Increased Prevalence of Obesity and Obesity-Related Postoperative Complications in Male Meningioma Patients

Manish K. Aghi, M.D., Ph.D., Emad N. Eskandar, M.D., Bob S. Carter, M.D., Ph.D., William T. Curry, Jr., M.D., and Fred G. Barker, II, M.D.

Several observations suggest a hormonal influence on the growth of benign meningiomas. The female preponderance of meningioma, with a 2.2:1 female:male ratio reported during the past decade,[3,10] has been used to argue that female sex steroid hormones, such as estrogens and progesterones, may stimulate meningioma growth. The putative role of female sex steroid hormones in stimulating meningioma growth is supported by the findings that 80 to 90% of meningiomas express the progesterone receptor and 40% express the estrogen receptor,[15] with half of the receptors expressed by meningiomas shown to be functional.[18]

Clinical evidence that progesterone can stimulate meningioma growth derives from the finding that, although the incidence of meningiomas in pregnant women is comparable to that in nonpregnant women, meningiomas frequently grow during pregnancy,[9] when progesterone levels increase 100-fold. Data supporting a role for estrogens in stimulating meningioma growth comes from the finding, reported in the Nurses' Health Study, that meningioma risk rises in females with a high body mass index (BMI) category, although in a fashion that was not quite statistically significant ($P = 0.06$).[8] This suggests a role for estrogens in meningioma growth because estrogens can be synthesized by adipocytes, which express the aromatase enzyme that converts testosterone to estradiol, the main biologically active estrogen, making adipocytes the primary site of extraglandular estrogen formation in nonpregnant women.[6] Aromatase expression in the gluteal (subcutaneous abdominal) fat, which is abundant in obese individuals, is 10 times higher than in visceral (omental) fat, whose quantities vary less between obese and non-obese individuals.[21]

In men, obesity has been shown to increase serum estradiol from 20 to 30 pg/mL to 40 pg/mL.[21,25] By comparison, postmenopausal women average 5 pg/mL serum estradiol and premenopausal women range from 30 to 300 pg/mL during the menstrual cycle.[1] In addition, obesity in the cardiac surgery patient population has been shown to have significant postoperative consequences, increasing the length of hospital stay, the rate of postoperative renal failure, and the period of mechanical ventilation.[23] We, therefore, hypothesized that a disproportionate number of symptomatic men with meningiomas would be obese, and that male meningioma patients would have increased postoperative complications caused by their obesity.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the records of male patients who underwent initial craniotomy for benign meningioma at Massachusetts General Hospital between 2001 and 2005. Cases were identified and obtained from searching both a departmental computerized database and hospital computerized records. Five patients with multiple meningiomas were excluded from the analysis. From the same two databases, control cases of male patients undergoing initial craniotomy for unruptured aneurysm or high-grade glioma during the same time period were identified and matched to the male meningioma cases by year of surgery. Aneurysm cases could not be matched to meningioma cases by year of surgery because of the smaller number of aneurysm cases compared with glioma cases. Meningioma and high-grade glioma diagnoses were confirmed on histological analysis of permanent sections of surgical specimens.

BMI (weight/height^2 in kg/m^2) was calculated for each patient using the information obtained during routine preoperative patient testing, with each patient measured with the same calibrated weighing scale and ruler by a team of nurses in the preoperative clinic at Massachusetts General Hospital. Age-based male BMI percentiles for the US population were obtained from the National Institutes of Health (NIH) tables.[13] According to the NIH guidelines,[13] a BMI of 30 kg/m^2 or more was considered obese, a BMI of 25 to 29.9 was considered overweight, a BMI of 18.5 to 24.9 was considered normal, and a BMI below 18.5 was considered underweight. Records were reviewed for postoperative complications, including readmission to the hospital, deep venous thrombosis,

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pulmonary embolism, fever higher than 101.0°F reported to surgeon's office after hospital discharge, and wound infection.

Statistical Analysis

Student's *t* test was used as a parametric test to compare the differences in the body mass and BMI percentiles between male meningioma patients and the two control male patient groups (those undergoing craniotomy for unruptured aneurysm or high-grade glioma). The χ^2 test was used to compare binomial variables, the complication rates in male meningioma patients versus the two control male groups. The correlation between BMI and MIB-1 labeling index was assessed by dividing BMI into three categories (no patients in the series were underweight, therefore, the three categories were normal, overweight, and obese, as defined above) and dividing MIB-1 labeling index into tertiles, then recording each patient's category and calculating the Spearman rank correlation coefficient. *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient Populations

There were 32 male patients in each of the three groups, those undergoing initial craniotomy for benign meningioma, unruptured aneurysm, or high-grade glioma. Their demographic characteristics are summarized in *Table 38.1*. The three male neurosurgical patient groups were of comparable age, with mean ages of 50 years (meningioma), 53 years (aneurysm), and 51 years (glioma). Smoking, which has been shown to reduce BMI in males by 0.16 kg/m^2 for every 10 cigarettes smoked per day,[2] did not vary in a statistically significant fashion between the three patient groups; 47% of meningioma patients smoked, compared with 53% of aneurysm patients and 36% of glioma patients (P = 0.5).

