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COMORBIDITY BETWEEN OBESITY AND MIGRAINE, POSSIBLE IMPACT OF GLP-1 RECEPTOR AGONISTS ON THE COURSE OF MIGRAINE – A NARRATIVE REVIEW

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ABSTRACT

Background: Migraine and obesity share several metabolic triggers. It is a well-documented problem. Excess body weight actively fuels systemic inflammation and insulin resistance, which frequently pushes episodic headaches into a chronic daily struggle. Pharmaceutical companies originally designed GLP-1 receptor (GLP-1R) agonists for diabetes and weight control. However, neurologists are now looking at these drugs because they show strong anti-inflammatory and nerve-protecting effects.
Aim: We wanted to map exactly how obesity connects to migraine biology. We also evaluated whether prescribing GLP-1R agonists makes sense as a real-world headache treatment.
Material and methods: Our team searched databases like PubMed, Embase, Web of Science, and Google Scholar. We mostly pulled studies published between 2016 and 2026. We rejected isolated case reports entirely, focusing on randomized trials or solid observational data instead. Artificial intelligence helped us fix grammar and check text patterns — human experts handled all the actual analysis.
Results: The drugs appear to work in two main ways. On a cellular level, GLP-1R agonists shut down hyperactive microglial cells, lower CGRP levels in the trigeminal system, and physically block TRPV1 pain receptors. Systemically, they force the body to lose weight, drop the fluid pressure inside the skull, and help the brain absorb glucose better. It isn't a perfect fix, though. Many patients report temporary new headaches when they first start the medication. On top of that, recent models show these drugs can cause OnabotulinumtoxinA therapies to wear off much faster than usual.
Conclusions: Using GLP-1R agonists to treat chronic migraine makes biological sense. It is an especially logical option for patients dealing with severe obesity. However, doctors still have to watch out for early side effects and drug interactions. We need massive clinical trials before anyone can confirm their long-term safety.

KEYWORDS
Migraine, Obesity, GLP-1 Receptor Agonists, Neuroinflammation, Metabolic Dysfunction

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1. Introduction

Migraine is one of the most common neurological disorders and also one of the most disabling, carrying heavy personal costs and a major socio-economic load worldwide [21]. How migraine evolves and worsens is closely tied to metabolism. In that picture, obesity stands out as an especially relevant, changeable risk factor, one that is linked to migraine shifting from an episodic problem to a chronic one [3, 5, 9]. The biological connection between obesity and migraine is not a single pathway but a set of interacting processes. Obesity and metabolic syndrome are associated with persistent, low-grade systemic inflammation along with insulin resistance [3, 5]. Fat tissue is not passive storage, it behaves like an active neuroendocrine organ. Through the release of adipocytokines and inflammatory cytokines, including IL-6 and TNF-α, it can intensify neurovascular inflammation, push the release of neuropeptides such as calcitonin gene-related peptide (CGRP), and reduce the body's threshold for triggering a migraine attack [9, 12]. GLP-1 receptor (GLP-1R) agonists were first developed to treat type 2 diabetes and obesity, but they have drawn growing interest for broader effects on the central nervous system [6, 8, 18]. Their actions go beyond glucose and weight control. Evidence points to neuroprotective activity, anti-inflammatory effects, and changes in neural signaling that may be significant for headache disorders [5, 6, 8]. Findings from preclinical and clinical work suggest these drugs can influence neuroinflammation, dampen microglial activation in pain-related networks, and may also affect cerebrospinal fluid dynamics by lowering intracranial pressure [6, 8, 18]. Taken together, the weight loss benefit plus the anti-inflammatory and neuroprotective profile of GLP-1R agonists creates a credible case for considering them in chronic or treatment-resistant migraine, especially when obesity is also present [1, 5, 6]. This narrative review examines the layered pathophysiological ties between obesity and migraine, then assesses current evidence on proposed direct and indirect mechanisms, clinical effectiveness, and the practical challenges that come with positioning GLP-1R agonists as a new disease-modifying approach to migraine care [5, 6].

