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The Role of Obesity Treatment in the Management of Idiopathic Intracranial Hypertension

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Abstract:

Introduction: Idiopathic intracranial hypertension (IIH) is a rare neurological condition characterized by elevated intracranial pressure in the absence of a detectable cause. It predominantly affects obese women of childbearing age. The underlying pathophysiological mechanisms remain unclear, but increasing evidence suggests a significant role of obesity-related metabolic and hormonal disturbances.

Materials and methods: A review of selected literature in the PubMed database was conducted, using the following keywords: “idiopathic intracranial hypertension”, “pseudotumor cerebri”, “obesity”

Summary: The development of IIH appears to be multifactorial, involving impaired cerebrospinal fluid dynamics, venous outflow obstruction, and endocrine dysfunction. Obesity contributes through increased intra-abdominal and intracranial pressure, altered secretion of adipokines (such as leptin), and chronic low-grade inflammation. The review highlights the role of obesity as a modifiable risk factor and the impact of weight loss on symptom relief and disease progression.

Conclusions: Understanding the link between obesity and IIH is crucial for effective prevention and treatment. Multidisciplinary care, including neurologists, ophthalmologists, and nutritionists, should focus on weight management and early detection of visual complications. Further research is needed to clarify the molecular mechanisms involved and to develop more targeted therapeutic strategies.

Keywords: idiopathic intracranial hypertension; pseudotumor cerebri; obesity

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1. Introduction

Idiopathic intracranial hypertension (IIH) is a disease characterized by increased cerebrospinal fluid pressure (ICP >25 cmH_2O), normal fluid composition, normal results from neuroimaging studies, and swelling of the optic disc (Lowe et al., 2025).

It primarily affects young women of childbearing age. Patients primarily complain of chronic headaches, vision deterioration due to optic nerve disc swelling, and pulsatile tinnitus. Double vision (paralysis of the sixth cranial nerve) and nausea are also common. The disease often progresses over time and tends to recur after a period of stabilization (Kwaśniak-Butowska et al., 2016).

According to the literature, the majority of patients are women who are overweight or obese (Adderley et al., 2019).

2. Epidemiology

Idiopathic intracranial hypertension is most prevalent among obese women of reproduction age. Its incidence ranges from 0.3 to 1.6 cases per 100,000 people; however, in obese women, the incidence increases significantly to between 2.7 and 11.9 cases per 100,000 people (Raoof et al., 2011).

A minor rise in body weight — ranging from 5% to 15% — is linked to a heightened probability of developing diseases and experiencing relapses, even among individuals with a BMI below 30 kg/m^2 (Daniels et al., 2007; Ko et al., 2011).

Men are affected by the disease nine times less often than women and are diagnosed, on average, 10 years later. For men, visual impairment is often the first symptom, and they are twice as likely to experience permanent visual deterioration (Bruce et al., 2009).

3. Symptoms

The most common and classic clinical presentation of idiopathic intracranial hypertension (IIH) is a headache accompanied by optic disc edema. Headaches affect more than 90% of patients with IIH and significantly impact their quality of life. The nature of the pain can vary widely but often resembles a migraine. While some patients experience an

improvement in symptoms when intracranial pressure (ICP) is lowered, more than half of patients experience chronic headaches despite normalized ICP (Mollan, Grech, et al., 2021).

The presence of optic disc swelling is a vital indicator of IIH, playing a crucial role in the diagnostic process (Dandy, 1937).

IIH may present with various visual disturbances, including transient episodes of blurred vision, chronic visual haze, and double vision resulting from retrobulbar nerve (VI) paralysis. Other symptoms may include pulsatile tinnitus, dizziness, and cognitive impairment, such as difficulty concentrating or memory deterioration (Mollan et al., 2018).

In some patients, IIH may be asymptomatic or present with few symptoms. In these cases, swelling of the optic disc may be detected by chance during a routine eye exam or when diagnosing another eye condition. Compared to patients with the classic form of IIH, those with this presentation have significantly lower cerebrospinal fluid opening pressure, fewer clinical symptoms, better visual function, and less frequently require medical treatment (Vosoughi et al., 2022).

