New-Onset Orthostatic Intolerance Following Bariatric Surgery

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Background: *As bariatric surgery has become an increasingly popular treatment for obesity, we have seen an increasing number of patients present after bariatric surgery with new-onset syncope, near-syncope, and lightheadedness.*

Methods: *We retrospectively reviewed patients who had had bariatric surgery referred to our institution for evaluation of orthostatic intolerance. We reviewed history, physical examination, type of bariatric surgery procedure, and tilt table test results in these patients. There were 14 women and one man with mean age 42 ± 6 years, preoperative body mass index was 49.3 ± 6.0 kg/m², and mean postoperative weight loss was 55.9 kg. Mean onset of symptoms was 5.2 ± 3.9 months after surgery. Presenting symptoms were lightheadedness in 15 (100%), near-syncope in 11 (73%), and syncope in nine (60%). All but one patient had a positive tilt table test with eight (53%) having a neurocardiogenic response, three (20%) having a dysautonomic response, and (20%) having a postural tachycardia response. The likely mechanism of orthostatic intolerance is autonomic insufficiency in combination with reverse course of obesity-related hypertension. The majority of the patients (12 out of 15) responded to standard therapy for autonomic insufficiency.*

Conclusion: *Some patients may develop significant orthostatic intolerance due to autonomic insufficiency following bariatric surgery, and awareness of the potential association between bariatric surgery and new orthostatic intolerance is important for providing timely care. (PACE 2008; 31:884–888)*

autonomics, orthostatic intolerance, syncope, bariatric surgery

Introduction

Over the last several decades, the prevalence of obesity in the United States has reached epidemic proportions. Currently, more than 30.5% of the U.S. population are obese (body mass index [BMI] ≥30 kg/m²) and 4.9% are morbidly obsess (BMI ≥40 kg/m²).[1] Obesity is associated with an increased risk of developing significant health disorders, including type 2 diabetes mellitus, hypertension, dyslipidemia, obstructive sleep apnea, and neoplasia. In addition, obesity is the second most common cause of death from a modifiable behavioral risk factor, accounting for 111,909 excess deaths annually.[2]

It is not surprising then that there has been an dramatic growth in bariatric surgery[3] brought about to a great extent by the disappointing results of both conservative weight management programs, for example, those using moderate calorie reduction combined with increased physical activity,[4–6] very low calorie diets (400–800 calories per day),[7] or pharmacotherapies[8] (e.g., sibutramine, or listat) in conjunction with the favorable public perception of minimally invasive surgical techniques. Commonly performed procedures include Roux-en-Y gastric bypass (RYGBP), biliopancreatic diversion with duodenal switch, and adjustable silastic gastric banding. Though interest in the vertical banded gastroplasty (VBG), popular in the 1980s and early 1990s, has been waning, relatively large numbers of these patients remain within the U.S. population.

However, as weight loss surgery has become more popular, the reported incidence of neurologic-related complications has increased, most notable those involving the somatic nervous system.[9] Up to this point severe orthostatic intolerance due to a disruption in the autonomic nervous system have only rarely been reported following bariatric surgery. In this article, we present a series of 15 patients who developed new-onset symptoms of severe orthostatic intolerance following bariatric surgery.

Method

A retrospective nonrandomized analysis was preformed on 15 patients referred to our clinic for orthostatic intolerance (OI) after bariatric surgery

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from September 1997 to December 2006. The study was approved by the institutional review board. OI refers to a heterogeneous group of disorders of hemodynamic regulation characterized by insufficient cerebral perfusion resulting in symptoms during upright posture relieved by recumbency. Symptoms included syncope, near syncope fatigue, palpitations, exercise intolerance, lightheadedness, diminished concentration, and headache.[10] Collected data included demographic information, preoperative comorbidities, preoperative and postoperative weight, height, presenting symptoms, laboratory data, tilt-table response, and treatment outcomes. The protocol used for tilt table testing has been described elsewhere, but basically consisted of a 70-degree baseline upright tilt for a period of 30 minutes, during which time heart rate and blood pressure were monitored continually.[11] If symptomatic hypotension and bradycardia occurred, reproducing the patient's symptoms, the test was ended. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoproterenol started with a dose sufficient to raise the heart rate to 20–25% above the resting value. Upright tilt was then repeated for a period of 15 minutes. These data were categorized into three groups based on the positive tilt-table pattern: neurocardiogenic, dysautonomic, and postural orthostatic tachycardia syndrome (POTS).[10–12]

