Weight Loss as a Predictor of Resolution of Symptoms in Subjects with Idiopathic Intracranial Hypertension

By

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CERTIFICATE OF APPROVAL

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ABSTRACT:

Intracranial hypertension is a disorder of increased cerebrospinal fluid pressure that may result in symptoms of headache, vision loss and pulse synchronous tinnitus. Idiopathic intracranial hypertension (IIH) differs from secondary intracranial hypertension (SIH) in that there is no known cause of idiopathic intracranial hypertension. Overweight or obese women of child-bearing age are at increased risk of IIH. Patients are diagnosed with IIH using the Modified Dandy Criteria that includes the following requirements: 1) signs and symptoms of increased intracranial pressure, 2) no localizing findings on neurological exam, 3) normal MRI/CT with no evidence of venous obstructive disease, 4) opening CSF pressure>25 cm H_20 with normal CSF constituents, 5) awake and alert patient, and 6) no known cause for increased pressure found. Physicians often begin by advising patients to lose weight and also may start them on a carbonic anhydrase inhibitor to lower intracranial pressure. If weight loss and medical management fail to manage symptoms, surgical management may be attempted. Shunting is performed to alleviate intractable headache and potential vision loss. Decompression of the optic nerve may be performed to prevent vision loss and blindness. In some patients cerebral venous sinus stenting may be of benefit if venous sinus stenosis is present. Since obesity is common among many patients with IIH and some studies have suggested weight loss can reduce symptoms of IIH, it is valuable in symptom management to understand whether weight loss is a successful predictor of improvement in symptoms. This study examined whether absolute weight loss, percent weight loss, or BMI change are associated with improvement in patient reported headache, vision and tinnitus. Logistic regression models were used to determine which of these primary predictors were associated with improvement. Weight loss was associated with a greater likelihood of improvement in

headache, vision and tinnitus symptoms. Patients who lose weight have an increased likelihood of having improvement in headache, vision and tinnitus symptoms. Weight loss should continue to be a recommendation to patients with IIH.

CHAPTER 1: INTRODUCTION

Research Question: Among subjects with idiopathic intracranial hypertension (IIH) who are overweight or obese at diagnosis, does absolute weight loss, percent weight loss or change in BMI affect the likelihood of improvement of symptoms (headache, vision and tinnitus)?

Specific Aims:

Aim #1: To describe initial weight, enrollment weight, and weight loss among a sample of patients with idiopathic intracranial hypertension.

Aim #2: To build three separate logistic regression models examining predictors of improvement (yes/no; a dichotomous variable) in three separate outcomes: headache, tinnitus and vision. IH Registry subjects complete subjective questionnaires describing the change in their symptoms of headache, tinnitus and vision. Patients report that their symptoms are "much better," "somewhat better," "about the same," "somewhat worse," or "much worse" than they were at diagnosis of IIH. Each of the three models will use as potential predictors for symptom reduction, the variables of absolute weight change, percent weight change, BMI change, age at diagnosis, sex of patient (male/female), BMI at diagnosis and other surgery to treat IIH (yes/no).

Hypothesis #1: Greater absolute weight loss, percent weight loss and BMI change from diagnosis to enrollment will be predictors of improvement of symptoms in patients with idiopathic intracranial hypertension.

Aim #3: Among a group of IIH patients who have lost weight, compare those who have had bariatric surgery and those who have not in order to determine whether there is a difference in symptom improvement.

Aim #4: Among patients with a percent body weight loss of less than 6%, 6-20% or greater than 20%, determine whether there is a significant difference in improvement of symptoms of vision, headache and tinnitus.

Background and Significance:

Intracranial hypertension is a disorder of increased cerebrospinal fluid (CSF) pressure resulting in signs and symptoms of headache, pulse synchronous tinnitus, papilledema (swelling of the optic nerve), and potentially blindness. Intracranial hypertension may be idiopathic (of unknown origin) or may occur in response to a medication or other medical condition. This latter type is known as secondary intracranial hypertension. Idiopathic intracranial hypertension (IIH) disproportionately affects overweight and obese women of childbearing age (4). The disorder occurs rarely, with an incidence of 0.9 per 100,000 in the general population and 1.6 per 100,000 in females (13). Patients in the at-risk population (obese women in child-bearing years) have an incidence of 19 per 100,000 (5).

This disorder resulted in economic costs of $444 million in 2007 in the United States. There is also an associated loss of quality of life for many patients with idiopathic intracranial hypertension (7). Headaches can be disabling and visual loss may, in severe cases, lead to blindness. The disabling effects of the disorder make it an important area of study (13). Due to the tremendous financial and personal costs of IIH in the United States and around the world, it is vital to develop better strategies for preventing and treating signs and symptoms of IIH. IIH has an enormous impact on people's lives and their ability to be productive citizens.

Management (Medical & Surgical):

Medical and surgical management of this disorder is difficult, but there are several approaches in current use to manage this complex disorder. When a patient with IIH is overweight or obese, medical management typically begins with weight loss advice provided by a physician or dietician (4). In addition, for both overweight and normal weight patients, physicians prescribe medication with carbonic anhydrase inhibition properties, which include acetazolamide (Diamox), topiramate (Topamax), furosemide (Lasix), and methazolamide (Neptazane). Carbonic anhydrase inhibitors are useful in lowering CSF pressure because they inhibit carbonic anhydrase, an enzyme necessary to produce cerebrospinal fluid. Therefore, when patients take these types of medications, CSF production is reduced and CSF pressure is decreased.

When medical management of the condition does not offer sufficient reduction of symptoms, surgical intervention may be attempted. Surgical interventions include optic nerve sheath decompression (to protect the optic nerve from CSF pressure), cerebral venous sinus stenting (to improve blood circulation through stenotic areas, lumboperitoneal shunting, and ventriculoperitoneal shunting (to maintain normalized levels of CSF by removing excess fluid through shunts placed in the lumbar spine or ventricles of the brain, draining fluid into the peritoneum, plural cavity, or atrium).