A number of radiological features of intracranial hypertension (known as RAD-IH) have also been described, such as the presence of an empty sella (Bidot et al., 2015).

Although these lesions are often present in patients with IIH, caution should be exercised when interpreting them. The presence of these features does not automatically indicate a diagnosis of IIH, as they may also appear in other diseases or represent a remnant of a previous intracranial hypertension episode (Chen et al., 2021).

Most patients with incidentally detected RAD-IH features do not have swelling of the optic disc and thus do not meet the criteria for a diagnosis of IIH (Aung et al., 2023).

In such cases, performing lumbar puncture or including treatment, such as acetazolamide, may be unwarranted and potentially harmful (Fisayo et al., 2016).

4. Pathophysiology

4.1. Obesity

In people with IIH, adipose tissue is mainly located in the trunk area and is more prone to accumulating fat than in obese people without IIH (Kesler et al., 2010).

A 2021 study compared the adipose tissue of subjects who developed IIH with a control sample of subjects with comparable body mass index (BMI). The subjects exhibited increased expression of genes related to lipogenesis. Changes in metabolism also indicated a greater capacity to absorb branched-chain amino acids (BCAAs), promoting additional fat deposition

in the tissue. The authors suggest that patients with IIH have adaptive abnormalities in adipose tissue that can lead to metabolic, structural, and fat distribution abnormalities (C. S. Westgate et al., 2021).

4.2. Increased intracranial pressure in patients with IIH

The complex metabolic changes accompanying IIH can affect the production and resorption of cerebrospinal fluid, leading to excess fluid in the cranial cavity (Canac et al., 2020).

Cine MRI with phase contrast revealed increased cerebrospinal fluid (CSF) flow through the cerebral vasculature in patients with IIH, which may indicate increased CSF production by the choroid plexus. After treatment, this flow decreased, indicating an association with disease activity (Akay et al., 2015; "(PDF) Evaluation of Cerebrospinal Fluid Flow Dynamic Changes in Patients with Idiopathic Intracranial Hypertension Using Phase Contrast Cine MR Imaging," 2024).

Invasive intracranial pressure monitoring and lumbar puncture also revealed increased intracranial pressure and elevated cerebrospinal fluid outflow resistance (Kaipainen et al., 2021).

Animal studies suggest that obesity directly alters the dynamics of the cerebrospinal fluid, resulting in excess fluid and a subsequent increase in ICP. Although results are sometimes inconsistent, a variety of experimental models provide a better understanding of this complex process (C. S. J. Westgate et al., 2022).

4.2.1. Metabolic and endocrine factors

Patients with IIH showed greater insulin resistance and higher fasting insulin levels compared to those of the same age and similar BMI, but without IIH. The study indicates that people with IIH have more than double the risk of cardiovascular disease, hypertension and type 2, and gestational diabetes (Adderley et al., 2019, Thaller et al., 2022).

Increased serum leptin levels were also observed. Leptin is a hormone secreted by adipose tissue. Compared to individuals with similar BMIs and genders, higher levels of leptin were secreted by adipose tissue (Abdelghaffar et al., 2022).

Elevated leptin levels were also observed in CSF patients, which suggests the presence of leptin resistance in the hypothalamus (Hornby et al., 2018).

However, there are studies that do not confirm this phenomenon, so the significance of this phenomenon remains unclear (C. S. Westgate et al., 2021).

Numerous metabolic abnormalities have been observed in patients with IIH that may be responsible for the headaches. These include decreased urea concentrations in CSF and urine, an elevated serum lactate/pyruvate ratio, elevated acetate concentrations, and increased ketone bodies in CSF. Elevated acetate levels in CSF sensitize the trigeminal nerve, and changes in urea concentration contribute to osmotic gradients and fluid shifts into the

CSF. These shifts can also be associated with headaches. After 12 months of weight loss, many of these metabolic changes regressed, highlighting the role of weight loss in treating IIH (Grech et al., 2022).