2. Research materials and methods

To construct this narrative review, a comprehensive literature search was conducted across multiple scientific databases, including PubMed, Embase, Web On Science and Google Scholar. The search strategy utilized a combination of specific keywords and descriptors to capture relevant literature, such as "migraine and obesity", "migraine", "GLP-1" and "GLP-1 in migraine". To receive access to the most recent data, we targeted peer-reviewed articles published in the latest years – between 2016 and 2026, except for three particular articles published in 2010 and 2014 containing important points of view regarding the research. Priority was given to high-quality evidence, including original research articles, randomized controlled trials (RCTs), prospective and retrospective observational studies, systematic reviews, and meta-analyses. Publications such as isolated case reports, letters, editorials, and expert opinion pieces were generally excluded during the screening process. Finally, the reference lists of the selected articles were manually screened to identify and include any additional pertinent studies that were not captured in the initial database searches.

2.1. AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI was used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Research results

3.1. Migraine pathophysiology and foregoing treatment options

Migraine is not a simple headache, it is a disabling neurological disorder that develops through a mix of processes in both the central and peripheral nervous systems. Much of its biology points to activation of the trigeminovascular system. Once this pathway is switched on, a neurogenic inflammatory reaction follows, with the release of pain-related neuropeptides, especially calcitonin gene-related peptide (CGRP) and substance P. Those mediators drive vasodilation and make meningeal nociceptors more sensitive, which amplifies pain signaling [15, 17, 21]. Alongside this, cortical spreading depression (CSD), the traveling wave of neuronal and glial depolarization, is generally taken as the physiological foundation of migraine aura, and it also feeds into later neuroinflammation and the onward relay of pain signals [17, 21]. Evidence has also been building around the idea of central “generators” in the brain, including the hypothalamus, playing a part early in the attack during the premonitory phase. Added to that are broader contributors such as mitochondrial dysfunction, reduced brain energy availability, and oxidative stress, all of which appear to fit into the wider disease mechanism [13, 17, 21]. Treatment has traditionally been grouped into acute and preventive approaches. Acute, or abortive, therapies mainly involve non-steroidal anti-inflammatory drugs (NSAIDs), ergot alkaloids, and triptans (5-HT receptor agonists). These agents act largely by constricting cranial vessels and by limiting the release of pro-inflammatory neuropeptides [15, 17]. Preventive options, by contrast, are meant to cut down on how often attacks occur and how severe they are, and they span multiple drug classes. For example, beta-blockers such as propranolol, anticonvulsants such as topiramate and valproate, calcium channel blockers such as flunarizine, tricyclic antidepressants such as amitriptyline, and OnabotulinumtoxinA (Botox) injections [3, 17]. In practice, care is often broader than medication alone. A complete management plan commonly brings in behavioral interventions and lifestyle changes, including diet changes, exercise, relaxation training, and cognitive behavioral therapy, with the goal of reducing triggers, raising the threshold for attacks, and improving overall quality of life [3, 13, 16,].

3.2. Impact of body mass and metabolic dysfunction on migraine headaches and The Pathophysiological Link Between Obesity and Migraine.

It's well known that carrying extra weight, having metabolic issues, and dealing with obesity are major, fixable factors that can trigger migraines, make them worse, or turn them into a chronic daily struggle [2, 3, 11]. When doctors look at large groups of people, they consistently find that as body fat measures go up – parameters like BMI, abdominal fat, waist-to-height ratio, and body roundness index – migraines happen a lot more often, almost in a straight line of cause and effect [9, 19]. This pattern is especially visible in younger patients and women of reproductive age, mostly because of changes in hormone levels and the different ways their bodies naturally store fat tissue [11, 12, 19]. Under the surface, the biological connection between the two is not simple. It usually comes down to constant, low-level inflammation and insulin resistance that is caused by metabolic impairment [2, 3, 13]. Fat tissue acts like a gland that constantly produces hormones like leptin and adiponectin, along with pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis

factor-alpha (TNF-α). This stimulates the nervous system, causes local inflammation within blood vessels, and basically lowers the body's natural defense against migraine episodes [15, 19, 20]. The nerves responsible for head pain are right in the middle of this inflammation. Moreover, patients with obesity often have elevated calcitonin gene-related peptide (CGRP) levels, which acts as a major pain chemical and directly connects metabolic issues to migraine headaches [1, 3, 15]. The hypothalamus is another major overlap point. Because this part of the brain controls both hunger signals and pain feeling using the exact same chemicals – like orexin and serotonin – it bridges the gap between metabolic functions and causes of migraine [2, 19]. Additionally, recent studies point out that poor communication between the intestines and the brain, insulin resistance within the brain, and disturbances in the endocannabinoid system just make the whole problem more complicated [3, 13]. It leads to a vicious cycle that goes both ways. Getting frequent migraines prevents people from being active and leads to weight gain, but the good news is that losing weight on purpose – whether through changing habits, dieting, or bariatric surgery – has a proven track record of making migraine attacks happen less frequent, end faster, and hurt a lot less [3, 16, 20].

3.3. Direct Mechanisms of GLP-1 Agonists in Migraine Alleviation

Glucagon-like peptide-1 receptor (GLP-1R) agonists exert direct neuromodulatory and anti-inflammatory effects that can alleviate migraine through both central and peripheral pathways [5, 18]. Central to this process is the dense expression of GLP-1 receptors on microglial cells and astrocytes within the trigeminocervical complex and the trigeminal nucleus caudalis (TNC) [6, 7]. Activation of these microglial receptors suppresses the central sensitization characteristic of chronic migraine by inhibiting microglial proliferation and morphological changes, a process primarily mediated through the downstream PI3K/Akt signaling pathway [6, 7, 18]. This microglial modulation profoundly alters the neuroinflammatory environment by suppressing the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and TNF-α, while simultaneously stimulating the release of the anti-inflammatory cytokine IL-10 to provide pain relief [5, 6, 7]. Concurrently, GLP-1R activation directly downregulates the expression of critical pain mediators, significantly decreasing the levels of CGRP and c-Fos in the TNC [1, 5, 6, 7]. Beyond these central neuroinflammatory mechanisms, there is evidence for a direct peripheral analgesic effect: certain exendin-derived GLP-1R agonists (such as exenatide and lixisenatide) can bind to the extracellular face of the TRPV1 channel – a key transducer in trigeminal nociceptors – acting as noncompetitive inhibitors and alleviating pain independently of weight loss or central neuromodulation [18].

3.4. Indirect Mechanisms of GLP-1 Agonists on Migraine

While they certainly modulate nerves directly, glucagon-like peptide-1 receptor (GLP-1R) agonists also relieve migraines through a variety of background physical and metabolic changes. One of the most obvious indirect benefits is weight loss, which naturally calms down body-wide inflammation, brain insulin resistance, oxidative stress, and blood vessel issues – all well-known metabolic culprits that make migraines heavier and more chronic [3, 5]. These drugs also do a remarkable job of balancing cerebrospinal fluid (CSF) flow by actively lowering intercranial pressure (ICP) [1, 8, 18]. They manage this because GLP-1 receptors are concentrated tightly into the choroid plexus; when activated, they block the Na+/K+ ATPase pump to essentially decrease CSF production [1, 8]. Lowering ICS relieves the severe headaches tied to idiopathic intracranial hypertension (IIH), but researchers suspect it might also indirectly limit the release of CGRP and calm central sensitization in the TNS, offering a much broader angle for preventing migraines altogether [1]. On a deeper level, these medications also elevate the brain's energy supply and fix disturbed insulin signaling by signaling through the phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB, Akt) pathway (PI3K-PKB/Akt), which promotes glucose absorption within the cortex and hippocampus. Restoring this metabolic balance might actually make the brain more resistant to cortical spreading depolarization – the main cause of migraine auras – making patients much less vulnerable to the attacks [18]. Based on those widespread benefits, these drugs also quiet down several other major pain-signaling networks, actively fighting inflammation and blocking pain through the body's serotonin, nitric oxide, and opioid systems [22]. In the long term, using a GLP-1R agonist literally changes genes' expression in pain pathways, keeping inflammatory responses restrained and releasing natural analgesics like β-endorphin to effectively decrease nerve hypersensitivity, which is responsible for chronic pain [23].

Table 1. Possible usage and target points of GLP-1 agonists in migraine.

