SMD = 0.219$; $p < 0.0001$) and laxatives (68.5% vs. 74.6%; $SMD = 0.134$; $p = 0.0028$).

Table 1. Baseline characteristics of patients receiving intravesical BOTOX injection for overactive bladder, with and without concomitant GLP-1 receptor agonist therapy (Semaglutide). Values are shown before and after 1:1 propensity score matching. Continuous variables are presented as mean ± standard deviation; categorical variables are presented as number (%). Standardized mean differences (SMD) are reported to assess covariate balance between groups.

Characteristic	OAB + BOTOX (Before Matching)	OAB + BOTOX + GLP1 RA (Before Matching)	P-Value (Before Matching)	SMD (Before Matching)	OAB + BOTOX (After Matching)	OAB + BOTOX + GLP1 RA (After Matching)	P-Value (After Matching)	SMD (After Matching)
Age at Index (Mean ± SD)	62.4 ± 17.6	59.4 ± 13.2	< 0.0001	0.1935	59.3 ± 13.9	59.4 ± 13.2	0.8073	0.011
Female	15,971 (80.2%)	904 (91.1%)	< 0.0001	0.315	913 (92.0%)	904 (91.1%)	0.4668	0.0327
Male	3,563 (17.9%)	63 (6.4%)	< 0.0001	0.3594	59 (5.9%)	63 (6.4%)	0.7085	0.0168

Not Hispanic or Latino	15,513 (77.9%)	800 (80.6%)	0.0435	0.0671	802 (80.8%)	800 (80.6%)	0.9093	0.0051
White	15,858 (79.7%)	752 (75.8%)	0.0034	0.0927	770 (77.6%)	752 (75.8%)	0.339	0.0429
Black or African American	1,706 (8.6%)	127 (12.8%)	< 0.0001	0.1373	115 (11.6%)	127 (12.8%)	0.4104	0.037
Hispanic or Latino	1,333 (6.7%)	69 (7.0%)	0.7498	0.0103	71 (7.2%)	69 (7.0%)	0.8608	0.0079
Asian	339 (1.7%)	10 (1.0%)	0.0955	0.0601	10 (1.0%)	10 (1.0%)	1	< 0.0001
Overweight/Obesity (E65-E68)	5,216 (26.2%)	756 (76.2%)	< 0.0001	1.1554	755 (76.1%)	756 (76.2%)	0.958	0.0024
Hypertension (I10)	8,944 (44.9%)	575 (58.0%)	< 0.0001	0.2631	564 (56.9%)	575 (58.0%)	0.6175	0.0224
Stress Incontinence (N39.3)	5,398 (27.1%)	389 (39.2%)	< 0.0001	0.2591	391 (39.4%)	389 (39.2%)	0.9268	0.0041
BMI 40-44.9 (Z68.41)	880 (4.4%)	214 (21.6%)	< 0.0001	0.5275	219 (22.1%)	214 (21.6%)	0.7858	0.0122
BMI 45-49.9 (Z68.42)	431 (2.2%)	110 (11.1%)	< 0.0001	0.3647	104 (10.5%)	110 (11.1%)	0.6641	0.0195
BMI 29-29.9 (Z68.29)	453 (2.3%)	53 (5.3%)	< 0.0001	0.1608	48 (4.8%)	53 (5.3%)	0.6096	0.0229
BMI 28-28.9 (Z68.28)	457 (2.3%)	40 (4.0%)	0.0005	0.0993	37 (3.7%)	40 (4.0%)	0.7273	0.0157

BMI 27-27.9 (Z68.27)	461 (2.3%)	37 (3.7%)	0.0044	0.0827	38 (3.8%)	37 (3.7%)	0.9063	0.0053
Antimicrobials (AM000)	17,619 (88.5%)	976 (98.4%)	< 0.0001	0.4075	928 (93.5%)	976 (98.4%)	< 0.0001	0.2479
Antiemetics (GA605)	12,021 (60.4%)	832 (83.9%)	< 0.0001	0.5427	745 (75.1%)	832 (83.9%)	< 0.0001	0.2185
Laxatives (GA200)	11,381 (57.2%)	740 (74.6%)	< 0.0001	0.3739	680 (68.5%)	740 (74.6%)	0.0028	0.1344
Anti-infectives, vaginal (GU300)	7,163 (36.0%)	585 (59.0%)	< 0.0001	0.4731	518 (52.2%)	585 (59.0%)	0.0025	0.1362

2.1. Urinary Retention

For urinary retention outcomes, 212 patients in the BOTOX-only cohort and 241 patients in the BOTOX + GLP-1 RA group were excluded due to a documented history of urinary retention prior to the index event. Among the remaining patients, retention occurred in 67 of 780 patients (8.59%) in the BOTOX-only cohort, compared to 37 of 751 patients (4.93%) in the combination cohort. This translated to an absolute risk difference of 3.66% (95% CI: 1.16%–6.17%; p = 0.0044).