Central Obesity's Role in IIH:

There is evidence that central obesity increases intra-abdominal pressure, which can also increase cerebral spinal fluid pressure (16). Sugerman conducted a non-randomized,

prospective study that suggested that patients' central obesity was linked to their intra-abdominal pressure. Patients in this study were severely obese (N=6) and had been diagnosed with IIH. Mean BMI (body mass index) for patients was 45 kg/m^2 indicating fairly severe obesity in these patients.

Evidence that weight loss improves IIH:

Based on historic medical literature, central obesity may play a role in IIH; there is also evidence that weight loss may reduce signs and symptoms of IIH. Physicians recommend weight loss as one tool of medical management (5). Johnson et al (1998) discuss the role that weight loss may play in decreasing signs and symptoms of IIH, specifically papilledema. The authors found that a 3.3% weight loss was associated with a one-grade reduction in papilledema while a 6.2% weight loss was associated with complete reduction of papilledema. These findings suggest that there may be a role for weight loss in the treatment of IIH and that even modest weight losses may be associated with decreases in signs of IIH. The size of this sample (N=15) was small and the mean body mass index at baseline was fairly large (BMI=40.7 kg/m^2). While acetazolamide was part of the treatment given to patients in this study, patients who were only on acetazolamide but did not lose weight were not able to reduce their papilledema. These findings suggest that combining weight loss with the use of acetazolamide could be helpful in reducing symptoms of IIH in these patients.

Sinclair et al studied patients on a low calorie diet and monitored intracranial pressure and papilledema (2010). Results demonstrated that patients were able to significantly

reduce intracranial pressure, as well as signs of papilledema. In addition, researchers found that women were still showing these effects three months after the diet was stopped. According to a study by Skau et al (2010), it is possible to improve signs of idiopathic intracranial hypertension. These researchers found that 65% of patients in their study were able to go into remission from their signs. The study compared patients whose weight loss was 3.5% of BMI or greater with those whose weight loss was less than 3.5% BMI. Patients with weight loss greater than 3.5% showed significant reduction in CSF pressure, while patients who did not lose as much weight did not have these improvements.

Glueck et al (2006) discuss the role that metformin and lifestyle modification may play in weight loss among patients with IIH and comorbid polycystic ovary syndrome (PCOS). These researchers found that patients with PCOS and comorbid IIH who took metformin, a medication used to normalize ovarian function and insulin levels, lost an average of 7.7% of their body weight. In addition to this significant change in body weight, there was a significant change in papilledema. At the beginning of the study 95% of the subjects in the metformin-PCOS group had papilledema versus 30% at the end of the study. That study suggests that there may be a role for metformin in weight loss therapy for patients with PCOS and IIH and that weight loss with metformin may lead to reduction in the proportion of patients with papilledema. The authors note that many women with IIH have comorbid PCOS and therefore these findings may be useful to many patients in the IIH population.

There is evidence that absolute weight loss results in improvement of IIH signs. Kupersmith et al (1997) conducted a study of female IIH patients put on a low-calorie rice diet and examined changes in papilledema and visual field dysfunction. All of the women (N=58) included in the study were at least 10% over their ideal body weight. The study found that those patients who lost greater than or equal to 2.5 kg (approximately 6 lbs) over a 3-month period were more successful in improving papilledema and visual fields than patients who were not able to lose 2.5 kg.

Bariatric surgery as a way to achieve weight loss:

Amaral et al (1987) describe a case of a morbidly obese young woman with bilateral papilledema due to idiopathic intracranial hypertension who underwent gastric exclusion surgery. Due to her treatment with steroids she had gained weight since the time of her diagnosis; however, following the gastric exclusion surgery she underwent a 37 kg (approximately 82 lbs) weight loss over a follow-up period of six months. Gastric exclusion surgery is a weight loss procedure utilized in patients who are morbidly obese. Her weight loss resulted in the resolution of her papilledema and headache as well as a decrease in her CSF pressure and visual field improvement.

Bariatric surgery is one method that has been used to facilitate weight loss in patients with idiopathic intracranial hypertension suffering from particularly severe obesity. In a case report by Nadkarni et al (2004), two women with IIH resolved their symptoms following bariatric surgery. These findings suggest that there is a role for weight loss surgery in treatment of IIH. In addition, Bouldin et al (2006) states that gastric bypass

surgery is more effective for patients with idiopathic intracranial hypertension than shunting. These researchers advocate the use of bariatric surgery as a tool to reduce symptoms of IIH in obese patients. They note that animal models suggest an association between intra-abdominal obesity and increased intracranial pressure.

A literature review by Fridley et al (2011) reviews the evidence with respect to bariatric surgery treatment for individuals with IIH. These authors were interested in whether bariatric surgery would lead to resolution of papilledema and visual field deficits. Patients initially presented with symptoms of headache, pulsatile tinnitus, transient visual obscurations and vision loss. The literature review found that 92% of patients in this sample who had bariatric surgery (most commonly Roux-en-Y surgery) experienced resolution of their general symptoms of IIH (presenting symptoms) following surgery (N=61). In addition, researchers examined a subset of patients using fundoscopy to look for papilledema. Of those patients who underwent fundoscopy, 97% experienced resolution of papilledema. The total number of patients who had bariatric surgery was 35; 34 patients experienced resolution of their papilledema. These findings provide support for using bariatric surgery as a treatment for obese patients with IIH.

