



# The Effect of Bariatric Surgery on Migraine Headache in Morbid Obese Patients

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## Abstract

**Background:** Migraine is a common and chronic neuro-inflammatory disease with progressive and episodic headache manifestation that leads to considerable disability. Many studies recognized that obesity is a risk factor for progression of migraine. Furthermore, both migraine and obesity is highly prevalent and important risk factors of chronic cardiovascular disease, stroke, and other inflammatory disease. Thus, it is very important if weight loss could alleviate the migraine headache and its related comorbidities.

**Aim:** The present review article was conducted to assess the potential effect of Bariatric surgery on improvement of migraine headaches in morbid obese patients.

**Search Strategy:** Scopus, PubMed and web of science electronic database were systematically searched with key words of "Bariatric surgery", "gastric Bypass"; "Morbid Obesity" and "Migraine headache" for interventional studies investigated the impact of Bariatric surgery on migraine headache.

**Results:** The findings suggest significant improvement in headache frequency, duration, migraine-induced discomfort and migraine derived symptoms (nausea, phono and photophobia and) occurs as early as 3 months after bariatric surgery. Moreover, patients who had higher weight loss were more likely to experience a 50% or higher reduction in headache frequency, duration and severity.

**Conclusions:** The entire evidences suggest patients with indications of bariatric surgery will benefit from the improvements in the Migraine headache after surgery. However, it remains unclear whether Bariatric-induced endocrine, gut-brain axis alterations, or reduction in adipokine contribute to migraine improvement, so further studies are needed to confirm and clarify these findings.

**Keywords:** Gastric Bypass, Bariatric Surgery, Morbid Obesity, Migraine Headache, Surgical Weight Reduction

## 1. Background

Migraine headache, a recurrent neurovascular disorder, is distinguished by episodic, pulsatile, unilateral headache accompanied with nausea, vomiting, and disturbance in psychological status, usual patient's activity and quality of life. Migraine also undergoes a great economic burden to persons and society (1). The prevalence of migraine in the whole population has been calculated about 34.5% in women and 20.1% in men (2).

An increasing number of studies suggest a significant role of obesity on migraine outcomes. Migraine and obesity are both significantly prevalent disease in the general population. And several studies have suggested that obesity and migraine share common pathophysiological characteristics including endothelial dysfunctions (3, 4), de-

rangements in adipocytokines (5, 6), systemic inflammation (4), derangements in adipocytokines (5, 6), hematological moderators that favor a prothrombotic phenotype (3), and dyslipidemia (1). In addition, both obesity and migraine are important risk factors for chronic cardiovascular disease, myocardial infarction (7-9), ischemic stroke, and other inflammatory disease (10, 11). Several studies showed that obesity is a risk factor for migraine development and frequency of headache in adults (12-14). The relationship between obesity and migraine would be important, since the increasing prevalence of obesity (15) may lead to an elevation in the prevalence, severity and frequency of migraine and may be a possible target for prevention. moreover, it may increase the risk of comorbidities that have recently been related to migraine, such as ischemic stroke (16) and other ischemic vascular events

(17, 18). Migraine Headache and obesity are affected by a different of psychological, physiological, and Dependent on behavioral mechanisms, which most of them are influenced by body weight reduction. Particularly in patients suffer from morbid obesity that has higher frequency of migraine headache. Recently, it has been showed that surgical weight loss with bariatric surgery can improve migraine headache in morbidly obese patients (19, 20).

Some studies have reported a positive effect of bariatric surgery on decreasing migraine headache, however some other studies have not found any relationship between bariatric surgery and improvement of migraine headache. This review study was conducted with the aim of evaluating the effects of bariatric surgery on migraine headache in subjects with morbid obesity.

## 2. Methods

### 2.1. Protocol

The present systematic review was performed according to the PRISMA guidelines (21). The study did not require any ethics committee approval because of its non-experimental design.