Kaplan-Meier (KM) analysis, excluding patients with pre-existing retention, demonstrated significantly improved retention-free survival in the GLP-1 RA combination group (log-rank p = 0.0064). The estimated hazard ratio for retention was 1.74 (95% CI: 1.16–2.59), indicating a significantly higher risk of urinary retention in the BOTOX-only group over the one-year follow-up period.
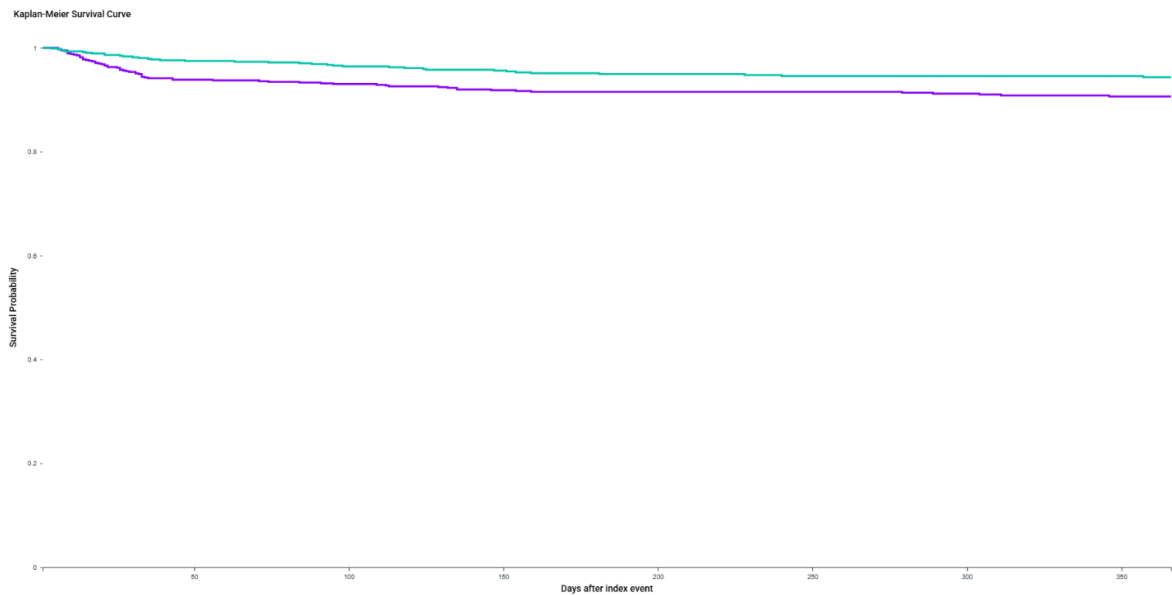
Figure 1. Kaplan-Meier curves for urinary retention-free survival over one year following BOTOX injection, with or without concurrent GLP-1 receptor agonist therapy. Patients treated with combination therapy (OAB + BOTOX + GLP-1 agonist) had significantly higher retention-free survival compared to those receiving BOTOX alone (log-rank p = 0.0064). At one year, the retention-free survival probability was 94.3% in the combination group versus 90.6% in the BOTOX-only group. The hazard ratio for urinary retention in the BOTOX-only group was 1.74 (95% CI: 1.16–2.59), indicating a 74% increased risk relative to combination therapy.

2.2. Urinary Tract Infection

For urinary tract infection (UTI) outcomes, 475 patients in the BOTOX-only cohort and 504 in the BOTOX + GLP-1 RA cohort were excluded due to a documented history of UTI prior to the index date. Among the remaining patients, 69 of 517 (13.3%) in the BOTOX-only group developed a new UTI, compared to 43 of 488 (8.8%) in the GLP-1 combination group. This yielded a risk difference of 4.54% (95% CI: 0.67%–8.40%).

KM analysis over one year demonstrated a higher UTI-free survival probability in the GLP-1 RA combination group (88.7%) compared to the BOTOX-only group (84.5%), with a statistically significant log-rank test ($\chi^2 = 4.136$, p = 0.0420).
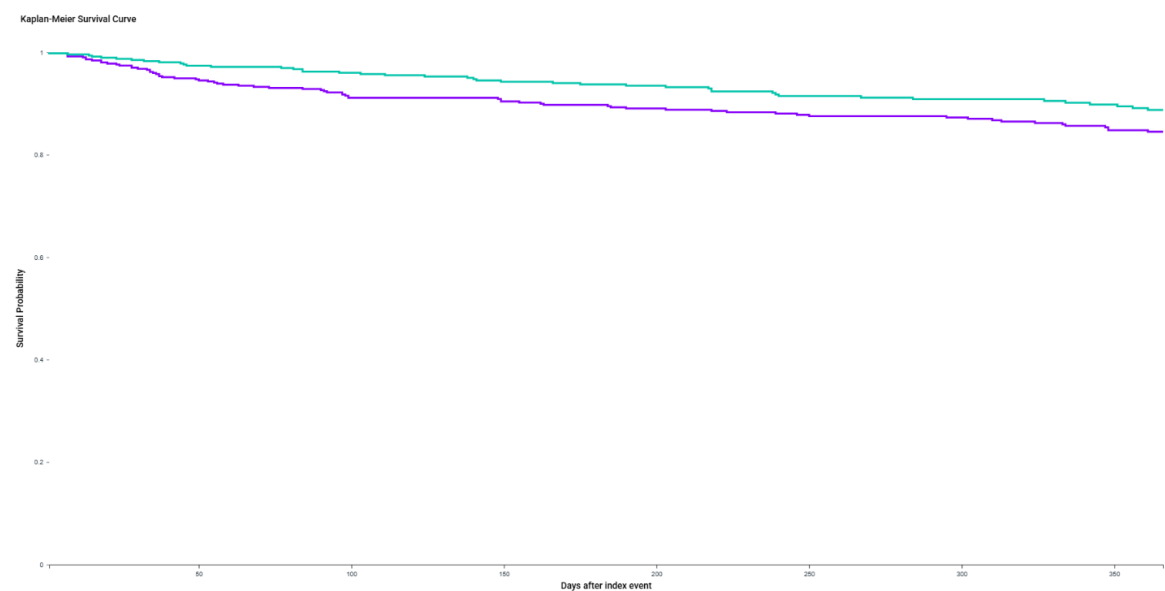

Figure 2. Kaplan-Meier curves for urinary tract infection (UTI)-free survival over one year following BOTOX injection, with or without concurrent GLP-1 receptor agonist therapy. Patients receiving combination therapy (OAB + BOTOX + GLP-1 RA) demonstrated significantly higher UTI-free survival compared to those receiving BOTOX alone (log-rank p = 0.042). At one year, survival probability was 88.7% in the combination group versus 84.5% in the BOTOX-only group. The hazard ratio for UTI in the BOTOX-only group was 1.48 (95% CI: 1.01–2.17), indicating a 48% increased risk relative to combination therapy.