Sugerman et al (1995) found that of eight patients who underwent bariatric surgery for treatment of IIH, no patient experienced papilledema or intractable headache at follow-up. Mean weight loss for this group of patients was 57 kg (approximately 125 lbs) over a period of 34 months. Patients had a mean BMI at the beginning of the study of 49 kg/m^2, indicating morbid obesity.

Another study by Sugerman et al (1999) found similar results. In this study, bariatric surgery was performed on a sample of 24 patients with IIH. Follow-up results were promising. Although five patients were lost to follow-up, nineteen patients experienced a reduction of their BMI from a mean of 47 kg/m^2 (SD: 6 kg/m^2) to a mean of 30 kg/m^2. In addition, patients lost an average of 45 kg (approximately 100 lbs) at one-year follow-up. All but one patient experienced resolution of their pulsatile tinnitus and headache shortly after the procedure. These results again support the effectiveness of weight loss, and in particular, bariatric surgery, for obese patients suffering from IIH.

Weight loss not a panacea:

Despite evidence that weight loss, including weight reduction following bariatric surgery, can improve symptoms and signs of IIH, weight loss is not a perfect treatment for IIH and needs to be further studied. In a study by Michaelides et al (2000), researchers conducted a study of IIH patients who underwent bariatric surgery for morbid obesity (N=16). Researchers found that 81% (13 patients) completely resolved symptoms of pulsatile tinnitus through weight loss. All patients experienced resolution of papilledema. Three patients did not eliminate their pulsatile tinnitus in spite of weight loss through bariatric surgery. The study suggests that in spite of weight loss, there may be some patients who do not adequately resolve symptoms of IIH. The patients who did not eliminate their tinnitus had weight losses similar to those who did resolve their tinnitus. More research is needed to determine the role of weight loss in reduction of symptoms of IIH.

This study examines a large sample of patients with IIH who were overweight or obese at diagnosis in order to determine how effective weight loss (by bariatric surgery or other methods) is for reducing IIH signs and symptoms. Since the Intracranial Hypertension Registry is the largest registry of patients with IIH in the world, this study will shed additional light on the effectiveness of weight loss for a large sample of patients.

CHAPTER 2: METHODS

Study Subjects:

Subjects are patients with IIH who are enrolled in the Intracranial Hypertension Registry, a joint project of the Casey Eye Institute at Oregon Health & Science University and the Intracranial Hypertension Research Foundation.

Subjects are recruited to the Intracranial Hypertension Registry through physician referral and self-referral. Registry enrollees do not constitute a representative population-based sample. Often patients learn about the Registry through the Intracranial Hypertension Research Foundation website. Thus some patients are enrolled months or years after their diagnosis and treatment for IIH. Initial enrollment in the IH Registry involves an informed consent form, an authorization to release medical records, as well as a medical history questionnaire describing patient medical histories and experience in the diagnostic and treatment phase of intracranial hypertension. Research coordinators contact physicians and hospitals and request records that are then abstracted and entered into a secure database. A qualified physician reviews the abstracted records to determine whether the patient has a confirmed diagnosis of idiopathic intracranial hypertension (based on the Modified Dandy Criteria), secondary intracranial hypertension (i.e., IH due to another medical disorder or medication), or does not have enough information to make the determination at that point in time. Follow-up questionnaires are sent annually to IH Registry participants asking them questions about the course of their illness and changes that have occurred in the past year. Participants who are unable to fill out the initial

questionnaire and the follow-up questionnaires may complete these via telephone interview.

Selection Criteria:

A subject was considered for inclusion in this study if the subject was enrolled in the Intracranial Hypertension Registry and had a diagnosis of idiopathic intracranial hypertension confirmed by a qualified physician based on the Modified Dandy Criteria.

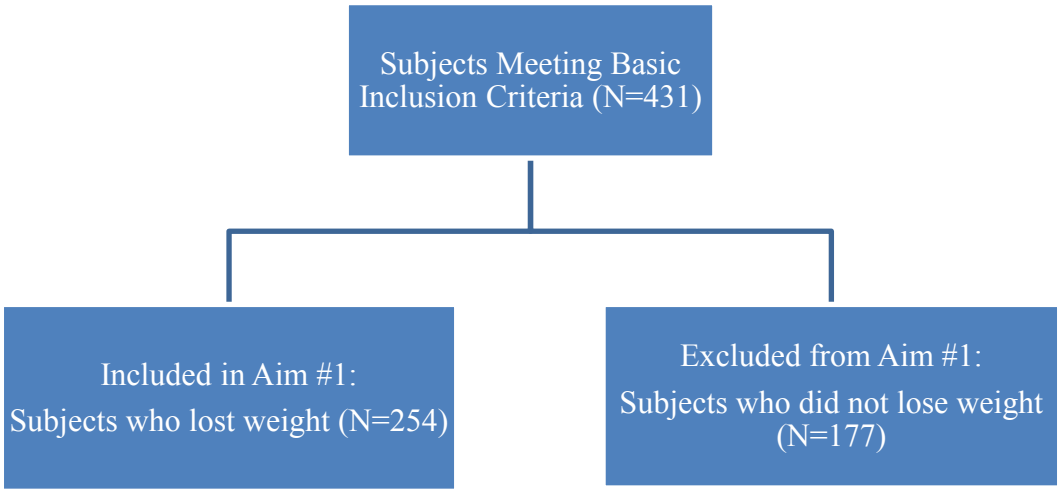
Inclusion Criteria:

1) Complete IH Registry Enrollment
2) Confirmed IIH diagnosis
3) Age 10 or older at diagnosis
4) BMI greater than 25.0 kg/m^2 at diagnosis

Subject Selection by Aim:

Aim #1: To describe initial weight, enrollment weight, and weight loss among a sample of patients with idiopathic intracranial hypertension.

