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Body weight, the potentially modifiable risk factor in idiopathic intracranial hypertension

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Abstract

Purpose of review

Idiopathic intracranial hypertension (IIH) prevalence increased in conjunction with rising obesity rates. Here, we highlight the importance of weigh management in IIH, and introduce glucagon-like peptide 1 (GLP-1) receptor agonists (RA) as potential treatment strategy for IIH.

Recent findings

Weight gain is a risk factor for IIH; and weight loss (via any treatment strategy) plays a key role in IIH management. GLP-1 is an incretin secreted by the distal small intestine in response to a meal. GLP-1 RA have been shown to improve glycaemic control (no. hypoglycaemia) and lower body weight in patients with and without type 2 diabetes. The choroid plexus has been found to express GLP-1 receptors and treatment with a GLP-1 RA significantly reduces cerebrospinal fluid secretion *in vitro* and intracranial pressure in rodents.

Summary

New research evaluating the pathophysiology of IIH supports GLP-1 RA as a potential treatment for IIH via weight loss dependant and independent mechanism to directly reduce intracranial pressure.

Summary box

1. Recent weight gain is a risk factor for development of idiopathic intracranial hypertension.
2. Weight loss has a key role in management of idiopathic intracranial hypertension.

3. Glucagon-like peptide 1 is a gut neuropeptide, and glucagon-like peptide 1 analogues are successfully used in patients with and without type 2 diabetes mellitus to aide weight loss, and improve long-term outcomes.

4. Glucagon-like peptide 1 receptors have been identified in the choroid plexus, and antagonism reduces cerebrospinal fluid secretion and reduces intracranial pressure in rodent models.

5. Glucagon-like peptide 1 receptor agonists may have a potential role in targeting obesity and intracranial pressure in idiopathic intracranial hypertension.

Idiopathic intracranial hypertension (IIH) is an increasingly observed condition characterized by raised intracranial pressure (ICP), papilloedema with the potential risk of permanent visual loss, and debilitating headache, which profoundly reduces quality of life [1][2]. IIH predominately affects females of reproductive age and importantly has an established association with obesity [3][4]. The predominant symptom of IIH is headache which are typically migraine-like. Obesity has also been shown to be a risk factor for headaches and migraine.[5] Obesity is a complex disease and the World Health Organization estimates that rates have tripled since 1975. Similarly, the incidence of IIH has increased by more than 250% between 2005 and 2017 in women and correlates with the female obesity rate [4]. The individuals weight threshold to develop IIH is not clear [6], although weight is not a reliable indicator of visceral adiposity. The population risk of developing IIH increases exponentially in those with a body mass index (BMI) >30 kgm^2 [4] (Figure 1) with weight gain (5-15%) a risk for both developing, and experiencing a recurrence of IIH [7].

For more than half a century weight loss has been identified as an effective treatment for IIH, with a reduction in body weight of between 3-15% resulting in disease remission [6-8]. Application of a very low-calorie diet to induce weight loss (approximately 15%) resulted in significantly lowered ICP, improved papilloedema and a 50% improvement in headache frequency and severity, with a concomitant reduction in analgesic use [8]. Weight loss specifically from the truncal region was noted to be associated with disease remission in IIH, with truncal fat mass also correlating with ICP[9]. These findings potentially implicate truncal adiposity in driving disease activity in IIH, however, the pathogenic role of obesity is not fully

understood. A unique profile of androgen excess has been identified in IIH (distinct to that observed in those with simple obesity and polycystic ovarian syndrome) which drives dysregulation of cerebral spinal fluid dynamics in-vitro [10]. The androgen excess in IIH is not of ovarian origin and is more likely to be generated from the truncal adiposity, a known source of androgen synthesis. IIH is also associated with a twofold risk of cardiovascular disease independent of patient obesity[4]. These studies imply that IIH is more than a disease of the central nervous system axis but a systemic metabolic disease.