Medicine	Pharmacological class	Target point	Mechanism
Liraglutide	GLP-1 agonist	GLP-1 receptors (choroid plexus, TNC, microglial cells), TRPV1 channels	Blockage of PI3K/Akt trial in microglia by activation of the GLP-1 receptor; Blockage of Na+/K+-ATPase in the choroid plexus (lowering of ICP); Inhibiting the release of CGRP, c-Fos and pro-inflammatory cytokines (IL-1β, TNF-α); Non-competitive inhibition of TRPV1 channel [1, 4, 6, 18]
Exenatide	GLP-1 agonist	GLP-1 receptors (choroid plexus, TNC, microglial cells), TRPV1 channels	Blockage of Na+/K+-ATPase in choroid plexus (lowering of ICP); Direct binding and non-competitive inhibition of TRPV1 channel in trigeminal nociceptors; Inhibition of nociceptive hypersensitivity [4, 6, 18]
Semaglutide	GLP-1 agonist	GLP-1 receptors	Central neuromodulation, reduction of neuroinflammation, lowering ICP by influencing the dynamics of CSF [4, 18]
Tirzepatide	Dual GIP/GLP-1 receptor agonist	GLP-1 and GIP receptors	Reduction of systemic inflammation, synaptic modulation (interaction with BoNT-A via cAMP-PKA) [18]

(*TNC* – trigeminal nucleus caudalis; *ICP* – intracranial pressure; *CSF* – cerebrospinal fluid; *BoNT-A* – OnabotulinumtoxinA)

3.5. Clinical Evidence and Efficacy

Clinical data now clearly show that GLP-1 receptor agonists reduce the daily burden of migraines. This is especially true for patients dealing with concurrent obesity. A recent pilot study tested liraglutide as an add-on therapy for obese patients suffering from high-frequency or chronic migraines; the medication proved to be highly effective and easy to tolerate, leading to noticeably better headache outcomes [1]. This aligns perfectly with early data from a massive 2026 real-world study tracking roughly 11,000 adults with chronic migraine. When those patients started taking a GLP-1 receptor agonist, their need for emergency care decreased drastically. Compared to a matched group taking topiramate, they had 10% fewer ER visits, 14% fewer hospitalizations, and filled 13% fewer triptan prescriptions; they were also 23 to 48% less likely to need another preventive drug added to their regimen [18].

We also see strong clinical proof in studies of idiopathic intracranial hypertension. This condition shares deep biological and clinical roots with chronic migraine. Both randomized trials and case-control studies confirm that treating these patients with exenatide, semaglutide, or liraglutide physically lowers ICP. The drugs also force significant weight loss, reduce headache frequency and the need for acetazolamide [5, 6]. Looking at all these clinical results together, it makes sense that these medications do more than just mask pain. They offer a practical way to alter the actual course of the disease, providing a highly effective option for patients fighting severe, treatment-resistant headaches [5, 18].

3.6. Potential Challenges, Adverse Effects, and Drug Interactions

Paradoxically, while glucagon-like peptide-1 receptor (GLP-1R) agonists show promise for migraine alleviation, they can also cause de novo headaches or exacerbate existing headache conditions, including severe presentations such as hemiplegic migraines [5, 10]. These events are most frequently reported during the early titration stages of treatment (e.g., the first 4 to 26 weeks) and are typically mild and transient [5, 18]. Evidence from adverse event reporting databases confirms a positive disproportionality signal for headaches, which is largely attributed to secondary factors like fasting hypoglycemia or dehydration resulting from common gastrointestinal side effects such as nausea and vomiting [5, 18].

A significant drug-procedure interaction has also emerged concerning the concomitant use of GLP-1R agonists and OnabotulinumtoxinA (BoNT-A), a standard preventive therapy for chronic migraine. Advanced computational microsimulation models demonstrate that GLP-1R agonists may meaningfully shorten the clinical durability of BoNT-A (decreasing its duration of effect from an average of 14 weeks to under 12 weeks) and increase the risk of early treatment "wear-off". This attenuation is mechanistically driven by GLP-1-induced synaptic modulation - specifically the cAMP-PKA-mediated phosphorylation of SNAP-25, which accelerates functional neuromuscular recovery - alongside systemic metabolic adaptations and lean mass reductions affecting toxin diffusion kinetics. Among the agents evaluated, the dual agonist tirzepatide demonstrated the strongest attenuation effect on BoNT-A, followed by liraglutide, dulaglutide, and semaglutide [14].