BMI in the Three Male Craniotomy Groups

The average BMI in male meningioma patients was 30.2 kg/m^2, exceeding the 30.0 cutoff that defines obesity. This also exceeded the average BMI in male patients with unruptured aneurysms (27.5 kg/m^2; P = 0.04) and that in male patients with high-grade glioma (25.9 kg/m^2; P = 0.0007) (*Fig. 38.1A*). The obesity rate in male meningioma patients was 47%, exceeding the 19% obesity rate in aneurysm patients (P = 0.02) and the 3% obesity rate in high-grade glioma patients (P = 0.000001) (*Fig. 38.1B*). The median age-normalized BMI percentiles in male meningioma patients was the 67th percentile, exceeding that of aneurysm (49th percentile; P = 0.02) or high-grade glioma patients (52nd percentile; P = 0.008) (*Fig. 38.1C*).

Postoperative Complications in the Three Male Craniotomy Groups

Obese male meningioma patients stayed in the hospital for 8 days during the initial surgical admission, compared with 7 days for non-obese male meningioma patients, a difference that was not statistically significant (P = 0.5). Rate of readmission to the hospital within 30 days of discharge was 53% for obese male meningioma patients, 20% for non-obese male meningioma patients, and 3% for all male aneurysm and glioma patients. Readmission duration ranged from 1 to 34 days. Readmitting diagnoses included stroke, cerebrospinal fluid leak, thrombophlebitis, seizure, and fever. Obese male meningioma patients were readmitted more often than non-obese male meningioma patients (P = 0.03), and male meningioma patients as a group were readmitted more often than male aneurysm or glioma patients (P = 0.00001)

TABLE 38.1. Demographic data for men in the three patient groups: Those undergoing craniotomy for meningioma, unruptured aneurysm, and high-grade glioma[a]

	Meningioma	Aneurysm	High-grade glioma
Number of men	32	32	32
Mean age (yr)	50	53	51
Median age (yr)	49	54	53
Percentage of smokers	47%	53%	36%
Mean BMI (kg/m^2)	30.2	27.5	25.9
Median normalized BMI percentile	67th	49th	52nd
Percent underweight/normal/overweight/obese	0%/7%/47%/47%	0%/28%/53%/19%	0%/38%/59%/3%
Percentage of patients readmitted	34%	3%	3%
Percentage with postoperative fever	44%	13%	16%
Percentage with DVT or PE	19%	0%	3%
Percentage with wound infection	6%	3%	0%

[a]BMI, body mass index; DVT, deep venous thrombosis; PE, pulmonary embolism.

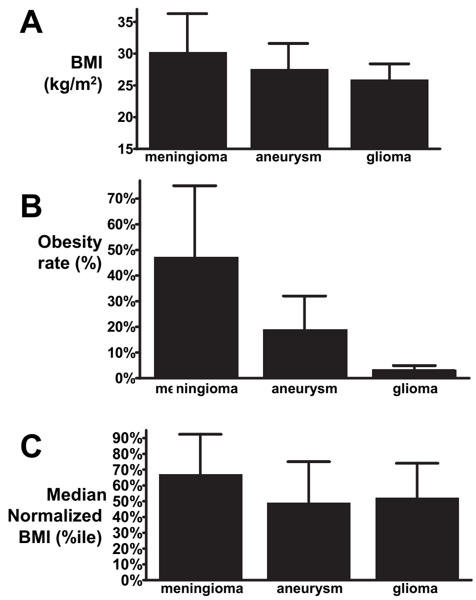

FIGURE 38.1. Male meningioma patients exhibited higher BMI (*A*), obesity rate (*B*), and median normalized BMI percentile (*C*) than male aneurysm and glioma patients. The average BMI in male meningioma patients exceeded the average BMI in men with unruptured aneurysms ($P = 0.04$) and that in men with high-grade glioma ($P = 0.0007$). The obesity rate in male meningioma patients exceeded that of aneurysm patients ($P = 0.02$) and high-grade glioma patients ($P = 0.000001$). The median age-normalized BMI percentiles in male meningioma patients exceeded that of aneurysm ($P = 0.02$) or high-grade glioma patients ($P = 0.008$). Error bars represent standard deviations (*A*, *C*) and 95% confidence intervals (*B*).