Figure 1: Flow chart for Aim #1



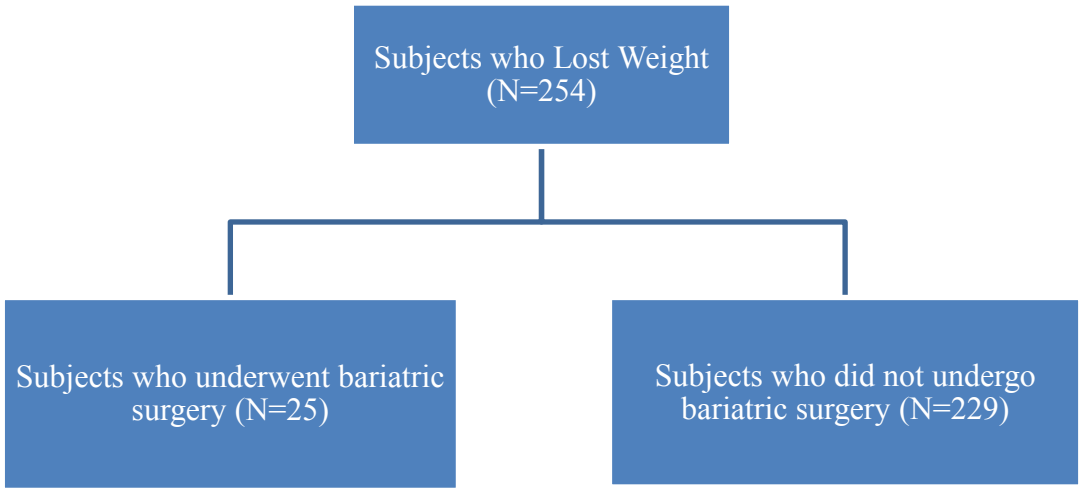
Aim #2: To build three separate logistic regression models examining predictors of improvement (yes/no; a dichotomous variable) in three separate outcomes: headache, tinnitus and vision. IH Registry subjects complete subjective questionnaires describing the change in their symptoms of headache, tinnitus and vision. Patients report that their symptoms are "much better," "somewhat better," "about the same," "somewhat worse," or "much worse" than they were at diagnosis of IIH. Each of the three models will use as potential predictors for symptom reduction, the variables of absolute weight change,

percent weight change, BMI change, age at diagnosis, sex of patient (male/female), BMI at diagnosis and other surgery to treat IIH (yes/no).

All subjects meeting the basic inclusion criteria (N=431) are included.

Aim #3: Among a group of IIH patients who have lost weight, compare those who have had bariatric surgery and those who have not in order to determine whether there is a difference in symptom improvement. Only subjects who lost weight (N=254) were included in this comparison. Subjects were divided into two groups, those who underwent bariatric surgery (N=25) and those who did not (N=229). Subjects in the latter group may have utilized other weight-loss methods, procedures or programs.

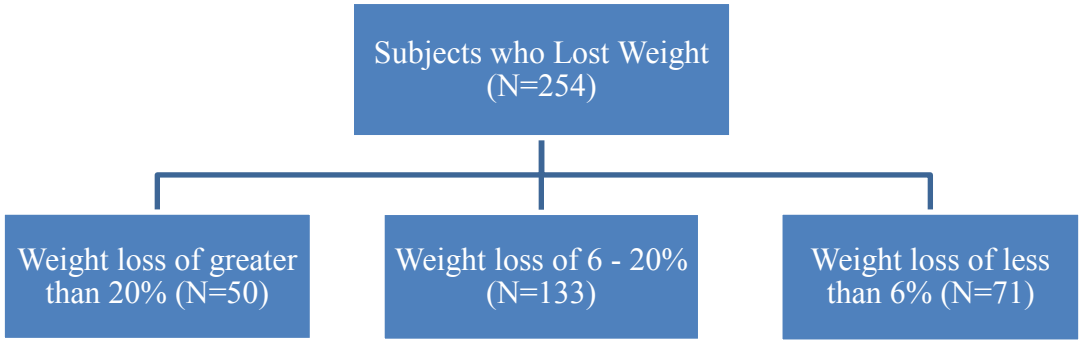
Figure 3: Flow chart for Aim #3



Aim #4: Among patients with a percent body weight loss of less than 6%, 6-20% or greater than 20%, determine whether there is a significant difference in improvement of symptoms of vision, headache and tinnitus. Only subjects who lost weight (N=254) were

included in this comparison. Subjects were then divided into three groups: those with greater than 20% weight loss (N=50), those with between 6-20% weight loss (N=133), and those with a less than 6% weight loss (N=71).

Figure 4: Flow chart for Aim #4



Sample Design:

Aim #2: To build logistic regression models examining predictors of improvement of symptoms.

Improvement of self-reported patient symptoms: Vision, headache and tinnitus were coded as 1 for "much better/somewhat better" and 0 for "about the same/somewhat worse/much worse" based on patient responses on IHR self-assessment questionnaires. Patient responses were subjective; patients compared their current symptoms with their symptoms at diagnosis. "About the same" was coded as "0" because from a medical

perspective, if a patient with symptoms does not make progress this is regarded as a treatment failure.

Table 1: Predictor Variables and Values

Absolute weight change, lbs	Continuous variable
Percent weight change	Continuous variable
Age at diagnosis (years)	Continuous variable
Sex of patient	1=female, 0=male
Surgery for IIH (other than bariatric surgery)	1=Yes, 0=No
BMI change, kg/m^2	Continuous variable
BMI at diagnosis, kg/m^2	Continuous variable

Aim #3: To divide patients who lost weight into two groups, one in which the patients had bariatric surgery and the other in which the patients did not. Patients who did not have bariatric surgery will be followed from time of diagnosis to time of enrollment. T-tests will be utilized to compare the mean absolute weight loss and percent weight loss between these two groups, and chi-square tests will be used to compare the proportion of people in the bariatric surgery group who had improvement of symptoms versus the proportion of people in the non-bariatric surgery group who had improvement of symptoms.