Another study analyzing serum and cerebrospinal fluid samples from patients with IIH and healthy subjects found decreased acylpyruvate levels in CSF and increased levels in serum. There were also changes in lipids and amino acids, as well as correlations of these changes with clinical symptoms. These disorders normalized following surgical weight reduction (Alimajstorovic et al., 2023).

The role of Androgens

Androgens affect CSF dynamics by binding to androgen receptors in choroid plexus cells. This can lead to increased production of cerebrospinal fluid and, in some cases, increased outflow, which can counteract an increase in intracranial pressure (O'Reilly et al., 2019).

These effects may explain the potential link to the pathogenesis of intracranial hypertension. However, most studies have been conducted in animal models, and the mechanisms are complex and dependent on the metabolic context (Wardman et al., 2024).

Elevated androgen levels in both serum and CSF have been observed in women with IIH. This is related to the endocrine effect of adipose tissue, which is exacerbated in patients with IIH by increased 5a-reductase activity leading to excessive synthesis and activation of androgens (O'Reilly et al., 2019).

Lower serum androstendione concentrations were also observed, contrasting with the high concentrations found in the CSF. This suggests that androstendione may locally convert to testosterone in the choroid plexuses, which could increase intracranial pressure. A similar phenomenon occurs in polycystic ovary syndrome (PCOS), which is often a comorbid condition in women with idiopathic intracranial hypertension (Abdelghaffar et al., 2022; O'Reilly et al., 2019).

The role of Glucocorticosteroids

Tissue metabolism of GCS in obese individuals occurs with increased activity of 11B-HDS1 (an enzyme that activates cortisone to cortisol) in adipose tissue and in choroid plexus cells (Sinclair et al., 2007).

Patients with IIH showed higher levels of this enzyme activity in both systemic circulation and adipose tissue and choroid plexus cells than patients with obesity but without IIH. (Csj et al., 2022).

An increase in local cortisol activation can affect sodium metabolism and retention, which can enhance CSF production and increase ICP. Importantly, treatment leading to weight

reduction normalizes enzyme activity and simultaneously lowers intracranial pressure, further confirming the link between impaired GCS regulation and mechanisms of IIH development (Aj et al., 2010).

In clinical trials, inhibition of the 11BHSD1 enzyme reduced ICP after 12 weeks, although the difference was not statistically significant compared to placebo (Markey et al., 2020).

A decrease in ICP correlated with a decrease in the serum cortisol/cortisone ratio. In addition, improvements in lipid profile and increases in muscle mass were observed, which may have metabolic implications in IIH (Hardy et al., 2021).

Thus, there is evidence of a role for glucocorticosteroids and 11BHSD1 in IIH, but there is no direct evidence for the role of GCSs as the main reason for the increase in ICP.

Change in expression of pro-inflammatory cytokines

Adipose tissue secretes numerous pro-inflammatory cytokines, which are associated with the accumulation of pro-inflammatory macrophages in adipose tissue. However, studies on the role of cytokines in IIH have yielded divergent results. For example, some studies have shown elevated levels of CCL2 in the CSF of patients with IIH compared to healthy volunteers. Other studies no differences in CCL2 levels, but elevated IL-1B and IL-8 and reduced TNF-a. However, other studies have shown reduced serum TNF-a levels in patients with IIH (Samancı et al., 2017, Dhungana et al., 2009, Fahmy et al., 2021).

Due to conflicting data from different studies, further work is needed to clearly define the expression of pro-inflammatory cytokines in IIH.

4.2.2. Venous outflow disorders in IIH

Resorption of CSF into the venous system takes place through the arachnoid granules, this requires a pressure gradient - the pressure in the subarachnoid space must be 3-5 mmHg higher than that in the venous sinuses of the brain. Disruption of this process can cause an increase in ICP (Fargen et al., 2023).

Obesity is associated with an increase in intra-abdominal pressure, which can lead to an increase in central venous pressure. This increase in pressure can impede venous outflow from the brain and indirectly increase intracranial pressure. However, most obese individuals do not develop IIH. This suggests that obesity alone does not fully explain the pathophysiology of IIH.

