Migraine and Obesity: Possible Link to Inflammation

Abstract

Migraine is a common neurological disorder. It is characterized by recurrent attacks of pulsatile headaches. Data achieved through familial hemiplegic migraine suggest that; mutations in channel proteins can lead dysregulation of calcium and sodium levels and hyperexcitability in nervous system. Even though, genetic tendencies can be responsible for migraine, accumulating data show that many metabolic or environmental factors can also trigger migraine attacks and its severity. Calcitonin gene-related peptide, nitric oxide, adipokines, neuropeptides, amino acids, and cytokines are all molecules shown to be involved both in migraine and obesity pathogenesis. In this paper, we take the metabolic approach to the problem and review the possible mechanisms take part in the pathogenesis of migraine to explore its relationship with obesity and inflammation.

Keywords: Migraine; Obesity; Leptin; Adiponectin; Inflammation

Introduction

Headache (cephalalgia) is described as pain anywhere in the region of the head or neck and mainly can be classified into two broad categories as primary and secondary. Primary headache is not being caused by any known underlying problems and includes three types of headaches as migraine, trigeminal autonomic cephalalgias, and tension-type [1,2].

Migraine is defined by recurrent attacks headache disorders lasting 4-72 h and usually accompanied by other symptoms such as scintillating lights and scotomas when affecting the visual cortex or paresthesia and numbness of the face and hands. Migraine has two major subtypes as migraine without aura and migraine with neurological aura symptoms that hold about 25% of the headache cases [1,3]. Even though migraine affects both genders and occurs life-long, prior from the puberty women aged 18-65 are more frequently diagnosed with migraine [4]. Migraine activities can be triggered by many factors such as acute stress as emotional factors or physical and dietary factors. In addition to the naturally occurring changes in endogenous sex hormones over the lifespan (e.g. puberty and menopause), exogenous sex hormones (e.g. hormonal contraception or hormone therapy) are also suspected to be triggers as the accumulating data support the view of an elevated risk of migraine with significant drops in estrogen levels [5-7].

Recent studies also suggest that migraine is associated with cardiovascular disorders, ischemic stroke, metabolic syndrome and obesity which are a public health problem like migraine [8-10]. This paper reviews the pathogenesis of migraine and to examine its relationship with obesity and inflammation events.
Inflammation molecules involved in the pathogenesis of migraine is shown in Table 1.

**Pathophysiology of Migraine**

The first approaches had defined migraine as a vascular disease and a phenomenon of intracranial vasospasm in cerebral arteries, causing vasodilation. The extracranial terminal branches of the external carotid artery were suspected to be the reason of pain in the aura [11,12]. Newer data imply that migraine headache is caused by an inappropriate activation of trigeminovascular system, that is, pain sensitive innervation of dural, arachnoid, and pial vessels as well as large intracranial vessels by nociceptive fibers originating in trigeminal ganglion (TG) and travelling mainly through ophthalmic and to a much lesser extent through maxillary and mandibular divisions of trigeminal nerve [10,13,14]. Appropriately, “neurovascular disorder” definition has been used to address dysfunction of the cerebral nerves and blood vessels through cortical activation which is followed by brainstem activation with neurogenic inflammation and vasodilation [15-17].

Moreover, migraine is also defined as a complex genetic disorder. The complexity of the migraine depends upon the interplay of multiple genes and gene-environment interactions with a likely polygenic multifactorial inheritance causing brains to be more prone to hyper excitability [18]. Mutations in familial hemiplegic migraine, which is a monogenic form of migraine with motor prone to hyper excitability [18]. Other clinical conditions being presented with migraine headache are: Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (involved gene is MTT1: mtDNA), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (involved gene is NOTCH3:19q13.2) retinopathy, vascular, cerebral and renal involvement and Raynaud (involved gene is TREX1: 3p21.3). Several genetic mutations/polymorphisms and related gene products such as Dopamine Type 2 and 4 receptors, Glutathione S-transferase, Dopamine beta-hydroxylase, Hypocretin receptor, N-Methyl-D Aspartate (NMDA), Syntaxin 1A or Tumor Necrosis Factor-Alpha (TNF-α), associated with vasocostriction, inhibition the release of vasoactive neuropeptides, pro-inflammation, regulation of the neurotransmitters or vascular remodeling were found to be related [26-28].