Aim #4: To divide subjects who lost weight into three group—patients with weight loss less than 6%, 6-20% and greater than 20%. The percent of subjects who experienced improvement of vision (subjectively reported by patients), tinnitus and headache will be calculated.

CHAPTER 3: RESULTS

Aim #1: Descriptive Statistics

The majority of IIH patients in this sample were female (N=246) versus male (N=8). While some patients had undergone surgery to treat their IIH, there were a significant number of patients who had not (see table 2). Mean age at diagnosis was approximately 32 years old for non-bariatric surgery patients, and 31 years old for bariatric surgery patients. Patients treated with bariatric surgery had a mean BMI that was higher (47.2 kg/m^2) than non-bariatric surgery patients (39.1 kg/m^2). However, both bariatric and non-bariatric surgery had mean BMI's that placed them in the obese range. Patients who had bariatric surgery lost an average of 91.5 lbs (95% CI: 73.9-109.1 lbs; $p<0.001$), while those who didn't have bariatric surgery lost an average of 28.1 lbs (95% CI: 24.2-31.9 lbs lost; $p<0.001$).

Table 2: Improvement of symptoms and descriptive statistics for IIH patients who lost weight

Characteristic	Bariatric Surgery Patients (N=25)	Non-Bariatric Surgery Patients (N=229)	p-value
Sex (Male/Female)	1/24	7/222	0.798
Other surgery for IIH (Yes/No)	11/14	78/148	0.347
Mean age at diagnosis (years)	31.0 (9.8)	31.8 (9.5)	0.716
Mean BMI at diagnosis	47.2 (7.0)	39.1 (7.4)	<.001
Mean weight at diagnosis (lbs)	290.7 (50.1)	234.8 (48.9)	<.001
Mean weight at enrollment (lbs)	199.2 (49.7)	206.7 (44.5)	<.001
Patient weight loss (lbs)	-91.5 lbs (42.6)	-28.1 lbs (29.7)	<.001

Patient percent body weight loss	-31.3% (13.1)	-11.4% (9.9)	<.001
Improvement in headache	48% (12/25)	34% (74/216)	0.191
Improvement in tinnitus	35% (7/20)	33% (66/198)	0.880
Improvement in vision	35% (8/23)	32% (70/220)	0.772

Non-bariatric surgery patients had a mean percent body weight loss of 11.4%, while bariatric surgery patients had mean percent body weight loss of 31.3%.

Aim #2: Univariate Logistic Regression:

Univariate logistic regression was conducted between each outcome variable (vision, headache and tinnitus) and each predictor variable separately. Age at diagnosis, absolute weight change, percent weight change and BMI change were associated with improvement of vision symptoms for IIH patients. Tinnitus symptom improvement was predicted by age at diagnosis, percent weight change and BMI at diagnosis ($p<.20$). Absolute weight change, percent weight change and BMI change were associated with patients' headache improvement. Increased age at diagnosis was associated with decreased odds of self-reported vision improvement. For each additional 5 years of age at diagnosis, an individual has 0.888 times the odds of improvement in vision. Each additional 5 lb weight loss is associated with an odds of improvement of self-reported vision symptoms of 1.04, odds of improvement in headache of 1.03, and odds of improvement in tinnitus of 1.01.

Table 3: Univariate logistic regression results showing crude association (OR) between individual predictor variables (rows) and each of three separate outcomes--vision, tinnitus, and headache (columns) (N=431)

Predictor	**Vision** **N, OR (95% CI), p**	**Tinnitus** **N, OR (95% CI), p**	**Headache** **N, OR (95% CI), p**
Surgery (ref. level=no)	402, .80 (.5-1.25), .331	355, 1.22 (.77-1.91), .386	400, .766 (.5-1.16), .217
Sex (ref. level =male)	406, .93 (.32-2.71), .901	359, 1.7 (.46-6.3), .425	404, 1.1 (.40-2.99), .852
Age at diagnosis (per years)	405, .98 (.95-.99), .047*	358, .98 (.95-1.001), .063*	403, 1.0 (.98-1.02), .813
Weight change (per lb)	385, .99 (.98-.997), .003*	340, .997 (.99-1.00), .367	382, .99 (.98-.999), .023*
Percent Weight change (per 1% body weight change)	385, .98 (.97-.99), .003*	340, .99 (.98-1.00), .168*	382, .99 (.97-.998), .028*
BMI change (per kg/m^2)	381, .95 (.92-.99), .004*	338, .98 (.95-1.01), .367	376, .97 (.94-.99), .030*
BMI at diagnosis (per kg/m^2)	383, 1.02 (.99-1.05), .205	340, .97 (.94-1.00), .058*	378, .997 (.97-1.02), .854

*=p-value less than .20

Multivariate Logistic Regression:

Model for Tinnitus:

In the univariate models with tinnitus as the outcome variable, three variables were significant ($p<.20$); age at diagnosis, percent weight change and BMI at diagnosis. They were included in the multivariable logistic regression model. A full model with age at diagnosis, percent weight change and BMI at diagnosis produced the following values.

Table 4: Multivariable Model with Tinnitus as the Outcome Variable (N=337)

Variable	p-value	Odds ratio (95% CI)
Age at diagnosis	.205	.98 (.96-1.00)
Percent weight change	.020	.98 (.97-.997)
BMI at diagnosis	.012	.96 (.93-.99)

The subjects in this first analysis were included in subsequent models, with no subjects added or taken out.

Model for Vision:

The multivariable model for vision included age at diagnosis and percent weight change due to their statistical significance in univariate regression.