Magnetic resonance venography (MRV) studies have shown narrowing of the venous sinuses in most patients with IIH. However, the presence of these strictures did not correlate unequivocally with symptoms, suggesting that sinus stenosis may not be the primary cause of impaired outflow (Farb et al., 2003; Horev et al., 2013).

Further studies of this phenomenon demonstrate that an increase in ICP is followed by venous sinus constriction. This results in impaired CSF resorption and an increase in ICP due to a self-perpetuating mechanism where the primary cause is endocrine disruption or overproduction of CSF (Thaller et al., 2023).

4.2.3. Dysfunction of the glymphatic system

The glymphatic system transports cerebrospinal fluid and removes metabolites from the brain. Some studies have shown that impairment of this process plays a role in the pathogenesis of IIH (Eide et al., 2021).

It is unclear whether disruption of the glymphatic system and neuroglial-vascular interface is primary or secondary and whether it is reversible. Further research is needed to establish a cause-and-effect relationship and potential therapeutic targets (Eide et al., 2021).

5. Treatment

The treatment of idiopathic intracranial hypertension focuses on preventing irreversible vision loss and relieving symptoms, particularly pain, such as headaches. Many patients experience improvement through weight reduction and drug treatment (Mollan et al., 2018).

For cases that progress rapidly or do not respond to conservative therapy, surgery can be an important treatment option. (Kalyvas et al., 2021).

5.1. Weight reduction

Weight reduction is the only recognized disease-modifying treatment. It is usually recommended as the initial treatment, unless the disease presents suddenly and severely. (Mollan et al., 2018).

In the cohort study, an average weight loss of 15.7 kg resulted in an 8 cm H_2O reduction in intracranial pressure. This led to significant improvements in pain, optic disc swelling, and symptoms such as tinnitus, double vision, and transient visual disturbances. These improvements persisted for three months after the diet ended. Positive effects have been

demonstrated with both a low-calorie diet and a combination of dietary and lifestyle changes. (Abbott et al., 2023; Sinclair et al., 2010).

The randomized IIH:WT trial showed that, after 24 months, patients who underwent surgery had an average weight loss of ~26.6 kg and an average decrease in ICP of -8.2 cmH_2O compared to the conservative treatment group. Surgery, especially gastric bypass, often leads to complete remission of IIH: disc edema resolves, and vision improves or stabilizes. (Mollan, Mitchell, et al., 2021).

Because of its significant benefits, bariatric surgery is recommended for patients with IIH and a BMI of at least 35 kg/m^2. (Abbott et al., 2023).

Studies have shown that ICP reduction is strongly correlated with weight loss. About 24% weight loss (approximately 13 kg) can help patients achieve ICP normalization (≤25 cmH_2O). (Mollan et al., 2022).

It has not been clearly defined what form of obesity treatment is most effective in IIH or what specific weight reduction is needed to achieve remission of the disease.

5.2. Pharmacological treatment

5.2.1. Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, is the most widely used drug in IIH therapy. It works by inhibiting CSF secretion in the choroid plexuses. Despite its widespread use, the number of high-quality clinical trials evaluating its efficacy is limited. The IIHTT trial used acetazolamide alongside a low-sodium diet for six months and showed improvements in visual field, optic disc edema scores, and vision-related quality of life. However, there was no improvement in headaches or visual acuity. Side effects were also observed, including nausea, vomiting, paresthesia, fatigue, and taste disturbances. Acetazolamide is the most commonly used drug in IIH; however, data from randomized trials are limited, highlighting the need for more clinical trials. (NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee et al., 2014).

5.2.2. GLP-1-RAs

GLP-1 analogs (GLP-1-RAs) are a promising therapeutic option for treating patients with IIH, especially given that weight reduction is the only proven disease-modifying method. A study showed that patients treated with GLP-1-RAs achieved significantly greater weight loss

than those on a standard weight control program (UCWM) alone and were more likely to achieve the recommended weight reduction of at least 10%. Additionally, treatment with GLP-1-RAs was associated with improvements in pain symptoms. Notably, there was a reduction in the number of headache days per month, and no patient in this group developed chronic headaches after six months of therapy.