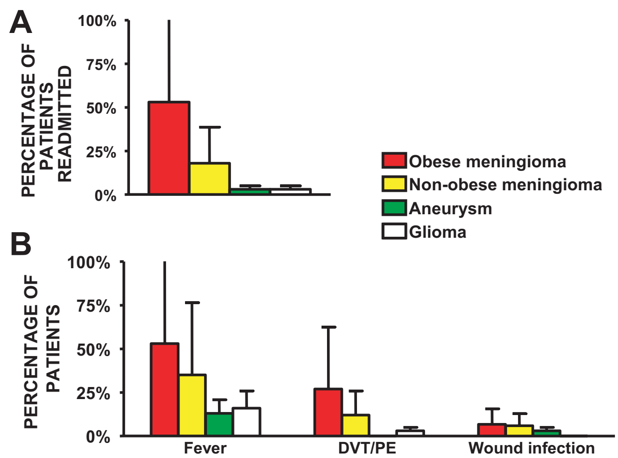

FIGURE 38.2. *A*, percentage of male patients readmitted to the hospital. *B*, percentage of patients with postoperative fever, DVT/PE, and wound infections after craniotomy in obese meningioma patients (*red*), non-obese meningioma patients (*yellow*), aneurysm patients (*green*), and glioma patients (*white*). Error bars representing 95% confidence intervals are shown.

(*Fig. 38.2A*). Postoperative deep venous thrombosis (DVT) or pulmonary embolism (PE) occurred in 27% of obese male meningioma patients, 12% of non-obese male meningioma patients, 3% of male glioma patients, and no male aneurysm patients. Obese male meningioma patients had a higher DVT/PE rate than non-obese male meningioma patients ($P = 0.2$), but the difference was not statistically significant, whereas male meningioma patients had a higher rate of DVT/PE than male aneurysm ($P = 0.002$) and glioma ($P = 0.3$) patients (*Fig. 38.2B*). Fever within 30 days of hospital discharge, which did not always lead to readmission, occurred in 53% of obese male meningioma patients, 35% of non-obese male meningioma patients, 16% of male glioma patients, and 13% of male aneurysm patients. Obese meningioma patients had higher rates of postoperative fever than non-obese male meningioma patients ($P = 0.3$), and male meningioma patients had higher postoperative fever rates than male aneurysm and glioma patients ($P = 0.1$), although neither difference was statistically significant. The incidence of postoperative wound infection was 7% in obese male meningioma patients, 6% in non-obese male meningioma patients, 3% in male aneurysm patients, and 0% in male glioma patients, differences that were not statistically significant ($P = 0.2–0.5$) (*Fig. 38.2B*).

Effect of BMI on MIB-1 Labeling Index

The labeling index of a meningioma stained with a monoclonal antibody to Ki67 (MIB-1), a nuclear protein related to cell proliferation, has been shown to predict the recurrence risk in benign meningiomas, with a labeling index above 3% correlating with higher risk of recurrence.[11,14] We investigated whether BMI correlated with meningioma recurrence risk as assessed by MIB-1 labeling index. There was a trend toward increasing MIB-1 labeling index with increasing BMI; with normal, overweight, and obese patients exhibiting MIB-1 labeling indices of 2.6%, 3.4%, and 3.9%, respectively, although the trend was not statistically significant (*Fig. 38.3*) ($P = 0.2$).

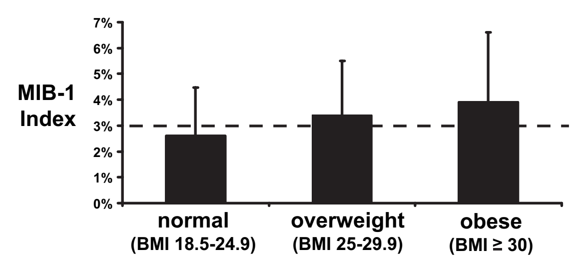

FIGURE 38.3. Mean MIB-1 labeling indices increased with increasing BMI category ($P = 0.2$), with the average in overweight and obese patients exceeding the 3% threshold (*dotted line*), above which, recurrence rate increases significantly. Error bars representing standard deviations are shown.