2.3. Urinary Antispasmodic Use

For urinary antispasmodic use, 848 patients in the BOTOX-only cohort and 875 in the GLP-1 combination cohort were excluded due to a history of prior antispasmodic use. Among the remaining patients, 17 of 144 (11.8%) in the BOTOX-only antispasmodics post-treatment, compared to 12 of 117 (10.3%) in the GLP-1 group. This yielded a risk difference of 1.55% (95% CI: -6.07% to 9.17%).

KM survival analysis demonstrated no significant difference in antispasmodic-free survival between cohorts over the three-year follow-up (log-rank p = 0.7234; HR 1.14, 95% CI: 0.55–2.39; p = 0.3984).
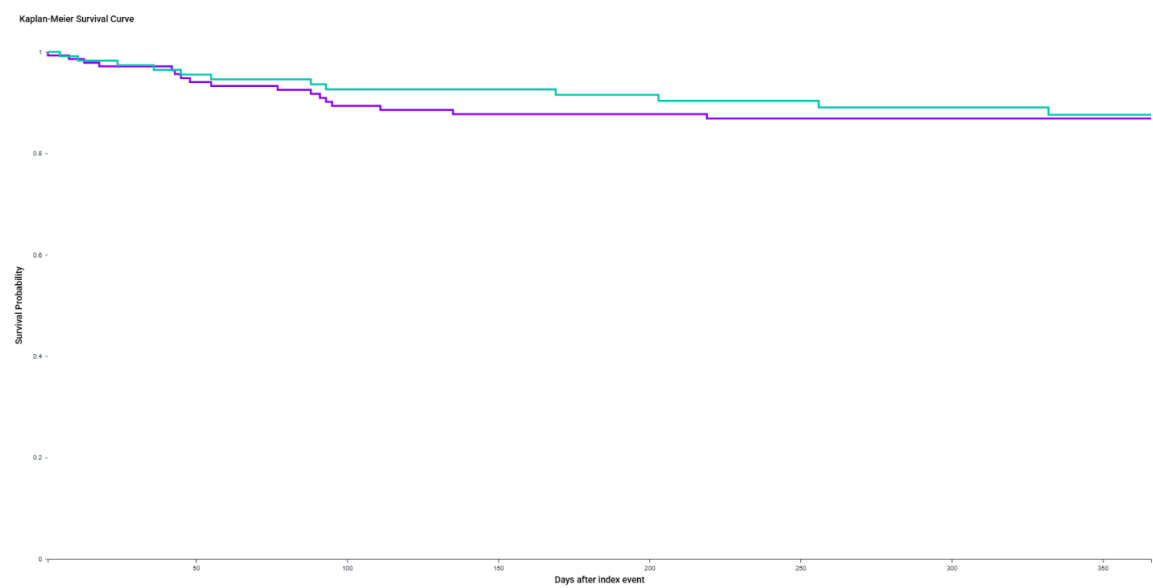
Figure 3. Kaplan-Meier curve for urinary antispasmodic-free survival among patients receiving BOTOX only versus BOTOX + GLP-1 receptor agonist therapy. After excluding patients with prior antispasmodic use (n=848 in the BOTOX-only cohort and n=875 in the combination cohort), 144 BOTOX-only patients and 117 BOTOX + GLP-1 patients remained for analysis. The 1-year antispasmodic-free survival probability was 86.85% in the BOTOX-only cohort and 87.59% in the combination cohort. No significant difference was observed between groups (log-rank p = 0.7234). The hazard ratio was 1.14 (95% CI: 0.55–2.39; p = 0.3984).

3. Discussion

Using a federated global claims database, we found that GLP-1 RA use, including semaglutide, was associated with clinical benefit in non-diabetic women receiving BOTOX for OAB. After 1:1 propensity matching and excluding patients with pre-existing diagnoses, GLP-1 RA use was linked to significantly lower incidence of urinary retention and UTIs (Table 2). Specifically, the risk of urinary retention was nearly halved in the GLP-1 RA cohort (4.9% vs. 8.6%; $p = 0.0044$). KM analysis also showed significantly improved retention-free survival (log-rank $p = 0.0064$; HR = 1.74).

Similarly, new-onset UTI rates were lower in the GLP-1 cohort (8.8% vs. 13.3%), This represented a 4.54% absolute risk reduction and better 1-year UTI-free survival (log-rank $p = 0.0420$). These results suggest a meaningful protective effect of GLP-1 RAs on bladder health outcomes in the OAB population, independent of diabetes status.

Table 2. Summary of our study's key findings.

Outcome	Event Rate (BOTOX group)	Event Rate (BOTOX+GLP-1 group)	Risk Difference (95% CI)	KM Log-Rank p	HR (95% CI)	
Urinary Retention	8.60%	4.90%	3.66% (1.16-6.17%)	0.0064	1.74	(1.16-2.59)
UTI	13.30%	8.80%	4.54% (0.67-8.40%)	0.042	1.48	(1.01-2.17)
Antispasmodic Use	11.80%	10.30%	1.55% (-6.07 to 9.17%)	0.7234	1.14	(0.55-2.39)

In contrast, rates of new antispasmodic medication use did not significantly differ between groups, either in absolute terms (11.8% vs. 10.3%; $p = 0.7234$) or time-to-event survival analysis (HR

= 1.14; 95% CI: 0.55–2.39). This may indicate slower or less effect on symptom severity, or that GLP-1 benefit is more specific to inflammatory or infectious outcomes than to urgency symptoms.