### 2.2. Eligibility Criteria

Entire published studies evaluating the effects of bariatric surgery on migraine headache in morbid obese patient were considered eligible for this study. Morbid obesity was operationally defined as  $BMI \geq 40$ . Study eligibility was limited in English language of studies.

### 2.3. Search Strategy

The search was performed in SCOPUS, PubMed and web of science electronic databases using the terms "migraine disorders", "migraine" and "headache" combined with the terms "Bariatric surgery", "gastric Bypass"; "Morbid Obesity" from the start of indexing to 15 July 2017. The key words for search in PubMed included both text words and Medical Subject Heading (MeSH) terms. For additional relevant studies a manual search amongst references of selected articles and reviews was also accomplished.

### 2.4. Study Selection

The investigator searched all title and abstract obtained by the initial search. The studies only with English language were considered. The papers investigated the effects of bariatric surgery on migraine headache which suspected that it might satisfy the eligibility criteria were selected and the full text of these articles was assessed. The reviewer evaluated each full-text article and the studies that investigated the migraine headache as outcome variables and obesity in comparison with normal weight persons as exposure variables were included.

## 3. Results

### 3.1. Morbid Obesity

Morbid obesity, which is determined by the world health organization as a body mass index (BMI) of  $> 40 \text{ kg/m}^2$ , has become an epidemic worldwide concern (22). Morbid Obese individuals have an elevated risk of mortality and morbidity, such as type 2 diabetes (T2DM), hypertension, cardiovascular disorders, stroke, respiratory problems, asthma, respiratory problems, gallbladder diseases, osteoarthritis, apnea of sleep, and several types of cancer (including breast, prostate and colon). Morbid Obesity also is related to menstrual irregularities, complexities in pregnancy, hirsutism, and psychosocial disorders (23, 24). One study which is conducted of 527,000 men and women in the age of 50 - 71 years old, those with a BMI of more than  $40 \text{ kg/m}^2$  had the higher risk of mortality (25). More than one billion adults are affected by obesity in world-wide. The complication associated with obesity is increased at BMI level of  $30 \text{ kg/m}^2$ . Statistic result of previous studies in Iran depicted that obesity altogether in Iran; obesity and morbid obesity were seen in 28%, 10% and 3.5% of the general society, respectively. Central obesity also was present in 43.4% and 9.7% of women and men respectively (26). The obesity pathophysiology is complex and remain unknown, but some of them includes genetic, behavioral, psychological factors (27). Heredity would contribute 67% of the people differences in BMI. Thought, the genetic predisposition is unlikely to consider completely for the prompt raise in the prevalence of obesity. Low physical activity and increment in the energy dense foods consumption may be an important indicator in obesity (28).

Unfortunately, despite effort of morbid obese patients, ambulatory treatments such as exercise, diet, and nutrient counseling do not provided sustained weight loss (25), and it is found that Bariatric surgery provides the highest level of effectiveness in obtaining sustained weight loss among seriously obese patients, as compared with that of all other treatments (29).

### 3.2. The effect of Bariatric Surgery on Treatment of Morbid Obesity

The term bariatric is a composition of "bar," which means weight; "iat," that means treatment; and "ic," that is pertaining to. thus, bariatric literally interoperated to "pertaining to the weight problem treatment." bariatric surgery Indications including a BMI of more than  $40 \text{ kg/m}^2$  without comorbid disorder; BMI of more than  $35 - 40 \text{ kg/m}^2$  along with 1 of the following: Type 2 diabetes mellitus, nonalcoholic fatty liver disease, hypertension, obstructive sleep apnea (OSA) and obesity-hypoventilation syndrome, asthma, or disturbed quality of life; and BMI of  $30 - 34$

kg/m<sup>2</sup> with disability to control comorbidities, such as T2DM (30). Bariatric surgery demonstrated that conditions such as T2DM, hyperlipidemia, hypertension, and OSA resolved in 60% - 80% patients after bariatric surgery, so this approach become an attractive method for sustained weight loss (31).