Table 5: Multivariable Model with Vision as the Outcome Variable (N=331)

Variable	p-value	Odds ratio
Age at diagnosis	.098	.98 (.95-1.00)
Percent weight change	.002	.97 (.96-99)

Model for Headache:

For the model with headache as the outcome variable, absolute weight change, percent weight change and BMI change were all significant in univariate regression. These were not included in a multivariate regression model together since they are similar variables.

Table 6: Univariate logistic regression results showing crude association (OR) between individual predictor variables (rows) and each of three separate outcomes--vision, tinnitus, and headache (columns) including only patients who lost weight (N=254)

Predictor	**Vision** **N, OR (95% CI), p**	**Tinnitus** **N, OR (95% CI), p**	**Headache** **N, OR (95% CI), p**
Surgery (ref. level=no)	240, .62 (.34-1.11), .111*	215, .74 (.40-1.37), .342	238, .58 (.33-1.02), .058*
Sex (ref. level =male)	243, .78 (.18-3.36), .740	218, 3.11 (.37-26.3), .298	241, 4.09 (.49-33.85), .191*
Age at diagnosis (per years)	243, .97 (.94-.99), .034*	218, .98 (.95-1.01), .227	241, 1.01 (.99-1.04), .359
Weight change (per lb)	243, .99 (.98-1.001), .107*	218, .99 (.99-1.00), .803	241, .99 (.99-1.001), .126*
Percent Weight change (per 1% body weight change)	243, .98 (.96-1.006), .167*	218, .99 (.97-1.02), .491	241, .99 (.96-1.007), .192*
BMI change (per kg/m^2)	242, .96 (.92-1.007), .102*	218, .99 (.95-1.04), .801	240, .97 (.92-1.009), .127*
BMI at diagnosis (per kg/m^2)	242, 1.01 (.98-1.05), .427	218, .97 (.93-1.00), .079*	240, .1.00 (.97-1.04), .763

*=p-value less than .20

Multivariable Logistic Regression:

Model for Tinnitus:

In univariate logistic regression analysis, BMI at diagnosis was the only variable that was significant at the $p<.20$ level.

Model for Vision:

Table 7: Multivariable Model with Vision as the Outcome Variable (N=240)

Variable	p-value	Odds Ratio (95% CI)
Surgery	.032	.49 (.26-.94)
Age at diagnosis	.021	.96 (.93-.99)
Weight change (per lb)	.066	.99 (.99-1.00)

Model for Headache:

Table 8: Multivariable Model with Vision as the Outcome Variable (N=238)

Variable	p-value	Odds Ratio (95% CI)
Surgery	.018	.48 (.26-.89)
Sex	.281	3.25 (.38-27.71)
Weight change (per lb)	.032	.99 (.98-.999)

Aim #3:

I performed t-tests comparing absolute weight loss in patients who had lost weight with and without bariatric surgery. Patients who had bariatric surgery had a mean weight loss of 91.5 lbs (N=25) twelve months after bariatric surgery, while non-bariatric surgery patients had a mean weight loss of 28.1 lbs (N=229). Of patients who lost weight, bariatric surgery patients lost significantly more weight than non-bariatric surgery patients ($p<.001$).

Similarly, bariatric surgery patients lost a significantly higher percentage of their body weight than non-bariatric surgery patients ($p<.001$). The mean percent weight loss for patients who had bariatric surgery was 31.3% (N=25), while the mean percent weight loss for non-bariatric surgery patients was 11.4% (N=229).

Patients who had bariatric surgery had measurements taken at the time of surgery and at one-year follow-up. Non-bariatric surgery patients had measurements taken at diagnosis and at enrollment. I am therefore comparing two slightly different variables,

but the aim was to ensure that I had an adequate follow-up period for those who had bariatric surgery.

However, chi-square tests for vision in patients with and without bariatric surgery (who had lost weight) found no statistically significant difference in improvement of vision symptoms between bariatric and non-bariatric surgery patients (p=.772).

In addition, chi-square tests for headache in patients who had lost weight with and without bariatric surgery found no statistically significant difference in improvement of headache symptoms between patients with and without bariatric surgery (p=.191).

When chi-square tests were conducted for tinnitus symptoms comparing patients with and without bariatric surgery, there was no significant difference in tinnitus symptoms between these groups (p=.880).

Improvement in headache, vision and tinnitus symptoms were similar for patients who lost weight with and without bariatric surgery.

Aim #4:

Patients who lost weight were divided into three groups—patients who had a weight loss of less than 6%, patients who lost between 6-20% of their weight, and patients who lost more than 20% of their weight.

Table 9 displays results for the percentage of patients who experienced improvement in headache, vision and tinnitus with percent weight loss less than 6%, 6-20% and greater than 20%. Patients who lost more than 20% of their starting body weight experienced an improvement in headache 45% of the time, an improvement in vision 43% of the time and an improvement in tinnitus 40% of the time. However,

patients who lost between 6-20% had only a 30% likelihood of improving headache, 31% likelihood of improving vision and 33% likelihood of improving tinnitus symptoms.

Table 9: Percentage of IIH Patients Experiencing Symptom Improvement for Weight Loss Categories of less than 6%, 6-20% and greater than 20%

Percent weight lost	Headache Improvement	Vision Improvement	Tinnitus Improvement
Less than 6%	27/66 (41%)	18/69 (26%)	19/63 (30%)
6-20%	38/126 (30%)	39/125 (31%)	38/115 (33%)
>20%	22/49 (45%)	21/49 (43%)	16/40 (40%)

Chi-square tests revealed that there was not a significant difference in outcomes among these three groups in terms of self-reported headache (p=.120), vision (p=.150) or tinnitus (p=.581) improvement.