KM survival analysis confirmed superior retention-free survival in the GLP-1 group (log-rank p = 0.0064; HR = 1.74), indicating a 74% increased risk in the BOTOX-only group over one year. These findings are consistent with prior literature suggesting that weight loss and systemic metabolic improvements can positively influence lower urinary tract function, including detrusor overactivity and bladder emptying [29–31].

A similar trend was observed for UTIs: 8.8% of the GLP-1 group developed incident infections compared to 13.3% in the BOTOX-only cohort, yielding a 4.54% absolute risk reduction (95% CI: 0.67–8.40%). KM analysis again demonstrated significantly improved UTI-free survival in the GLP-1 group (log-rank p = 0.042; HR = 1.48). Our data add to the ongoing debate over UTI risk linked to GLP-1 use [32–34].

To our knowledge, this study is the first to evaluate real-world urinary outcomes in a large non-diabetic OAB population treated with BOTOX and GLP-1 agonists. Recently, only one pilot survey had explored the impact of GLP-1 agonists on OAB symptoms [35]. Sandler et al. showed that respondents with more frequent baseline symptoms were more likely to report symptom improvement with semaglutide, even in the absence of a clear correlation with weight loss. These early insights, although anecdotal and subject to recall bias, align with our findings.

Weight loss itself clearly plays a role in OAB symptom relief. Semaglutide trials show an average 11.85% weight loss vs placebo, underscoring systemic therapeutic potential [36]. Given that obesity increases intra-abdominal pressure and weakens pelvic floor support, GLP-1-induced weight loss would alleviate the pathophysiologic contributors to OAB [37]. The American Urogynecology Society reviewed 43 publications (39 studies; 5 RCTs). They found high certainty evidence that behavioral weight loss yields modest urinary incontinence improvement at 1-2.9 years [29]. In addition to overweight populations, data from diabetic populations (versus simply overweight) show a clearly positive correlation when measuring UTI risk, particularly in women [38,39].

In addition to OAB, GLP-1 receptor agonists have gained interest across a spectrum of urologic conditions including erectile dysfunction, prostate cancer, male fertility, and urolithiasis [40–48]. These studies, ranging from retrospective database analyses to prospective surveys and preclinical models, suggest mostly potential benefits with mechanisms often attributed to weight loss, central neural modulation, anti-inflammatory effects, or metabolic improvements.

Beyond weight loss, several studies have linked chronic inflammation to OAB. Elevated C-reactive protein levels have been observed in affected patients correlating with worse OAB symptom scores [49–51]. It has been proposed that the loss of protective immunologic factors and increased cellular stress responses lead to heightened peripheral afferent nerve excitability and detrusor overactivity [52]. In support of this, preclinical studies in mouse models suggest that the antioxidant, resveratrol, can mitigate both systemic and bladder-specific oxidative stress, leading to improved bladder function [53]. UTIs, which are more prevalent in overweight individuals, may also contribute to this inflammatory cascade.

An intriguing, proposed mechanism of action for GLP-1 RAs, independent of their effects on obesity and inflammation, is neuromodulation. Studies suggest that, rather than acting primarily through GLP-1-producing neurons in the hindbrain or GLP-1 receptors in the vagus nerve, these drugs mediate weight loss via the arcuate nucleus (ARC) of the hypothalamus [54,55]. The ARC houses key regulators of appetite and metabolism, including pro-opiomelanocortin (POMC), neuropeptide Y (NPY), and agouti-related peptide (AgRP) neurons. Through its influence on the autonomic nervous system, the ARC modulates blood pressure, feeding behavior, glucose homeostasis, and innate immune responses [56]. Given this broad autonomic role, bladder control may also be affected by ARC dysfunction. Concurrently, metabolic syndrome and obesity, both known risk factors of OAB, may stem, in part, from ARC dysfunction. Notably, the extracellular perineuronal net surrounding ARC neurons undergoes remodeling in metabolic dysfunction [57].

Ultimately, if GLP-1 RAs can restore ARC neuronal function, they may offer therapeutic benefits even beyond metabolic regulation, potentially alleviating OAB symptoms.

One of the most common drawbacks to GLP-1 medication is the potential for gastrointestinal side effects [58]. This can be observed in our study with increased use of antiemetics (75.1% vs. 83.9%; $SMD = 0.219$; $p < 0.0001$) and laxatives (68.5% vs. 74.6%; $SMD = 0.134$; $p = 0.0028$). Activation of GLP1 receptors in the area postrema (AP) of the brain drives nausea/aversion while activation of the same receptors in the nucleus solitary tract plays a role in satiety [59]. Selective NTS targeting could preserve appetite suppression while minimizing nausea pathways.

Practically, these findings may help guide patient selection for BOTOX therapy. By identifying subgroups such as overweight or obese individuals using GLP-1 RAs who demonstrate more favorable risk-benefit profiles, physicians may be more inclined to recommend BOTOX treatment. This study also strengthens the viability of multimodal treatment in obese or overweight OAB patients, highlighting a tailored, more patient-centered approach to refractory disease. Ultimately, this work supports GLP-1 RA usage beyond metabolic indications in select urologic patients, such as those with treatment-resistant OAB, co-existing obesity, or heightened UTI risk.

On a larger scale, the public health implications of improving urinary symptoms are considerable. Urinary incontinence is associated with reduced mobility, impaired strength, and increased cardiovascular tone, all of which affect quality of life and independence, particularly in older women. Moreover, psychosocial burdens such as depression and social withdrawal further compound the clinical significance of OAB. Reducing incontinence-related events could therefore mitigate a spectrum of downstream complications.