Bariatric surgery currently remains the most effective approach of achieving long-term weight loss along with significant improvement in obesity-associated comorbidities and overall mortality (30, 32, 33). Although the bariatric surgery might be associated with some probably risks, including early postoperative complications (wound infection, anastomotic leak, deep vein thrombosis and etc.), but has a significantly effects on treatment of metabolic and inflammatory comorbidity related to obesity such as T2DM, Hypertension, cardiovascular disease, Fatty liver and also the neuroinflammatory disorders including Migraine headache (25, 27). Thus, the present review article was conducted to assess the potential association between morbid obesity and migraine as well as to evaluate the effect of Bariatric surgery on improvement of migraine headaches in morbid obese patients.

In this regard the Scopus, PubMed and Google scholar electronic database were systematically searched with key words of "Morbid Obesity", "Bariatric surgery", "gastric Bypass" and "Migraine headache" for interventional studies investigated the impact of Bariatric surgery on migraine headache.

### 3.3. *The Association Between Morbid Obesity and Migraine Headache*

Migraine headache is a common and chronic neurovascular condition, often leading to incapacitating effects on the suffering individual (34). Recently, various studies shows strong statistical relation between migraine headache and obesity (35). Information in large population databases about the relationship between migraine and obesity are conflicting; though, whole of the large society information investigating the migraine trends among generative age suggested that a relationship between episodic headache of migraine and obesity is exist (36-38). Moreover, obesity is related to the conversion of episodic migraine to chronic migraine (38). During the recent years, some investigation revealed that there are a considerable proportion of morbidly obese female among candidates for bariatric surgery who suffers from migraine. Horev et al. (39) show that incidence of migraine headache among morbid obese individual was 48% higher as compared with non-obese control groups (40). Furthermore this observation was supported by Peres et al. so that migraine headache was reported as 66% of obese patients in comparison with 18.5% of non-obese subjects (14). Moreover

other studies have suggested that there is the association between migraine and obesity among men and in reproductive age women (39) and also in youngster age (37).

In addition to greater incidence and prevalence of migraine in morbid obese patient, a large body of studies revealed that there is the higher incidence of migraine severity among morbid obese women (40, 41). Sample in a large survey in united states, Ford et al. showed that increase in BMI is correlated with the elevated in severe migraines headache prevalence as a non-linear status (35). Peterline et al. survey, also showed higher prevalence of migraine (OR = 1.39) among women with obesity in comparison with normal-weight and healthy women (36). Vo M et al. showed that morbid obese women had an almost 1.48-fold elevated risk of migraine headache in comparison with normal weight women, and also women with morbid obesity (OR 2.07; 95% CI 1.27 - 3.39) had the greatest chance of migraines (20).

Several epidemiological studies have confirmed that obesity has a strong statistical relationship with migraine; one of the most essential questions remaining is the direction of the migraine-obesity association. Vo et al. have suggested that subjects with a background of pediatric migraine headache had higher weight gain in age of young adults (42). To acquiring a clearer understanding of the interaction between migraine and obesity, considering a thing beyond BMI is important. However anthropometric indexes are a useful and inexpensive substitute for determining obesity in general. In normal situation, obesity should be evaluated as excess adipose tissue, rather than extra body weight (which includes the other region of the body including lean, skeletal organ and skin mass in addition to Fat tissue) (43). The body composition analyzer, (e.g., BIA and MRI) makes it possible to direct estimation of fat mass, in addition to evaluation of the subcutaneous from abdominal adipose masses. It seems that variety in the amount or ratio of subcutaneous and abdominal adiposity better clarified the association between migraine-obesity (2, 44). Moreover, it is well known that there is a substantial different in gene expression of very inflammatory indicator and receptors according to the site adipose tissue such as subcutaneous or abdominal. Recently, studies confirm that one of this cytokines, adiponectin, mainly released from subcutaneous fat mass, can be considered as an indicator of rapid response to treatment of migraine (12, 45).