While the therapeutic impact of weight loss in IIH is clear, the degree of weight loss and optimal strategy necessary to induce remission is not established and may be patient specific. A low salt diet is often cited, but there is minimal evidence in this population. Importantly, lifestyle and behavioural interventions typically result in 5% weight loss [11]. Weight loss drugs may have a role, although similarly they may not achieve the degree of weight loss necessary to impact disease activity (e.g. orlistat in conjunction with a lifestyle intervention achieves an additional 2.5kg weight loss above that achieved from lifestyle intervention alone)[12]. Maintenance of weight loss is also a challenge, with patients on average regaining one-third to one-half of the weight that was lost at one year, and returning to their original weight within 5 years [13].

Currently bariatric surgery is the most effective method to achieve lasting weight reduction with 15-30% weight loss over 15-20 years depending on surgical procedure [14]. The beneficial effects of bariatric surgery in IIH have been highlighted in a number of cases studies [15][16]. However, detailed evaluation with prospective and randomised controlled trials leading to class one evidence is currently lacking.

Intriguingly bariatric surgery may offer IIH patients sustained disease remission with a cost comparable to ventriculoperitoneal shunting with a programmable valve. The efficacy and evidence for bariatric surgery in the management of IIH will be assessed when a randomized controlled trial reports on evaluating bariatric surgery against a community weight loss program [17].

A number of novel hormonal and metabolic therapeutic targets are emerging for IIH, the most promising being GLP-1 receptor agonism. GLP-1 receptor agonists (exenatide, liraglutide, lixisenatide, semaglutide, albiglutide, dulaglutide) are widely used in the treatment of type 2 diabetes mellitus (they do not induce hypoglycaemia) and more recently to manage obesity [18]. In the context of IIH pathophysiology, the use of GLP-1 receptor agonists extends beyond the weight modifying effects (Figure 1). GLP-1 receptor has been identified in human and rodent choroid plexus epithelium, which, when stimulated with the GLP-1 receptor agonist exenatide, reduces CSF secretion through a cyclic adenosine monophosphate, protein kinase A signalling pathway with subsequent inhibition of Na^+K^+ adenosine triphosphatase ion channel activity (a key regulator of CSF secretion), thereby reducing ICP. Pathologically elevated ICP can be reduced by nearly 50% in rats with intracranial hypertension treated with exenatide, with effects sustained over a week [19]. This striking effect on ICP is not seen when rats are treated with clinically relevant doses of acetazolamide, the most commonly used medicine in IIH; of note topiramate significantly reducing ICP in vivo [20].

Mounting evidence demonstrates that weight gain and obesity are modifiable risk factors for IIH disease activity. Obesity is now recognised as a disease entity (World

Health Organisation, US Food and Drug administration (FDA) and American Medical Association) with growing realisation that it is not driven by personal choice but a relapsing and remitting disease determined by genetic, biological and environmental factors interacting. Obesity stigma amongst health care professionals, the public, and policy makers and weight bias internalization have been associated with poorer patient outcomes, detrimental effects on mental health and avoidance of health care.[21] Current obstacles to management include a lack of sensitivity when discussing obesity, apprehension of negative connotations, concerns about deleterious effects on the doctor patient relationship and a lack of knowledge [22]. Obesity management strategies in IIH are evolving with lifestyle and behavioural interventions, bariatric surgery and novel therapies, such as GLP-1 receptor agonists which directly target CSF secretion and have weight-lowering effects. The pathophysiology detailed above necessitates the performance of effective research programs and well-designed trials in IIH to 1) test the effects of GLP-1 agonists for co-morbid IIH and obesity 2) establish ideal strategies to promote weight loss, and 3) examine the functional role, and potential to therapeutically target, androgen excess.

As IIH rates are rising consistent with the global obesity epidemic, healthcare professionals and patients with IIH should not hesitate from assessment, discussion and management of obesity as this is central to sustained remission of IIH [23].

Legend

Figure 1:
Infogram detailing known pathogenic factors and potential targeted treatments for idiopathic intracranial hypertension.

Appendix 1

Name	Location		Contribution
Susan P Mollan FRCOphth 0000-0002-6314-4437	1	Birmingham Neuro-Ophthalmology, Queen Elizabeth Hospital, Birmingham, United Kingdom (UK)	Design and conceptualized article, and critical comments during manuscript revision.
Abd A Tahrani PhD 0000-0001-9037-1937	1 2	Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK Department of Diabetes and Endocrinology, Queen Elizabeth Hospital, Birmingham, UK	Critical review of the manuscript for intellectual content.
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