This study has several notable strengths. It represents one of the largest real-world analyses to date evaluating BOTOX treatment outcomes in patients with and without GLP-1 RA use, enhancing its generalizability to routine clinical practice. The use of a large geographically diverse dataset, TriNetX, allows for robust comparisons across patient subgroups and care settings. Rigorous adjustment for baseline covariates, including comorbidities and prior medication use, strengthens the internal validity of the findings. By focusing on a non-diabetic population, the study minimizes possible confounding effects of hyperglycemia on urinary outcomes. Furthermore, the inclusion of clinically meaningful outcomes such as urinary retention, UTI incidence, and antispasmodic use provides practical relevance for urologists and other clinicians managing OAB in a rapidly growing population of GLP-1 RA users.

Despite these promising results, barriers to clinical translation remain. GLP-1 therapies are expensive, resource-intensive, and typically require specialist oversight. The growing demand and limited supply further constrain widespread adoption. Adverse effects such as gastrointestinal intolerance may limit their use in some populations.

As a retrospective study, residual confounding is possible despite adjustment. Patient-reported outcomes, such as urgency episodes and symptom severity, were not available, limiting the ability to assess subjective treatment response. Moreover, our dataset did not stratify patients by OAB subtype or symptom severity, which may affect the generalizability of our findings. Additionally, detailed clinical data on BOTOX administration such as dose, injection technique, and bladder capacity were not consistently captured, which may influence both efficacy and adverse event profiles. Finally, the GLP-1 cohort had a relatively shorter duration of follow-up, which may bias KM survival estimates and lead to a gross underestimation of long-term or delayed adverse events in this group.

Future research should pursue randomized controlled trials with extended follow-up to validate our retrospective associations and clarify the role of GLP-1 in personalized OAB management. These studies should incorporate validated symptom scores or bladder diaries to better capture user experience. Studies should also explore how GLP-1 RAs may complement non-pharmacologic therapies such as pelvic floor training or behavioral interventions.

Key questions remain about the neuromodulatory role of GLP-1 RAs. Elucidating these mechanisms may deepen our understanding of bladder neuroendocrine regulation and broaden therapeutic applications. Does ARC dysfunction contribute to OAB independently of metabolic

syndrome? Could GLP-1 RAs improve bladder function through direct ARC modulation, beyond metabolic effects? Are observed benefits solely weight-related, or do these agents exert direct neurogenic or anti-inflammatory effects on bladder control? Further clinical studies are warranted.

4. Conclusions

In this large real-world study of non-diabetic patients with overactive bladder, concurrent use of GLP-1 receptor agonists was associated with a significantly lower risk of urinary retention and UTI following intravesical BOTOX treatment. These findings suggest that GLP-1 RAs may confer therapeutic benefits beyond weight loss, potentially through anti-inflammatory, metabolic, or neurogenic mechanisms. As GLP-1 usage continues to expand among overweight and obese populations, our results support its consideration as a promising adjunctive strategy for improving urinary outcomes in select OAB patients. Prospective studies are warranted to validate these associations and further define the role of GLP-1 RAs in the multimodal management of refractory OAB.

5. Materials and Methods

We conducted a retrospective cohort study using the TriNetX Research Network, a federated health research platform that aggregates de-identified electronic health record (EHR) data from participating healthcare organizations worldwide. As of 7/05/2025, the total number of non-diabetic male patients on semaglutide or other GLP-1 RAs across 115/150 healthcare organizations (HCOs) was 184,014 while the number of non-diabetic female patients on semaglutide or other GLP-1 RAs across 118/150 HCOs was 504,514. Patients with overactive bladder (OAB) who received intravesical onabotulinumtoxinA (BOTOX) injections were also identified. We then defined two cohorts for analysis: (1) OAB patients who received BOTOX alone and (2) OAB patients who received BOTOX in conjunction with a GLP-1 RA (semaglutide or equivalent).

Non-diabetic patients with OAB were initially identified using procedural and prescription data to capture BOTOX administration and GLP-1 RA exposure. Patients receiving both therapies within the same treatment period were assigned to the combination cohort. To minimize confounding, we performed 1:1 propensity score matching using a greedy nearest-neighbor algorithm with a caliper width of 0.1 pooled standard deviations. The covariates included in the propensity model were selected based on clinical relevance and potential influence on both treatment assignment and outcomes. These covariates comprised age at index (as a continuous variable), biological sex, race (White [2106-3], Black or African American [2054-5], Asian [2028-9]), and ethnicity (Hispanic or Latino [2135-2] and Not Hispanic or Latino [2186-5]). Additional variables included overweight and obesity status using ICD-10-CM codes E65–E68 and granular body mass index (BMI) categories defined by Z68.27 through Z68.42. We also adjusted for hypertensive comorbidity using ICD-10-CM codes I10–I11A. Covariate balance between treatment groups was assessed using standardized mean differences (SMD), with a threshold of <0.1 considered indicative of adequate balance.

Primary outcomes included incidence of urinary tract infection (UTI), urinary retention, and urinary antispasmodic use following BOTOX treatment. These were defined using the following codes: UTI (ICD-10-CM N39.0; urinary retention (ICD-10-CM R33); antispasmodic use (VA drug class).

For each outcome, absolute risk, risk difference, risk ratio, and odds ratio were calculated with corresponding 95% confidence intervals. Time-to-event data were evaluated using one-year Kaplan-Meier (KM) survival analysis, with survival curves compared using log-rank tests with estimated Hazard ratios (HRs). Proportionality assumptions were verified for all survival models. Median follow-up times were also reported for each matched cohort to assess observation period comparability. Patients with pre-existing diagnoses of the respective outcome prior to the BOTOX/ GLP-1 receptor agonist index date were excluded from each time-to-event analysis.