Another hypothesis about the obesity-migraine relationship emphasized to the role of obesity in modulation of pain and particularly migraine headache. Rossi et al. have showed that obesity induced from diet in mice prior to the trigeminal nociceptive pathway, explaining it responsive to another innocent stimuli (46). Rossi F et

al. used intradermal capsaicin in the mice innervated by the trigeminal nerve, and showed capsaicin in a low dose which did not show any effect on mice with a normal diet, but it was sufficient to induced stimulation of neurons in the trigeminal nucleus in the obese mice (47).

Regarding the relationship between obesity and migraine, the possible mechanisms could be described in one side by common inflammatory inter-mediators that with the stimulation of trigeminal vascular system cause neurogenic inflammation which occurs mainly in the pain attacks of migraine. Activation of trigeminal system nociceptor result in the secretion of proinflammatory mediators, most significantly calcitonin G-Related Protein (CGRP) and substance P (48, 49). In obese and morbidly obese subjects, CGRP concentration are heightened that show further elevation after fat and fatty foods consumption (50). Likewise, substance P which has been expressed in fat cells, may lead to adipocytes fat pool enlargement of and so the pro-inflammatory status accompanied with severe obesity (51). Moreover, the high concentration of pro-inflammatory adipocytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), which is together with excessive levels of adiposity (52), are increased with the begin of migraine headache attacks (53). Also the excessive amount of C-reactive protein (CRP) in systemic inflammation are further increased in both migraine and obese patients (54). So, the pro-inflammatory status that accompanied with more bode weight may be the cause of more exacerbation in inflammatory profiles in migraine patient ,and thus probably resulting in more frequent or much severe headaches attacks (12).

In regulation of eating behavior, various peptides and neurotransmitters released by the hypothalamus have an important role in migraine pathophysiology. For instance, serotonin, the neurotransmitter attach to receptors (HT1A, HT1B, HT2A and HT2C) which is involved in appétit control and level of energy intake through the HT1B and HT2C receptors and signaling the sense of satiety (55, 56). Besides the transient increases in serotonin concentration within the headache attacks, chronically, migraine disease is assumed to be accompanied with lower serotonergic activity (57), that could result in more intake of calories and thus more body weight (58). Serotonin moreover through various neuropeptides influences on eating behavior, such as orexin-A which is a regulating hormone for appetite and feeding, orexin-A also is related to arousal, reward center, induction of spontaneous exercise (59) so that, in obese women lower serum concentration of orexin-A was seen in comparison with control group (60), interestingly, other correlations between obesity and migraine may be through sleep dis-regulation. In narcolepsy patients which is a sleep disorder determined with orexin-A insufficiency,

Both problems are prevalent conditions in narcolepsy patients (61, 62).

Some adipocytokines including leptin and adiponectin which modulated body weight with its impact on appetite control and metabolism may enhance pro-inflammatory pathways communicating the migraine with obesity. So that, lower adiponectin concentrations has seen to be accompanied with a pro-inflammatory profile and have been involved in both obesity and migraine (3, 63). Likewise, leptin also may stimulate release of cytokines and thus elevated pain sensitivity (64). Although, the effect of leptin in pathogenesis of migraine is less known, a recent investigation showed lower leptin concentration in episodic migraine patients compared with controls (44, 65).

According to this explanations and the close relationship between migraine and obesity persuades the clinician that probable weight reduction could have a considerable effects on alleviation migraine headache.