CHAPTER 4: DISCUSSION

The aim of this study was to determine whether weight loss predicted improvement in vision, headache and tinnitus symptoms among a sample of patients with IIH. I hypothesized that among overweight IIH patients, absolute weight loss, percent weight loss and body mass index loss would predict improvement in IIH symptoms. Patient weight loss was predictive of improvement in vision, headache and tinnitus symptoms. Age at diagnosis was also significantly predictive of improvement in vision and tinnitus symptoms but was not predictive of improvement in headache symptoms. Patients diagnosed at older ages were less likely to experience improvement of vision and tinnitus. Losing weight is an effective way to treat symptoms of vision, tinnitus and headache in patients with IIH.

I also analyzed the percentage of patients experiencing symptom improvement in each of three weight loss categories (less than 6% weight loss, 6-20% weight loss, and greater than 20% weight loss). Patients in these groups did not experience a significantly different likelihood of symptom improvement in spite of the differences in weight loss. In addition, although some patients who experienced weight loss were successful in improving their symptoms, many were not. This result may be explained in part by patients who at baseline did not have severe symptoms and reported at follow-up that their symptoms were "about the same." This result would have been classified as a non-improvement, when in fact the patient would be doing well. Patients are in an variety of

different states at diagnosis, with some in severe pain and some in little pain, and this is something that could be studied in more depth in future research by the IH Registry.

The logistic regression models measured differences in symptom improvement based on gradual weight change (change per lb, per percent lost, etc), while the chi-square tests comparing the weight groups <6% weight loss, 6-20% weight loss and >20% weight loss examined broad differences between groups of patients. The chi-square tests were looking for a difference in any of the three groups regardless of the order. For example, if the >20% had significantly greater symptom improvement than the 6-20% group, but the <6% weight loss group had the most symptom improvement, the chi-square test would show a significant difference, but would not provide more information on whether there was a trend of symptom improvement for increasing weight loss. The chi-square test and the logistic regression models are different types of comparisons. Therefore, although the logistic regression models suggest that weight loss is associated with symptom reduction, the chi-square models were not significant. In addition, sample size could be a factor, since the chi-square tests included fewer subjects (N=254) while the logistic regression models included all subjects including those who had not lost weight (N=431).

The results from the logistic regression models suggest that weight loss is an effective tool for patients to improve their IIH symptoms. Surprisingly, some patients may lose 20% of their body weight or more and may not experience symptom improvement. While there may be a significant difference in outcomes between patients who gain weight (and were included in the logistic regression model) and patients "on average" who lose weight, there are many instances in which patients achieve a

significant weight loss but do not improve their symptoms. Thus, weight loss may be a reasonable goal for patients (and better than gaining weight), but weight loss alone (even in significant amounts) does not guarantee symptom reduction.

Patients who had bariatric surgery were no more likely to experience an improvement in headache, vision or tinnitus symptoms than non-bariatric surgery patients who also lost weight. Patients who had bariatric surgery had no greater improvement in symptoms than those who did not have bariatric surgery in spite of a significantly greater weight loss in those who had bariatric surgery compared to those who did not.

The results of this study are somewhat similar to previous studies in that the results indicate that weight loss is associated with alleviation of some symptoms of IIH. It is also noteworthy that age at diagnosis was significant in the models for vision and tinnitus. Future researchers may want to further explore the relationship between a patient's age at diagnosis and whether symptoms resolve. The mean age was impacted by the inclusion of patients aged 11-18, not typically included in studies. This is a gateway for future research into the role of obesity in the teenage population. However, this study does not support the finding that losing 6% or more of initial body weight is highly successful in reducing symptoms of IIH. Even among patients who lost 20% or more of their body weight, many did not experience a reduction in symptoms.

Strengths and Limitations:

Patient recall bias could be a factor in this study. Patients were asked whether, compared to the time of diagnosis, symptoms were "much worse", "somewhat worse", "about the same", "somewhat better" or "much better" at a subsequent time. Researchers

used a patient reported non-objective measurement to determine patient symptoms. This measure may not be as accurate as using physician reported results, and this is something that could be examined in future research. Bias in this case would likely be random, and would bias the results toward the null.

Patients who had bariatric surgery were followed for a shorter time (one year) than many patients who did not have bariatric surgery. Patients who had a longer follow-up period may be less likely to remember the degree of improvement (or deterioration) that they experienced with their IIH symptoms. However, it is not obvious that faulty memory would bias patients to feel they had more or less improvement in symptoms. Thus, although recall bias may be a factor in this study, it would most likely bias the findings towards the null.

One potential bias of registry data is that patients who enroll in registries may tend to be more affected by symptoms than those who do not. It is possible patients who enroll in registries are motivated to find solutions for their disorder whereas patients who have done well with medical management of signs and symptoms may be less likely to enroll since they are faring well. This study used registry data and therefore likely shows a more affected and less well-managed patient sample than would be the case if a broader range of patients (those in remission, those with managed symptoms) were included in the study.

A key strength of this study was the ability to utilize the largest database of patients with idiopathic intracranial hypertension in the world. All patient records are carefully abstracted and are reviewed by a physician at the Registry. This sample was large compared to the IIH patient samples available to many researchers. In addition, this

study compared results in patients with a 0-<6% weight loss, a 6-20% weight loss and a greater than 20% weight loss. Therefore, it was valuable that this study had a large enough sample size that it was possible to compare these groups of patients.

Future Studies:

Further research is needed to confirm the similarity of bariatric and non-bariatric surgery patients with respect to symptom improvement. In addition, future research into predictors of improvement in tinnitus symptoms could be useful. Determining whether there are other changes in diet or practices that could result in improvement in tinnitus would enable IIH patients to make appropriate changes.