All analyses were performed within the TriNetX platform, which computes frequencies, summary statistics, covariate balance diagnostics, and outcome models using embedded statistical modules. This study was conducted in accordance with institutional and platform-level policies for research involving de-identified data and was deemed exempt from IRB review.

Abbreviations

The following abbreviations are used in this manuscript:

OAB	Overactive bladder
UTI	Urinary Tract Infection
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
BOTOX	OnabotulinumtoxinA
KM	Kaplan-Meier
BMI	Body Mass Index
ARC	Arcuate Nucleus
AP	Area Postrema
NTS	Nucleus Tractus Solitarius
POMC	Pro-Opiomelanocortin
NPY	Neuropeptide Y
AgRP	Agouti-Related Peptide
SMD	Standardized Mean Difference
HR	Hazard Ratio
FDA	U.S. Food and Drug Administration
PCOS	Polycystic Ovary Syndrome
AUA	American Urological Association
EAU	European Association of Urology
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
EHR	Electronic Health Record
IRB	Institutional Review Board
VA	Veterans Affairs (used in context of drug classes
IQR	Interquartile Range
CI	Confidence Interval
TriNetX	A federated real world data research network/platform

References

1. Zhang L, Cai , Mo L, et al. Global prevalence of overactive bladder: a systematic review and meta-analysis. *Int Urogynecol J*. Published online 2025. doi:10.1007/s00192-024-06029-2. PMID: 39951109

2. UpToDate. Urgency urinary incontinence/overactive bladder (OAB) in females: Treatment. *UpToDate*. Updated 2025. Accessed June 27, 2025. https://www.uptodate.com/contents/urgency-urinary-incontinence-overactive-bladder-oab-in-females-treatment

3. Feloney MP, Stauss K, Leslie SW. Sacral Neuromodulation. Updated 2024 Apr 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567751/

4. Orasanu B, Mahajan ST. The use of botulinum toxin for the treatment of overactive bladder syndrome. *Indian J Urol*. 2013;29(1):2-11. doi:10.4103/0970-1591.109975

5. Cameron AP, Chung DE, Dielubanza EJ, et al. The AUA/SUFU guideline on the diagnosis and treatment of idiopathic overactive bladder. *J Urol*. 2024;212(1):11–20. doi:10.1097/JU.0000000000003985. PMID: 38651651

6. EAU Guidelines. In proceedings of the EAU Annual Congress, Madrid 2025. ISBN 978-94-92671-29-5.

7. Chen YH, Kuo JH, Huang YT, Lai PC, Ou YC, Lin YC. Evaluating the Efficacy and Safety of Botulinum Toxin in Treating Overactive Bladder in the Elderly: A Meta-Analysis with Trial Sequential Analysis of Randomized Controlled Trials. *Toxins (Basel)*. 2024;16(11):484. Published 2024 Nov 8. doi:10.3390/toxins16110484

8. Palm KM, Abrams MK, Sears SB, et al. The Response of the Urinary Microbiome to Botox. *Int Urogynecol J*. 2024;35(1):237-251. doi:10.1007/s00192-023-05703-1

9. Nitti V, Haag-Molkenteller C, Kennelly M, Chancellor M, Jenkins B, Schurch B. Treatment of neurogenic detrusor overactivity and overactive bladder with Botox (onabotulinumtoxinA): Development, insights, and impact. *Medicine (Baltimore)*. 2023;102(S1):e32377. doi:10.1097/MD.0000000000032377

10. Lo CW, Wu MY, Yang SS, Jaw FS, Chang SJ. Comparing the Efficacy of OnabotulinumtoxinA, Sacral Neuromodulation, and Peripheral Tibial Nerve Stimulation as Third Line Treatment for the Management of Overactive Bladder Symptoms in Adults: Systematic Review and Network Meta-Analysis. *Toxins (Basel)*. 2020;12(2):128. Published 2020 Feb 18. doi:10.3390/toxins12020128

11. Hsieh PF, Chiu HC, Chen KC, Chang CH, Chou ECL. Botulinum toxin A for the treatment of overactive bladder. *Toxins (Basel)*. 2016;8(3):59. doi:10.3390/toxins8030059

12. Semins MJ, Shore AD, Makary MA, Weiner J, Matlaga BR. The impact of obesity on urinary tract infection risk. *Urology*. 2012;79(2):266-269. doi:10.1016/j.urology.2011.09.040

13. Bausch K, Stangl FP, Prieto J, Bonkat G, Kranz J. Urinary infection management in frail or comorbid older individuals. *Eur Urol Focus*. 2024 Nov;10(5):731–733. doi:10.1016/j.euf.2024.08.007. PMID: 39217017

14. Hagovska M, Švihra J, Buková A, et al. The Relationship between Overweight and Overactive Bladder Symptoms. *Obes Facts*. 2020;13(3):297-306. doi:10.1159/000506486

15. Khullar V, Sexton CC, Thompson CL, Milsom I, Bitoun CE, Coyne KS. The relationship between BMI and urinary incontinence subgroups: results from EpiLUTS. *Neurourol Urodyn*. 2014;33(4):392-399. doi:10.1002/nau.22428

16. Jing W, Wei C, Huang Y, Fu T, Shen W, Xiao W. Relationship between the weight-adjusted-waist index and urinary incontinence in women: A cross-sectional study of NHANES 2007 to 2020. *Medicine (Baltimore)*. 2025;104(25):e42996. doi:10.1097/MD.0000000000042996

17. Zhang J, Chen W, Tang Z, et al. The Association between Obesity and Wet Overactive Bladder: Results from 2005 to 2020 National Health and Nutrition Examination Survey. *Obes Facts*. Published online May 11, 2025. doi:10.1159/000546104

18. Pomian A, Lisik W, Kosieradzki M, Barcz E. Obesity and Pelvic Floor Disorders: A Review of the Literature. *Med Sci Monit*. 2016;22:1880-1886. Published 2016 Jun 3. doi:10.12659/msm.896331

19. Fazel N, Masoumi SZ, Haghani S, Rajati F. The effect of weight loss on overactive bladder symptoms in overweight and obese women: a systematic review. *Nurs Midwifery Stud*. 2024;13(2):77–84. doi:10.5812/nms.154345

20. Collins L, Costello RA. Glucagon-Like Peptide-1 Receptor Agonists. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Updated February 29, 2024. Bookshelf ID NBK551568. PMID:31855395.