The treatment protocols employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere.[12–14] Briefly, a sequence of therapies was employed that included physical counter maneuvers as well as increased dietary fluids and sodium. If these were ineffective, pharmacotherapy was initiated in a sequence generally consisting of fludrocortisone, midodrine, methylphenidate, selective serotonin reuptake inhibitors, pyridostigmine, and erythropoietin either alone or in combination. The rational for this sequence and the doses employed are described in detail elsewhere. A treatment was considered successful if it provided symptomatic relief.

Results

The mean age of the group was 43 ± 7 years and 93% were women (patient 9 was male). The mean preoperative BMI was 49.3 ± 6.0 kg/m^2 (see Table I). The mean weight loss was 55.9 ± 16.3 kg and there was a mean change in the BMI of 40.6 ± 9.4%. The mean number of comorbidities was 2.3 ± 2.9. Preoperative comorbidities included hypertension in four (27%), obstructive sleep apnea in three (20%), and endocrine thyroid disease in two (13%). No patients had type 2 diabetes mellitus. Mean onset of symptoms was 5.2 ± 3.49 months after surgery. Presenting symptoms were lightheadedness in 15 (100%), near syncope in 11 (73%), syncope in nine (60%), and exercise intolerance in 15 (100%). Other patient complaints were palpitations in three (20%), cognitive impairment and diminished concentration in four (26%), and orthostatic headaches in two (13%). No patient had any symptoms of OI prior to bariatric surgery, nor did any display any degree of orthostatic hypotension prior to surgery.

Every patient underwent extensive laboratory testing that included a complete blood count; serum electrolytes; calcium; phosphorus; BUN; creatinine; glucose; cortisol; liver function studies; lipid profile; thyroid function; and blood levels of folic acid, iron, and vitamins D and B_{12}. All values were within normal limits in all patients. Twelve of the patients had undergone magnetic resonance imaging of the brain prior to referral, all of which were normal. All 15 patients had undergone echocardiographic and Doppler examinations, 13 of which were normal and two of which showed mild left-ventricular hypertrophy. Nerve conduction studies were preformed in five patients, all of which were normal. Three patients had undergone standard dual chamber pacemaker implantations prior to referral with little or no change in their symptoms. Twelve patients had been evaluated by a neurologist prior to referral and nine had been evaluated by an endocrinologist, and five by an ear, nose, and throat specialist.

All patients had head-up tilt table testing (TTT) and 14 (93%) had a positive tilt table study that reproduced their clinical symptoms. Among those having an abnormal tilt table pattern, eight (53%) had a neurocardiogenic response, three (20%) had a dysautonomic response, and three (20%) had a postural orthostatic tachycardic response. The majority of the patients (12–15) responded to a combination of therapies (midodrine, methylphenidate) directed at correcting their OI. Of the remaining patients, two were disabled by their symptoms and one patient was still having severe symptoms despite multiple medication trials. There did not seem to be a correlation between the change in BMI and the occurrence of OI. The mean follow-up period has been 18 ± 7 months.

Discussion

Bariatric surgery is becoming an increasingly popular treatment for morbid obesity. While the surgery is generally felt to have a low incidence of complications (principally perioperative), a number of long-term complications (principally neurologic) have been observed. Recent studies have reported that between 5% and 10% of patients undergoing[9,15–17] bariatric surgery may develop

Table I.