Importantly, the drugs were well tolerated, with no severe side effects reported. The most common side effects were gastrointestinal (e.g., nausea, vomiting, and diarrhea), and they were usually mild to moderate and occurred mainly during the dose escalation phase. Additionally, using GLP-1-RAs allowed for a reduction in acetazolamide doses, possibly due to their greater effectiveness in reducing body weight. Although no clear effect on visual function deterioration was demonstrated at the six-month follow-up, a longer follow-up period may be necessary to assess the drugs' effects on retinal structures.

GLP-1 analogs appear to be a valuable adjunct to IIH therapy due to their beneficial effects on body weight and pain symptoms, as well as their potential safety. This is especially true for patients who have not achieved the desired results with non-pharmacological approaches (Krajnc et al., 2023).

5.2.3. Other drugs used in IIH

Other drugs used to treat idiopathic intracranial hypertension include furosemide, topiramate, and octreotide. Furosemide is sometimes used with acetazolamide to equalize intracranial pressure. Topiramate, a weak carbonic anhydrase inhibitor, has also been shown to have a slimming effect in studies comparing it to acetazolamide. However, no significant differences were observed between the two drugs. Octreotide, a growth hormone receptor antagonist, has been studied for its effects on choroid plexuses and arachnoid villi. These studies have shown resolution of optic disc edema and a decrease in ICP, with no recurrence for three years after therapy. However, further study is required (Celebisoy et al., 2007; Gn et al., 2007; Mollan et al., 2018).

Table 1. A summary of the effects of obesity treatment on symptoms and intracranial pressure (ICP) in idiopathic intracranial hypertension (IIH) patients.

Treatment method	Average weight loss	ICP Change	Clinical effect
Low calorie diet	10-15% (approx. -15 kg/3 months)	-8,0 cmH2O	Significant reduction in headaches and papilloedema
Nutrition and movement program	5-15% (approx. -10-15kg/12 months)	-3 – 8 cmH2O	Reduced ICP, improve quality of life

Bariatric surgery	25-30% (approx. -25-30 kg.)	-6 do -12 cmH2O	In most patients, disc edema subsided, visual field and quality of life improved
Acetazolamide	7,5 kg	Not studied	Beneficial effects on ophthalmic symptoms and quality of life
GLP-1-RAs	10 – 12% b.w.	Not studied	Reduction of headaches and acetazolamide dosage

Source: Abbott et al., 2023; Krajnc et al., 2023; Mollan et al., 2022; Mollan, Mitchell, et al., 2021; NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee et al., 2014; Sinclair et al., 2010.

6. Summary and Conclusions

Idiopathic intracranial hypertension (IIH) is a multifactorial disorder of still uncertain pathogenesis, with obesity identified as its most important modifiable risk factor. The current literature points to several interrelated mechanisms linking excess body weight to elevated intracranial pressure. These include increased intra-abdominal and thoracic pressure leading to impaired venous return from the brain, disturbances in cerebrospinal fluid (CSF) resorption, and hormonal dysregulation involving leptin and other adipokines. Chronic low-grade inflammation and vascular abnormalities, such as transverse sinus stenosis, may further contribute to the disease process.

Despite the multifactorial nature of IIH, weight loss remains the most effective non-invasive intervention, associated with significant improvement in clinical symptoms, particularly headache and visual disturbances. However, not all patients respond equally, highlighting the need for an individualized approach. Pharmacological and surgical treatments may be necessary in selected cases, but their efficacy is often limited without addressing the underlying metabolic burden.

In conclusion, the management of IIH requires a comprehensive understanding of its complex pathophysiology and a multidisciplinary therapeutic strategy centered around weight reduction. Further research is warranted to clarify the causal mechanisms and to develop targeted therapies that reflect the metabolic and vascular profile of each patient.

Disclossure

Supplementary Materials

Not applicable.

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