21. Xu D, Nair A, Sigston C, et al. Potential Roles of Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RAs) in Nondiabetic Populations. *Cardiovasc Ther*. 2022;2022:6820377. Published 2022 Nov 16. doi:10.1155/2022/6820377

22. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389(24):2221–2232. doi:10.1056/NEJMoa2307563

23. Heerspink HJL, Apperloo E, Davies M, et al. Effects of Semaglutide on Albuminuria and Kidney Function in People With Overweight or Obesity With or Without Type 2 Diabetes: Exploratory Analysis From the STEP 1, 2, and 3 Trials. *Diabetes Care*. 2023;46(4):801-810. doi:10.2337/dc22-1889

24. Cena H, Chiovato L, Nappi RE. Obesity, Polycystic Ovary Syndrome, and Infertility: A New Avenue for GLP-1 Receptor Agonists. *J Clin Endocrinol Metab*. 2020;105(8):e2695-e2709. doi:10.1210/clinem/dgaa285

25. Jiang Z, Tan J, Yuan Y, Shen J, Chen Y. Semaglutide ameliorates lipopolysaccharide-induced acute lung injury through inhibiting HDAC5-mediated activation of NF-κB signaling pathway. *Hum Exp Toxicol*. 2022;41:9603271221125931. doi:10.1177/09603271221125931

26. Shnaien A, Mohammad A, Hassan E. Neuroprotective Effects of Semaglutide in Endotoxemia Mouse Model. *Iran J War Public Health.* 2023; 15 (2) :199-205.

27. Tan SA, Tan L. liraglutide and semaglutide attenuate inflammatory cytokines interferon-gamma, tumor necrosis factor-alpha, and interleukin-6: possible mechanism of decreasing cardiovascular risk in diabetes mellitus. Journal of the American College of Cardiology. 2019;73(9S1):1866.

28. Mosenzon O, Capehorn MS, De Remigis A, Rasmussen S, Weimers P, Rosenstock J. Impact of semaglutide on high-sensitivity C-reactive protein: exploratory patient-level analyses of SUSTAIN and PIONEER randomized clinical trials. *Cardiovasc Diabetol*. 2022;21(1):172. Published 2022 Sep 2. doi:10.1186/s12933-022-01585-7

29. Yazdany T, Jakus-Waldman S, Jeppson PC, et al. American Urogynecologic Society Systematic Review: The Impact of Weight Loss Intervention on Lower Urinary Tract Symptoms and Urinary Incontinence in Overweight and Obese Women. *Female Pelvic Med Reconstr Surg*. 2020;26(1):16-29. doi:10.1097/SPV.0000000000000802

30. Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. *N Engl J Med*. 2009;360(5):481-490. doi:10.1056/NEJMoa0806375

31. Zacche MM, Giarenis I, Thiagamoorthy G, Robinson D, Cardozo L. Is there an association between aspects of the metabolic syndrome and overactive bladder? A prospective cohort study in women with lower urinary tract symptoms. *Eur J Obstet Gynecol Reprod Biol*. 2017;217:1-5. doi:10.1016/j.ejogrb.2017.08.002

32. Ljungberg C, Bredahl Kristensen FP, Dalager-Pedersen M, Vandenbroucke-Grauls C, Sørensen HT, Nørgaard M, Thomsen RW. Risk of Urogenital Infections in People With Type 2 Diabetes Initiating SGLT2is Versus GLP-1RAs in Routine Clinical Care: A Danish Cohort Study. *Diabetes Care* 20 May 2025; 48 (6): 945–954. https://doi.org/10.2337/dc24-2169

33. Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. *Ann Intern Med*. 2019;171(4):248-256. doi:10.7326/M18-3136

34. Soogoor AR, Agrawal P, Pupo D, Kohn TP, Du Comb W, Alshak MN. MP45-11 Semaglutide Utilization In Weight Management and its Implications for Urinary Tract Infections and Urolithiasis. *Jour. of Urology [Internet].* 2024 May 1 [cited 2025 Jul 26];211 (5s):e746. doi:10.1097/01.JU0001008764.86460.8e.11

35. Sandler MD, Williams AD, Wein A, et al. Effects of Glucagon like Peptide-1 agonists on patients with overactive bladder: A pilot study. *Continence Reports*. 2025;14:100083.

36. Tan HC, Dampil OA, Marquez MM. Efficacy and Safety of Semaglutide for Weight Loss in Obesity Without Diabetes: A Systematic Review and Meta-Analysis. J ASEAN Fed Endocr Soc. 2022;37(2):65-72. doi: 10.15605/jafes.037.02.14. Epub 2022 Aug 23. PMID: 36578889; PMCID: PMC9758543.