**Obesity and Migraine**

Both, migraine with a prevalence of about 11% and obesity, with an estimated prevalence above 10%, are common in the population [29]. As conflicting results of the studies have hindered any definite conclusion neither about a possible increased risk of having migraine for obese subjects nor a possible increased risk of being obese in the presence of migraine, meta-analysis were recoursed. Meta-analysis of 2022 records from 15 studies reveals expression in both nervous tissue (sensory and motor) and the vasculature [21-23]. Low cerebral blood flow (CBF), mitochondrial abnormalities, increased nitric oxide or the existence of a P/Q type calcium channelopathies are also found to cause hyperexcitability of the brain in migraine [24-25].

### Pathological impacted systems

| Trigeminovascular | Calcitonin Gene-Related Peptide |
|-------------------|--------------------------------|
| **System Activation** | Neurokinin A |
| Pituitary Adenylate Cyclose-Activating Peptide | Vasorelaxant Intestinal Peptide |
| Serotonin (5-hydroxytryptamine) |
| **Monoaminergic Systems** | Dopamine and Norepinephrine |
| Elusive Amines: Tyramine, Octopamine |
| **Endocannabinoid System** | Cannabinoid (CB) type-1 receptor |
| **Aminosid and derives** | Glutamat, Tryptophan |
| Nitric Oxide |
| Nerve growth factor |
| Brain-derived neurotrophic factor |
| **Neurotrophins** | Tumor necrosis factor |
| Somatostatin |
| Glial-cell-line-derived neurotrophic factor |
| Hypothalamic Oxirenergic System |
| Adipokines |
| **Neurometabolic Systems** | Leptin |
| Neuropeptide Y |
| Gamma-Amino Butyric Acid |
| Substance P |
| **Endothelins** | Endothelin-1 |
| **Hormonal Alterations** | Estrogen |
| Progesterone |
the trigeminal ganglia, the cortex, and the pituitary gland) and in white adipose tissue (WAT) (adipocytes, pre-adipocytes) [36-38]. Elevated levels of CGRP in migraine is explained by electrical stimulation of the TG of nerves, the release of CGRP and other peptides cause an increase in cerebral blood fluid, dilation of the cerebral vessels and the local release of pro-inflammatory mediators [39-40]. It is suspected that the cross-talk between brain and adipose tissue is linked to inflammation, innervation of WAT and lipid mobilization [38]. Fat intake is also found to be associated with CGRP secretion. In a clinic-based study, CGRP was significantly higher in obese subjects relatively to controls. In model research studies after fat intake, the CGRP levels further increased, and after weight loss, concentrations remained unchanged or reveal that attenuation of alfa-CGRP action may provide opportunity to regulate body weight in obesity [41-43].

The study of Scher et al. was the first report establishing the possible link between migraine and obesity. In their study potential cases (180 + headaches per year, n=1134) and controls (two to 104 headaches per year, n=798) were interviewed two times over an average 11 months of follow-up and the results have indicated that the risk of migraine in overweight and obese subjects groups were higher, and new onset chronic daily headache (CDH) was associated with obesity [44].

Bigal et al. in one of their study among 30, 215 participants found that obesity was a stronger risk factor for transformed migraine than for chronic tension-type headache (CTTH), BMI on the prevalence of CTTH were significant in the morbidly obese group and the prevalence of CDH was higher in obese (5.0%) and morbidly obese (6.8%) patients. In another population-based study, they found that BMI group was not associated with the prevalence of migraine but the frequency of headache attacks, as headache days per month was higher in obese and the morbidly obese group. The proportion of subjects with severe headache pain is increased with BMI, doubling in the morbidly obese relative to the normally weighted (OR=1.9). Similar significant associations were found between BMI and category for disability, photophobia, and phonophobia. As they studied 18 968 individuals with migraine, 7564 with probable migraine (PM), and 2051 with severe episodic tension-type headache (S-ETTH) among individuals with migraine, very frequent headaches (10-14 d/mo.) occurred in 7.4% of the overweight (p=0.10), 8.2% of the obese and 10.4% of the morbidly obese subjects, compared with 6.5% of those with normal weight, in adjusted analyses. Their findings support the concept that obesity is an exacerbating factor for migraine but not for other types of episodic headaches [45-47].