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CONCLUSIONS

We found a significant elevation in BMI and age-based BMI percentiles in male patients undergoing craniotomy for benign meningioma compared with those undergoing craniotomy for unruptured aneurysm or high-grade glioma. Obese male meningioma patients also exhibited a higher rate of postoperative complications than non-obese male meningioma patients. These findings are consistent with our hypothesis that male obesity increases the growth of meningiomas until they become more frequently symptomatic, by means of increasing circulating levels of estrogens in obese males.

Obesity increases the risk of several hormone-related neoplasms. In women, obesity increases the risk of breast[4] and endometrial[12] cancer, particularly the latter. Obesity also increases the risk of male breast cancer, with risk estimates ranging from 1.63 to 5.45 in obese men compared to non-obese men.[22] Obesity is strongly associated with colon cancer risk in both men and women.[16] Moreover, in men, obesity has been shown to increase the risk of high-grade prostate cancer while reducing the risk of low-grade prostate cancer.[17] The effects of obesity on prostate and colon cancer risk are likely caused by increased levels of insulin-like growth factor, which stimulates unregulated cellular growth in prostate and gastrointestinal epithelium and is found at high levels in the circulation of obese patients because of insulin resistance. The effects of obesity on breast cancer in men and women and endometrial cancer in women probably reflects hyperestrogenemia from aromatase activity in adipose tissue, making breast cancer and meningioma, as described in this report, the only two neoplasms thought to occur more commonly in obese men because of hyperestrogenemia.

Most of these studies used BMI as a measure of obesity because BMI is highly correlated with absolute fat mass ($r = 0.84-0.91$), and is a better predictor of absolute fat mass than percent body fat and regional fat distribution, as well as being considerably easier to measure than these other variables.[19] The only notable previous report of a relationship between BMI and meningioma risk was the Nurses' Health Study, in which 121,700 registered nurses were followed prospectively for 20 years. One hundred twenty-five cases of cranial and spinal meningiomas were diagnosed in the cohort during the study period. Self-reported measures of height and weight were used to derive BMI.[8] In that study, the risk of meningioma rose with increasing BMI category, with a 61% greater risk for women with a BMI greater than 25 kg/m^2 compared with those with a BMI less than 22 kg/m^2, a trend that was not quite statistically significant ($P = 0.06$) in a multivariate model.[8] Because of the low levels of endogenous estrogen in men, adipose tissue makes a larger relative contribution to the circulating estrogen levels in men than in women, causing estrogen levels to double in obese men while only causing an 11% increase in obese women.[20,21,25] Thus, it would not be surprising if the correlation between obesity and meningioma risk was stronger in men than in women, although such a comparison would require a large study that enrolled members of both sexes.

An increased prevalence of obesity in patients undergoing craniotomy for meningioma suggests an increased incidence of meningioma in obese men, but there might be other explanations for our findings. For example, obese individuals of either sex might be more likely to have cerebrovascular disease and resultant transient ischemic attacks or strokes, which would lead to more frequent magnetic resonance imaging in this population, and more frequent incidental findings of meningiomas. However, in the present series, all 32 meningiomas were found during workup of symptoms thought to be attributable to the tumor. This suggests that obesity either causes the more frequent occurrence of meningiomas, or that it causes more rapid growth to a symptomatic size, or both.

Our results must, of course, be interpreted with the usual caution that applies to retrospective studies. The ideal study to delineate the contribution of BMI to benign meningioma risk would be a prospective study documenting more-frequent diagnoses with benign meningiomas in obese males compared with non-obese males. Such a study might also help confirm the trend toward higher MIB-1 index with higher BMI category that we identified.

The two most common data sources used to report the prevalence of overweight and obesity are the Behavioral Risk Factor Surveillance Survey, a national telephone survey conducted annually by the Centers for Disease Control and Prevention, in which height and weight are self-reported,[5] and the National Health and Nutrition Examination Survey,[7] which includes objective measures of BMI. Data from both sources indicate that the prevalence of overweight and obesity is increasing in the United States, with higher prevalence when direct measures are included. The prevalence of obesity in adults has increased by approximately 50% per decade during the past 20 years, from 15% from 1976 to 1980, to 23% from 1988 to 1994, to 31% from 1999 to 2002.[24] This increase in prevalence has been seen in all regions of the nation, among all racial and ethnic groups, in both sexes, among all educational levels, and among all age groups. Given this ongoing obesity epidemic in the United States, the number of obese individuals with the neoplasms described in this report and others will likely continue to grow, as will the incidence of the postoperative complications associated with tumor resection in obese individuals described in this report. Our study suggests that research comparing postoperative complications in obese and non-obese patients undergoing a broader range of general neurosurgical procedures may also be indicated.

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