37. Doumouchtsis SK, Loganathan J, Pergialiotis V. The role of obesity on urinary incontinence and anal incontinence in women: a review. *BJOG*. 2022;129(1):162-170. doi:10.1111/1471-0528.16848

38. Nitzan O, Elias M, Chazan B, Saliba W. Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. *Diabetes Metab Syndr Obes*. 2015;8:129-136. Published 2015 Feb 26. doi:10.2147/DMSO.S51792

39. Ahmed AE, Abdelkarim S, Zenida M, et al. Prevalence and Associated Risk Factors of Urinary Tract Infection among Diabetic Patients: A Cross-Sectional Study. *Healthcare (Basel)*. 2023;11(6):861. Published 2023 Mar 15. doi:10.3390/healthcare11060861

40. Able C, Liao B, Saffati G, et al. Prescribing semaglutide for weight loss in non-diabetic, obese patients is associated with an increased risk of erectile dysfunction: a TriNetX database study. *Int J Impot Res*. 2025;37(4):315-319. doi:10.1038/s41443-024-00895-6

41. Varnum AA, Pozzi E, Deebel NA, et al. Impact of GLP-1 Agonists on Male Reproductive Health-A Narrative Review. *Medicina (Kaunas)*. 2023;60(1):50. Published 2023 Dec 27. doi:10.3390/medicina60010050

42. Alhajahjeh A, Al-Faouri R, Bahmad HF, et al. From Diabetes to Oncology: Glucagon-like Peptide-1 (GLP-1) Receptor Agonist's Dual Role in Prostate Cancer. *Cancers (Basel)*. 2024;16(8):1538. Published 2024 Apr 18. doi:10.3390/cancers16081538

43. Pourabhari Langroudi, A., Chen, A.L., Basran, S. *et al.* Male sexual dysfunction associated with GLP-1 receptor agonists: a cross-sectional analysis of FAERS data. *Int J Impot Res* (2025). https://doi.org/10.1038/s41443-025-01061-2

44. Fang A, Frigo DE, Hahn A, et al. GLP-1 Agonist Use Among Men With Localized Prostate Cancer: A Narrative Review and Rationale for Prospective Clinical Trials. *Urology*. 2025;201:152-158. doi:10.1016/j.urology.2025.04.056

45. Salvio G, Ciarloni A, Ambo N, et al. Effects of glucagon-like peptide 1 receptor agonists on testicular dysfunction: A systematic review and meta-analysis. *Andrology*. 2025;1-13. https://doi.org/10.1111/andr.70022

46. Nomiyama T, Kawanami T, Irie S, et al. Exendin-4, a GLP-1 receptor agonist, attenuates prostate cancer growth. *Diabetes*. 2014;63(11):3891-3905. doi:10.2337/db13-1169

47. Zhou L, Dong M, Feng G, et al. Semaglutide mitigates testicular damage in diabetes by inhibiting ferroptosis. *Biochem Biophys Res Commun*. 2024;715:149996. doi:10.1016/j.bbrc.2024.149996

48. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse Effects of GLP-1 Receptor Agonists. *Rev Diabet Stud*. 2014;11(3-4):202-230. doi:10.1900/RDS.2014.11.202

49. Chung SD, Liu HT, Lin H, Kuo HC. Elevation of serum c-reactive protein in patients with OAB and IC/BPS implies chronic inflammation in the urinary bladder. *Neurourol Urodyn*. 2011;30(3):417-420. doi:10.1002/nau.20938

50. Liu HT, Jiang YH, Kuo HC. Increased serum adipokines implicate chronic inflammation in the pathogenesis of overactive bladder syndrome refractory to antimuscarinic therapy. *PLoS One*. 2013;8(10):e76706. Published 2013 Oct 1. doi:10.1371/journal.pone.0076706

51. Pillalamarri N, Shalom DF, Pilkinton ML, et al. Inflammatory Urinary Cytokine Expression and Quality of Life in Patients With Overactive Bladder. *Female Pelvic Med Reconstr Surg*. 2018;24(6):449-453. doi:10.1097/SPV.0000000000000492

52. Grundy L, Caldwell A, Brierley SM. Mechanisms Underlying Overactive Bladder and Interstitial Cystitis/Painful Bladder Syndrome. *Front Neurosci*. 2018;12:931. Published 2018 Dec 12. doi:10.3389/fnins.2018.00931

53. Meng X, Zhou J, Zhao CN, Gan RY, Li HB. Health Benefits and Molecular Mechanisms of Resveratrol: A Narrative Review. *Foods*. 2020;9(3):340. Published 2020 Mar 14. doi:10.3390/foods9030340

54. Singh I, Wang L, Xia B, et al. Activation of arcuate nucleus glucagon-like peptide-1 receptor-expressing neurons suppresses food intake. *Cell Biosci*. 2022;12(1):178. Published 2022 Oct 29. doi:10.1186/s13578-022-00914-3

55. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124(10):4473-4488. doi:10.1172/JCI75276

56. Jais A, Brüning JC. Arcuate Nucleus-Dependent Regulation of Metabolism-Pathways to Obesity and Diabetes Mellitus. *Endocr Rev*. 2022;43(2):314-328. doi:10.1210/endrev/bnab025

57. Beddows CA, Shi F, Horton AL, et al. Pathogenic hypothalamic extracellular matrix promotes metabolic disease. *Nature*. 2024;633(8031):914-922. doi:10.1038/s41586-024-07922-y

58. Wright EE Jr, Aroda VR. Clinical review of the efficacy and safety of oral semaglutide in patients with type 2 diabetes considered for injectable GLP-1 receptor agonist therapy or currently on insulin therapy. *Postgrad Med*. 2020;132(sup2):26-36. doi:10.1080/00325481.2020.1798127

59. Huang KP, Acosta AA, Ghidewon MY, et al. Dissociable hindbrain GLP1R circuits for satiety and aversion. *Nature*. 2024;632(8025):585-593. doi:10.1038/s41586-024-07685-6