Winter et al. [48] in a cross-sectional study evaluated the association of BMI with migraine in migraine specifics 63 467 women aged ≥ 45 years, of whom 12,613 (19.9%) reported any history of migraine and 9195 had an active migraine. Obese women had increased risk for low and high migraine frequency with the highest estimation for women who reported daily migraine. Among the women with active migraine, BMI was found to be associated with increased risk of phonophobia and photophobia also decreased risk of a unilateral pain characteristic and migraine aura. Their data confirm previous findings that the association between BMI with migraine is limited to migraine frequency and specific migraine features. The results indicated that obesity was not comorbid with migraine, but influence the frequency of attacks and their severity.

In pediatric population Hershey et al. in 2009 reported (on the data on height, weight, age, and gender frequency of headache and disability collected from 913 consecutive patients at 7 pediatric headache centers in which migraine is followed-up for 3-6 months [n=213 and n=174 respectively]) that, BMI was associated with frequency of headaches and disability at baseline in multivariate analyses. Changes in BMI significantly showed correlation with headache frequency. Their results suggested that weight loss can contribute to a reduction in the frequency of headaches over time in overweight children [49]. Kinik et al. [50] found a positive correlation between BMI and number of attacks (p=0.026, r=0.20) in the selected pediatric group similarly according to their results; obesity appeared to be related to the frequency of headache attacks in children and adolescents with migraine.

Findings of Peterlin et al. [51] suggest that the prevalence of migraine in obesity varies based on adipose tissue distribution, gender, and age. In their study, migraine prevalence was increased with total body obesity, independently of abdominal obesity, in adult men and women who are less than 55 years of age. Although, after 55 years of age, migraine prevalence was not associated with obesity in men, migraine prevalence was decreased in women older than 55 years who had abdominal obesity. They also indicated that these differences may be a result of the sexual dimorphism of adipose tissue distribution and its function. In short, the studies suggest that even though obesity is not a risk factor for migraine, it is associated with increased migraine frequency and therefore, seems to contribute migraine progression.

**Inflammation-Mediated Link between Obesity and Migraine**

Besides the total body and abdominal obesity’s recently found link to migraine, role of fasting and certain foods are frequently reported as typical triggers of migraine pain [52]. Recently Food and Drug Administration approved “topiramate” drug for migraine prevention in adolescents which has well-established appetite-suppressant side effects that eating disorder symptoms due to topiramate therapy draw the attention to the relation between appetite and migraine [53-54].

Centrally, appetite is controlled by the hypothalamus which is defined as “the melanocortin system (arcuate nucleus; ARC)” and its target, as the melanocortin receptor [55]. The system contains orexigenic and anorexigenic neuropeptides that are the main regulators of energy expenditure and appetite. The primary orexigenic, feeding stimulating peptides are agouti-gene-related protein (AgRP) and neuropeptide Y (NPY), and the primary anorexigenic peptides are pro-opiomelanocortin (POMC) and cocaine- amphetamine-regulated transcript (CART). There is a feedback regulation of the central and peripheral signals involved in feeding and energy balance. Signals from adiponectin,
leptin and ghrelin act on the melanocortin system to produce reciprocal activation or inhibition of the POMC/CART neurons while inhibiting or activating the NPY/AGRP neurons. Signals from the ARC neurons are transmitted to the other hypothalamic nuclei including the paraventricular (PVN) nucleus, which express adiponectin and leptin receptors, as well as the ventromedial and lateral hypothalamus nuclei. In the lateral hypothalamus, there are 2 groups of neurons that orexin neuropeptide stimulate: First one is feeding, and the other one is the melanin-concentrating hormone that inhibit food intake [51,55-57].

Adipose tissue is also modulated centrally by the hypothalamus, and it peripherally produces several molecules, such as adiponectin and leptin [52,58]. Adiponectin is a collagen-like plasma protein regulating several metabolic processes and is important in the control of glucose and fatty acid metabolism which is found negatively correlated with triglycerides and positively correlated with HDL cholesterol [59]. Adiponectin levels play a role in T2DM, obesity, and metabolic syndromes and reported to be negatively correlated with the BMI. In the study of Peterlin et al. independent of total body obesity as estimated by BMI, abdominal or visceral obesity was greater for those with a chronic daily headache than episodic migraineurs [60]. Anti-inflammatory properties of adiponectin are often emphasized too. However, adiponectin can exert either pro- or anti-inflammatory properties depending on the form and multimer of adiponectin involved that varies in molecular weights (high (HMW), middle (MMW), or low (LMW) molecular weight) and forms. In a study episodic migraineurs showed a similar trend toward higher levels of total and high molecular weight adiponectin though neither measure reached statistical significance [61]. HMW: LMW ratio of adiponectin was suggested to be potential novel biomarkers for episodic migraine and either antagonist of high molecular weight adiponectin or agonists of low molecular weight adiponectin, or both suggested to be potential targets for headache management. On the other hand human adiponectin activates the pro-inflammatory nuclear factor kappa β (NF-κB) pathways as well as induces the secretion of NO and the pro-inflammatory cytokines, IL-6 and TNF-α. HMW adiponectin induces the secretion of IL-6. In contrast, LMW adiponectin can inhibit endotoxin-mediated release of IL-6. Adiponectin bears a remarkable similarity to leukocyte activating agent IL-2 and regulates both innate and adaptive immune responses and generally increases levels of pro-inflammatory cytokines and activation of monocytes via the production of cytokines such as TNFα and IL-6 and can induce the expression of nitric oxide and prostaglandin in cultured macrophages [52,59-63].