#### 3.4. *The Effect of Weight Loss on Migraine Headache*

Due to the influences of weight reduction on many of the physiological, behavioral, and psychological status, it correlated the obesity to migraine; and well approve that weight loss may be a way of alleviating frequency and intensity of headaches in morbid obese patients. In regard of physiological pathway, body weight reduction by changing the signaling pathways in CNS rises the orexin-A and thus could attenuate or even prevent the migraine headache attacks (66), and also the weight loss via increment in adiponectin and decrement of leptin results in decrement of inflammatory adipocytokines, CRP (67) and sympathetic system tone which play a substantial role in attenuating the central and peripheral pro-inflammatory pathways and also the alleviation in the pain and attacks of migraines headache. moreover, psychological status including temper, mood (66) and stress-managing ability (68) improves considerably with weight loss which itself attenuate migraine headache (13, 69).

likewise, improvement of quality of sleep and (70). Decreases in fatty food consumption and that may occur with reducing weight could decrease headache frequency and severity develops in physical activity are forcefully associated to weight reduction (70-72). Eventually, weight reduction may impact migraine headache in obese and morbid obese subjects through improvements in status that are co-morbidity with both disease, including high blood pressure, diabetes (73) and dyslipidemia (74), depression (75) and sleep apnea (71).

Low physical activity has been shown to be related with almost 21% elevated the odds of headache attacks in migraineurs and a 50% increased risk of migraine attacks in

adolescents migraineurs. furthermore, limited data propose that aerobic activity may decrease attacks frequency in episodic migraine sufferer (76, 77). Regarding the associations between obesity and increased headache frequency, severity, and disability in migraineurs have been suggested in previous investigations (42, 46). Large weight reductions achieved via bariatric surgery might have a positive impact on migraine headache.

### 3.5. The Effect of Bariatric Surgery on Migraine Headache

With the increase of prevalence and severity of morbid obesity, the assumption of more aggressive techniques including the bariatric surgery was increased (78). Restrictive Gastric surgeries, such as gastric-banding and banded gastroplasty, induce weight reduction with the restricting the compliance of the stomach to houses food and also by reducing the speed of nutrients intake flow (79). Interestingly Lots of the co morbidities of obesity such as hypertension and type 2 diabetes have been demonstrated to be alleviated or even be treated following this operation (80). So this intervention has a wonderful worldwide effects on persons, families, and community by the both direct and also indirect pathways (81).

In spite of these probable mechanisms correlating morbid obesity with migraine, a few studies have assessed the effects of bariatric surgery on migraine headache. Sugerma et al. investigated the impact of the bariatric surgery on intracranial idiopathic hypertension, which is recognized as a disease related to obesity and accompanied with persistent, intensive headaches symptom. And Weight reduction following 4 months after-surgery was correlated with attenuation of headache attacks in all patients; also, headaches relapsed in some patients who subsequently had body weight regain. Recently, one study assessed the impact of weight, obesity, and weight changes on several migraine headache characteristics in pediatric headache patients (70% had migraine). Percentile of BMI was positively correlated with migraine attacks at the first visit. And then further reductions in BMI was correlated with more decreasing in frequency of headache attacks 3 month and 6 month following the monitoring of children with overweight or obesity in initial visit, but was not seen for non-obese individuals (82).

Novak et al. assessed the migraine attacks frequency, and related symptoms in 29 reproductive age woman with severely obesity who have been included in migraine headache criteria before and also after bariatric surgery (57). Their results demonstrated that as early as 3 months post-bariatric surgery headache frequency and disability considerably improved and also this positive effect is sustained in 6 months following the surgery.

Among the 23 patients with episodic migraine who enrolled in this study, the average of headache frequency in one month decreased from 4 at initial of the study to 2 days monthly headache at 3 months after bariatric surgery. The further decreasing was seen, to only 1 headache day, 6 months following surgery. The 6 women who suffer from chronic migraineurs also confirmed considerably down falls in attacks frequency after 3 and 6 months following-bariatric surgery. Furthermore, like their findings about the headache frequency, Novak et al. revealed that headache-associated disability significantly was alleviated as soon as 3 months after surgery (57). Specially, these alleviating effects of bariatric surgery on migraine patient's disability was sustained statistically significantly, in comparison with baseline, after 6 months. So, Novak et al.'s survey shows that in morbid and severe obese women with migraine the gastric bypass surgery may result in significantly attenuation in attacks frequency, duration and also headache-related disturbance, moreover betterment in the existence of migraine-related sign in subsequent attacks.