Patient Characteristics Categorized by Tilt Table Test Pattern

Patient	Age (yrs)	Procedure	Change in BMI %	Time to symptom onset (months)	Presenting Symptoms*			
					Fatigue	Palpitations	Near Syncope	Syncope
Neurocardiogenic syncope								
1	44	RYGBP	40.5	1	−	+	−	+
2	38	VBG	34.4	3	−	−	−	+
3	35	RYGBP	48.7	2	−	+	+	−
4	33	RYGBP	38.5	4	−	+	+	+
5	46	RYGBP	45.8	1	−	+	−	+
6	48	RYGBP	39.3	7	+	−	+	+
7	35	RYGBP	36.4	1	−	−	+	+
8	41	VBG	59.2	9	−	−	+	+
Postural Orthostatic Tachycardia Syndrome								
9	41	RYGBP	26.2	8	+	+	+	−
10	45	RYGBP	51.7	3	−	+	+	−
11	45	RYGBP	35.9	6	+	−	+	+
Dysautonomia								
12	36	RYGBP	33.0	10	−	−	+	−
13	56	RYGBP	47.5	5	+	−	+	−
14	52	RYGBP	46.5	12	−	+	+	+
Normal Tilt Response								
15	42	RYGBP	25.3	6	−	−	+	−

*All patients had exercise intolerance.
BMI=body mass index; RYGBP=Roux-en-Y gastric bypass; VBG=vertical banded gastroplasty.

significant complications of the somatic nervous system. These reported complications have involved almost all parts of the neuraxis including the brain, cerebellum, spinal cord, as well as the peripheral nerves.[9]

We report on 15 patients who developed autonomic nervous system involvement as a consequence of bariatric surgery that resulted in highly symptomatic orthostatic intolerance. No patient in these series had any personal or family history or symptoms of OI prior to surgery nor did any patient have any history of hypotension. In each patient, the only causative factor for their OI that could be identified was their weight loss surgery. The internal between bariatric surgery and onset of symptoms in our study was 5.2 ± 3.49 months, roughly similar to the time intervals between surgery and neurological symptoms that have been reported previously in the literature (8.4 ± 4.2 months).[15–17] The magnitude of weight loss, a change in BMI of 40 ± 9.4%, was also similar to that reported in patients who developed somatic disorders after weight loss surgery.

Orthostatic intolerance refers to a heterogeneous group of disorders of hemodynamic regulation characterized by insufficient cerebral perfusion resulting in symptoms upon standing and relieved by becoming spine. Symptoms may include syncope, near syncope, lightheadedness, exercise intolerance, palpations, cognitive impairment, headache, and fatigue. OI reflects an inability of the autonomic nervous system to adequately respond to the orthostatic stress of gravity. The autonomic disorders resulting in orthostatic intolerance can be divided into these broad groups: Reflex syncope, postural tachycardia syndrome, and autonomic failure. The details of these conditions and their diagnosis are reviewed in detail elsewhere.[10–12]

Neurological complications of the somatic nervous system are not uncommon following bariatric surgery with a reported incidence of between 5% and 10%. Abarbanel et al. reported on 23 patients who developed severe somatic nervous system problems after bariatric surgery, including severe polyneuropthy, myotonic syndrome,

and Wernicke-Korsakoff encephalopathy.[16] Other investigators have described Wernicke's encephalopathy and a Guillian-Barre-like syndrome in seven of 110 patients who underwent bariatric surgery.[15] Recently, Juhasz-Pocsine reported on 26 patients who developed major neurological conditions that occurred after bariatric surgery.[17] These included encephalopathy, myelopathy, polyradicoloneuropathy, and polyneuropathy. While many of these patients suffered from a variety of nutritional deficiencies (such as B_{12}, thiamine, and copper), many investigators have found it difficult to correlate specific nutritional deficiencies with the neurological complications observed. In addition, correction of the nutritional deficiencies encountered after bariatric surgery often did not yield dramatic therapeutic results. No patient in our study had any significant measured nutritional deficiency.