Leptin is primarily produced by adipocytes, is also produced by several other tissues including brain and has roles in energy homeostasis, appetite suppression, modulation of immune and inflammatory processes. Leptin receptors are expressed in the arcuate nucleus and dorsomedial hypothalamus. Elevated serum leptin is found to be associated with an increase in the anorexigenic pro-opiomelanocortin expression and a decrease in orexigenic NPY and AgRP [64-66]. It was suggested that chronic exposure to inflammation may be associated with decreased leptin levels [67]. Leptin also induces the production of NO and several cytokines, including TNF- and IL-6 in monocytes and macrophages and increases IL-6 production in pro-inflammatory [68-70]. Studies evaluating leptin levels in migraineurs have been inconclusive. Guldiken et al. [71] found leptin levels were significantly lower in migraineurs than controls, and suggested that low leptin levels and fat mass may be related to the pathogenesis of migraine. Berilgen et al. [72] have evaluated leptin levels in the patients with migraine before and after amitriptyline hydrochloride therapy and their results suggest that serum leptin levels were higher at 4- and 12-week follow-up when compared to baseline levels. Schutt et al. [54] reported that leptin was decreased from baseline following 20 weeks of treatment with topiramate in case series. Bernecker et al. [73] reported the crude leptin levels in non-obese female migraineurs participants were higher than controls, but this relationship was no significant after adjustment for age and BMI. Dearborn et al. [74] evaluated leptin levels in a case-cohort study of non-diabetic older migraine and non-migraine control subjects with <27 kg/m² BMI. In the study, leptin did not significantly differ in migraineurs as compared to non-migraine controls. On the other hand, multiple recent studies with a focus on surgical weight loss in obese migraineurs have suggested that weight loss may be beneficial for improving headache pain and frequency. Bond et al. [75] conducted a prospective clinic-based study to evaluate changes in headache frequency and severity after bariatric surgery in 24 episodic migraineurs with severe obesity (BMI ≥ 35 kg/m²). Their findings showed significant postoperative reductions in headache severity as well as a reduction in the percentage of participants with a moderate-to-severe disability. Novack et al. [76] investigated the changes in headache frequency in obese premenopausal women with migraine after bariatric surgery. Their results show the improved headache-related disability, decreased headache duration and improved headache-associated symptoms following surgery.

Ghrelin, a novel growth hormone-releasing and food intake stimulant which is found to reduce the pain threshold when ejected to mice hypothalamus [77] has been suggested to be used in therapeutically in migraineurs [78]. Previous to our study [79] we reported that depressed (or anxious) migraineurs have a positive association between ghrelin and BMI, whereas for the non-depressed (or non-anxious) migraineurs this association was negative [80].

**Conclusion**

Obesity and migraine are both highly prevalent disorders in the general population, influenced by genetic and environmental risk factors. Both migraine and obesity are related to inflammation events. Adiponectin and leptin have been shown to have reciprocal relationships with several of these cytokines. We summarized the relationship between obesity and migraine as: i) Obesity may be associated with frequent headaches and higher disability scores. ii) Obesity as a pro-inflammatory state may be related to the neurovascular inflammation in the patients with migraine. iii) Increases in the plasma CGRP levels of obese subjects may be related to the trigeminovascular inflammation in migraine. iv) Leptin and adiponectin can activate pro-inflammatory cytokine release that is involved in the pathogenesis of migraine, but
have been shown to have reciprocal relationships with several of cytokines. Future studies evaluating the association between adipocytokines and cytokines in migraineurs may be of interest. In conclusion, the effect of obesity on migraine outcome is important. Weight control should be a part of the migraine treatment.
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