Later study which was an open, non-controlled, clinical trial of morbid obese subjects admitting for bariatric surgery conducted by Bond et al. (83). They evaluated 24 morbid obese, pre- and post-reproductive age patients suffered from episodic migraine. frequency of migraine headache was assessed from 3 months before and also after 3 months and 6-month following surgery (83).

Bond's study investigated whether migraine headache were improved in severe obese migraineurs 6 months after bariatric surgery, the most effective treatment for clinical severely obese individuals (29). The result of this study showed that headache frequency was considerably decreased from before to 6 months post-operatively (11.1 vs. 6.7 headache days), with almost half of subjects demonstrating at least a 50 percent discretion (83, 84).

In patients who experience higher weight losses, nevertheless the type of operation, having more probable to having 50% betterment of attacks frequency. Results also demonstrated significant decreases in headache severity and related disturbances. Before surgery, 12 (50%) of the subjects reported moderate to severe disturbances, indicating a high need for drug treatment (85). thought, at 6 months after surgery, just 3 (12.5%) of the participants showed this degree of disability. notably, headache improvements occurred post-operatively in spite of that 70% of subjects were still obese, revealing that body weight reduction helps to alleviating headache in the absence of complete improvement of obesity (83).

The statistical accuracy and generalizability of finding from small sample size, uncontrolled clinical models are also limited.

More recently, in the retrospective study conducted by Gunay et al. (86) in morbid obese migraineurs who undergone R-en-Y gastric bypass surgery, almost 90 % of patients has reported complete or partial attenuation of their headache (86).

In addition, patients who had greater weight reduction were more likely to experience a 50% or higher reduction in headache frequency. These findings confirmed the recently proposed concept that weight reduction may be an important section of a migraine management plan for morbid obese individuals (87). Although large weight reductions resulting from bariatric surgery appear to positively affect migraine headache (44) morbidly obese migraine sufferer experience a significant improvement headaches after considerable weight loss via bariatric surgery. More studies are needed to clarified whether more modest, weight reduction through behavioral intervention can be effective similar for migraine improvements (83).

While this information are promising to show that bariatric surgery likely have a potential effect in the controlling of migraine headache in subjects with morbidly obesity, in attention to that none of these studies considered a control group. So, the controlled studies with the larger sample size evaluating bariatric surgery in attention to migraine prevention are required yet. Moreover, the others weight-reduction strategies (including diet therapy and physical activity) for obese individuals without indications (BMI < 35) or the subjects that do not opt the bariatric surgery could be considered.

Taken together, this current information suggested that morbid obesity seems to be correlated with migraine headache. So that the odds of suffering from migraine headache of all types (episodic or chronic) are elevated in morbid obese patients. Furthermore, with the deteriorating obesity status, the risk of having migraine rises. The probable Mechanisms hypothesized for the migraine and obesity linkage have considered to be in relation to the common pathophysiologic disorders (such as, alters in hypothalamic pathway activation and also the regulation of common peptides and neurotransmitters [including serotonin, adiponectin], or associated with the lifestyle factors [e.g., poor physical activity in migraine patients because of pain]).

#### 4. Conclusions

Evidence indicates a plausible link between migraine and morbid obesity, a wide range of behavioral, physiological and psychological mechanisms may be subscribe to the common comorbidity of these two diseases, that fortunately the greater part of which could be effectively im-

proved via body weight reduction particularly with significant weight loss in severely obese patients. The entire evidences in those review study suggest patients with indications of bariatric surgery will benefit from the improvements in the Migraine headache after surgery. However, it remains unclear whether Bariatric-induced endocrine, gut-brain axis alterations, or reduction in adipokine contribute to migraine improvement, so further studies are needed to confirm and clarify these findings.

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#### Footnotes

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