Beyond headaches and drug interactions, GLP-1R agonist therapy carries a risk for broader systemic and psychiatric adverse effects. Patients may experience severe but rare gastrointestinal and metabolic complications, including acute cholecystitis, pancreatitis, and acute kidney injury secondary to profound dehydration [5, 10, 18]. Furthermore, recent pharmacovigilance data, real-world cohorts, and regulatory reviews have brought attention to potential psychiatric risks, including new or worsening depression, anxiety, and suicidal ideation [4, 10, 18]. These multifaceted risks highlight the critical need for personalized patient screening, comprehensive monitoring, and careful consideration of pre-existing neurological or psychiatric vulnerabilities before initiating GLP-1R agonist therapy [5, 10].

4. Discussion

Treating migraines with GLP-1 receptor agonists is a massive shift in how we handle the disease, specifically for patients who struggle with treatment-resistant headaches and obesity or metabolic problems [5]. These medications go after the biological root causes shared by both conditions – including persistent systemic inflammation, oversensitive pain networks, and disrupted ICP – meaning they might actually change the course of the disease rather than just masking the symptoms [3, 5, 8]. Laboratory models back the thesis up, showing that the peptides heavily suppress pain and inflammation by directly engaging the body's serotonin, nitric oxide, and opioid systems [22]. The drugs also force positive genetic shifts in microglia, effectively inhibiting the inflammatory responses and nerve hypersensitivity that are the main cause of the chronic pain [23].

However, doctors still have to be careful when prescribing them, because their effects on the central nervous system are complicated and can go both ways [5]. While they work incredibly well to relieve the constant headaches of idiopathic intracranial hypertension and chronic migraine, they can inexplicably trigger brand-new headaches or worsen conditions such as hemiplegic migraines, especially as patients adjust to the dose [5, 6, 10]. We also see significant drug interactions; recent data suggest that the medications (especially dual-action ones like tirzepatide) can cause botulinum toxin treatments for migraines to wear off much faster than usual, meaning doctors have to monitor overlapping prescriptions closely [14]. Taking it and other rare but serious risks – including severe stomach complications or suicidal thoughts – into consideration, it becomes obvious that these drugs are not a harmless, universal fix [5, 10]. We would need large, placebo-controlled trials to figure out which pain-relieving and brain-protecting benefits are directly caused by the drug, and which ones are only connected to weight loss [5, 8]. Finding specific biological markers that predict a good response might eventually be the only way to tailor these treatments, helping doctors maximize the long-term benefits while keeping vulnerable patients safe from side effects [5, 14].

5. Future Directions and Conclusion

Bringing glucagon-like peptide-1 receptor agonists into migraine care is a highly promising, albeit complicated, shift in treatment [5, 8]. Laboratory studies and real-world data clearly show these medications protect cerebral tissue, calm inflammation, and improve metabolism; even so, we still desperately need large, placebo-controlled trials to prove they actually alter the disease course and are safe over the long term [6, 8]. Future studies have to lean on strict methods, like causal mediation analysis, to untangle these mechanisms, separating the direct ways the drugs alter the nervous system – such as blocking TRPV1 channels or suppressing microglia – from the secondary benefits of simply losing weight and improving metabolism [6, 18]. Basic science must also dig deeper into how activating the GLP-1 receptor influences other major pain networks – like the serotonergic, nitrergic, and opioidergic pathways [22] — and how it induces permanent genetic changes in microglia to decrease the inflammation behind chronic pain [23]. To figure out exactly how individual patients will respond, researchers need to rely on advanced cellular models, active patient registries, and reliable biological markers; this will help flag vulnerabilities, such as early side effects or harmful interactions. Ultimately, GLP-1 receptor agonists provide a practical way to attack the combined metabolic and inflammatory root causes of chronic migraine, carving out a new path for personalized care that is particularly useful for treatment-resistant patients struggling with obesity or metabolic syndrome. As these medications find their permanent place in neurology, strict clinical monitoring and highly tailored prescribing strategies will be the only way to maximize the benefits while keeping patient risks to an absolute minimum [5, 18].

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