While the etiology of OI following bariatric surgery is unknown, proposed mechanisms include weight loss-related reduction of baseline blood pressure and alteration of autonomic responsiveness. The persistent reductions in blood pressure produced by weight loss may be sufficient to explain this phenomenon. Support for this contention is provided by Hoeldtke et al. who described five patients with new-onset OI following either rapid weight loss (three patients) or a viral illness (two patients).[18] Four patients (80%) demonstrated normal sympathetic responses to physical stimulation; specifically tachycardia in response to standing and Valsalva maneuver. These same patients had normal norepinephrine production in response to postural stress. One patient in this series developed OI following bariatric surgery and despite aggressive medical intervention her symptoms remained so severe that she was unable to sit.

Support for an altered autonomic responsiveness etiology is found in a case report by Rubinshtein et al. of new-onset orthostatic hypotension (OH) following VBG.[19] The patient's BMI decreased from 44 kg/m^2 to 22 kg/m^2 within 8 months following surgery and she soon after began experiencing OI. A detailed clinical and laboratory evaluation was preformed, including serum electrolyte levels, renal and liver function test, thyroid function tests, plasma rennin and aldosterone levels, complete blood cell count, viral serologic testing, marker levels for collagen vascular diseases, catecholamine levels, serotonin metabolites, and prophyrin levels. All levels were reported as normal. The autonomic system work-up revealed normal cardiac innervations; mild abnormalities on the cold pressor test, suggesting efferent or processing abnormality of the sympathetic skin response, again suggesting an autonomic abnormality. Interestingly, the patient's symptoms resolved after an 8 kg weight regain.

These authors suggest given the clinical history and the reversibility of the symptoms after weight gain that the etiology of OH may be effects of rapid weight loss on the autonomic nervous system. Support for the contention that the autonomic nervous system is altered by weight loss is provided by an animal study showing impaired beta-cell secretory response due to alterations in autonomic nervous system activity during malnutrition.[20] Human studies of anorexia nervosa patients demonstrate an increase in parasympathetic activity that normalizes with weight gain.[21,22] Interestingly, tilt table abnormalities as documented in one study were unaffected by weight gain.[15] This observation suggests that the physiologic changes due to weight loss associated with anorexia nervosa may not be analogous to those changes due to weight loss following bariatric surgery.

The majority (14 out of 15) of the patients in our case series had abnormal head upright tilt table studies that reproduced their symptoms, suggesting that intermittent autonomic abnormalities resulting in hypotension and/or bradycardia resulted in OI. No further evaluations to assess autonomic dysfunction were pursued in this patient group. In addition to an autonomic abnormality, we also believe factors linking obesity to hypertension are reversed after bariatric surgery. The end result of rapid weight loss is decreased blood volume, stroke volume, cardiac output, and peripheral vascular resistance. In certain predisposed individuals, the combination of these complex metabolic and autonomic changes may be sufficiently great so as to result in OI. While it would be of great interest to see if symptoms resolved in our patient group with weight gain, none of our patients has gained significant weight since diagnosis. They appear to fear obesity more than OI.

Our study had a number of important limitations. The sample size was small and only reflected patients referred to us for evaluation. However, many patients may not be diagnosed and the incidence of OI following bariatric surgery may be underappreciated. Patients underwent a variety of different evaluations prior to referral. Treatments varied from patient to patient but were based on well-established regimes worked out on experience with similar patients.

An additional consideration is the role of preoperative blood pressure on the incidence of OI. The direct relationship between blood pressure and weight is well established; one study suggests that each 10 kg increase in body weight is associated with an increase in systolic blood pressure

of 3.0 mmHg and in diastolic blood pressure of 2.3 mmHg.[23] If this relationship persists during weight loss, it seems likely that patients who are normotensive preoperatively are more likely to achieve postoperative blood pressures below the threshold necessary to develop OI.

Though potentially relatively small, the true incidence of OI after bariatric surgery is unknown and the impact on those affected may be considerable. Potentially, the OI could be severe enough to result in either markedly reduced or occasionally incapacitated activity levels, situations that could contribute to recurrent weight gain. Further investigations will be necessary to determine incidence of OI following bariatric surgery and to identify those patients at greater risk for developing OI following bariatric surgery and further comprehend the underlying pathophysiology.

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