In addition, future research could examine whether there are differences in the effectiveness of weight loss between different age groups. This study suggested that there may be a relationship between age at diagnosis and the likelihood of symptom improvement. Researchers could divide subjects into groups based on their age at diagnosis and study whether subjects in each weight group who are able to lose weight have the same ability to improve their symptoms.

In this study, I compared patients with and without bariatric surgery, and found that they had no significant difference in improvement of vision, headache and tinnitus symptoms. Patients who had bariatric surgery tended to have a higher initial weight than patients who did not have bariatric surgery. However, both bariatric and non-bariatric surgery patients had similar mean follow-up weights (206.7 lbs for bariatric surgery patients and 199.2 lbs for non-bariatric surgery patients). T-tests showed that these mean weights at follow-up were statistically significantly different; however, there is likely a

substantial amount of overlap in the distribution curves of follow-up weight for bariatric and non-bariatric surgery patients. Future research could evaluate whether patients who were at the lower end of the distribution curve (lost more weight) are more likely to experience improvement of symptoms than patients who are at the higher end of the distribution curve (lost comparatively less weight). Researchers could determine whether there is a threshold weight at which symptoms are more likely to improve.

CHAPTER 5: CONCLUSIONS

IIH patient weight loss was associated with improvement in vision, tinnitus and headache symptoms. Bariatric surgery patients had a significantly greater weight loss than non-bariatric surgery patients, but there was no greater improvement in symptoms among bariatric surgery patients compared to non-bariatric surgery patients. Overweight IIH patients should continue to be advised to lose weight in order to treat their symptoms, but should be aware that although "on average" weight loss is a good idea (see logistic regression models), for many individuals weight loss will be ineffective even at levels greater than 20%.

References:

1. Amaral, J.F. Tsiaris, W. Morgan, T. & Thompson W. R. (1987). Reversal of benign intracranial hypertension by surgically induced weight loss. Archives of surgery, 122, 946-949.

2. Baldwin, M.K., Lobb, B., Tanne, E. Egan, R. (2010). Weight and visual field deficits in women with idiopathic intracranial hypertension. Journal of Women's Health, 19(10), 1893-8.

3. Bouldin MJ, Ross LA, Sumrall CD, Loustalot FV, Low AK, Land KK (2006). The effect of obesity surgery on obesity comorbidity. American Journal of the Medical Sciences, 331(4), 183-93.

4. Bruce B.B., Blousse V &Newman NJ. (2011) Update on idiopathic intracranial hypertension. American Journal of Ophthalmology, 152,163-169.

5. Corbett JJ, Thompson HS. (1989). The rational management of idiopathic intracranial hypertension. Archives of Neurology, 46(10), 1049-51.

6. Fridley J. Foroozan, R. Sherman, V., Brandt M & Yosher, D. (2011). Bariatric surgery for the treatment of idiopathic intracranial hypertension. Journal of Neurosurgery, 114, 34-39.

7. Friesner, D., Rosenman, R., Lobb, BM, & Tanne, E. (2011). Idiopathic intracranial hypertension in the USA: the role of obesity in establishing prevalence and healthcare costs. Obesity Reviews, 12(5), e372-e380.

8. Glueck, C.J., Golnik, K.C., Aregawi, D, Goldenberg, N., Sieve, L. Wang, P. (2006). Changes in weight, papilledema, headache, visual field and life status in response to diet and metformin in women with idiopathic intracranial hypertension with and without concurrent polycystic ovary syndrome or hyperinsulinemia. Translational Research, 215-222.

9. Johnson, L.N., Krohel, G.B. Madsen, R.W. March, G.A.. (1998) The Role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). Ophthamology, 105, 2313-2317.

10. Kupersmith M.J. Gamell, L, Turbin, R. Peck, V. Spiegel, P. Wall, M. (1998). Effects of weight loss on the course of idiopathic intracranial hypertension in women. American Academy of Neurology, 1094-1098.

11. Michaelides EM, Sismanis A, Sugerman HJ, Felton WL 3rd. (2000) Pulsatile tinnitus in patients with morbid obesity: the effectiveness of weight reduction surgery.

12. Nadkarni, T., Rekate, H, & Wallace, D. (2004). Resolution of pseudotumor cerebri after bariatric surgery for related obesity. Journal of Neurosurgery, 101, 878-880

13. Radhakrishnan, K, Ahlskog, E, Cross, S.A., Kurland, L.T. & O'Fallon, M. (1993) Idiopathic Intracranial Hypertension (Pseudotumor Cerebri): Descriptive Epidemiology in Rochester, Minn, 1976 to 1990. Arch Neurol, 50(1), 78-80.

14. Sinclair AJ, Burdon MA, Nightingale PG, Ball AK, Good P, Matthews TD, Jacks A, Lawden M, Clarke CE, Stewart PM, Walker EA, Tomlinson JW, Rauz S. (2010). Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ, 341, 2701.

15. Skau M., Sander B, Milea D., Jensen R (2011) Disease activity in idiopathic intracranial hypertension: a 3 month follow-up study. Journal of Neurology, 258(2), 277-83.

16. Sugerman, H.J. Demaria E. J. Felton W. L. Nakatsuka, M & Sismanis, A (1997) Increased intra-abdominal pressure and cardiac filling pressures in obesity associated pseudotumor cerebri. Neurology, 49, 507-511.

17. Sugerman, H.J., Felton, W. L. Salvant, J.B. Sismanis, A, & Kellum J.M, (1995) Effects of surgically induced weight loss on idiopathic intracranial hypertension in morbid obesity. Neurology, 45, 1655-1659.

18. Sugerman H.J. Felton W.L. Sismanis A. Kellum J. M. DeMaria E.J. & Sugerman E.L. (1999). Gastric surgery for pseudotumor cerebri associated with severe obesity. Annals of Surgery, 5, 634-642.