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Pathophysiology of Obesity Comorbidity: The Effects of Chronically Increased Intra-abdominal Pressure

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Severe obesity is associated with multiple comorbidities that reduce the life expectancy and markedly impair the quality of life. Morbidly obese patients can suffer from central (android) obesity or peripheral (gynoid) obesity or a combination of the two. Gynoid obesity is associated with degenerative joint disease and venous stasis in the lower extremities. Android obesity is associated with the highest risk of mortality related to problems due to the metabolic syndrome or syndrome X, as well as increased intra-abdominal pressure (IAP). The metabolic syndrome is associated with insulin resistance, hyperglycemia, and type 2 diabetes mellitus (DM), which in turn are associated with nonalcoholic liver disease (NALD), polycystic ovary syndrome, and systemic hypertension [1–7]. Increased IAP is probably responsible in part or totally for obesity hypoventilation, venous stasis disease, pseudotumor cerebri, gastroesophageal reflux disease (GERD), stress urinary incontinence, and systemic hypertension. Central obesity is also associated with increased neck circumference and sleep apnea. Other comorbidities are not specifically associated with either the metabolic syndrome or an increased IAP, such as degenerative joint or disc disease.

A previous clinical study of patients with obesity hypoventilation syndrome noted extremely high cardiac filling (pulmonary artery and pulmonary capillary wedge) pressures, as high as or higher than in patients with congestive heart failure (CHF), but most of these patients were not in heart failure. It was initially hypothesized that this could have been secondary to hypoxemic pulmonary artery vasoconstriction; however, the pressures remained elevated immediately following gastric surgery for obesity despite postoperative mechanical ventilation and correction of both hypoxemia and hypercarbia. This pressure returned to normal within 6 to 9 months after surgically induced weight loss [8]. High lumbar cerebrospinal fluid (CSF) pressures were noted in obese women with pseudotumor cerebri (also known as idiopathic intracranial hypertension). Resolution of headache and marked decreases in CSF pressures were noted when restudied 34 ± 8 months following gastric bypass (GBP) surgery (Fig. 1) [9]. The cause(s) of these phenomena remained unexplained until women with stress overflow urinary incontinence, in whom resolution of the problem occurred within months following GBP surgery, underwent measurement of urinary bladder pressures (UBPs) in the gynecologic urodynamic laboratory before and 1 year following obesity surgery [10]. These women were noted to have extremely high UBPs that normalized following surgically induced weight loss. Their pressures were as high as, or even higher than, UBPs noted in critically ill patients with an acute abdominal compartment syndrome where treatment is urgent surgical decompression [11–13]. It was hypothesized that severely obese patients with central obesity have a chronic abdominal compartment syndrome with high UBPs, as an estimate of an increased IAP, and this would be related to a number of obesity comorbidity problems [14].

Animal Studies

Several studies were performed to evaluate the effects of acutely elevated IAP in a porcine model, using either an infusion of iso-osmotic polyethylene glycol normally used for bowel cleansing (Go-Lytely®), on the cardiovascular, pulmonary, and central nervous systems. Polyethylene glycol was chosen, as it is not osmotically active nor absorbed into the central circulation in significant amounts to cause significant changes in intravascular volume. UBPs correlated well ($r = 0.98$, $p < 0.0001$) with directly measured IAP in this model. Acutely elevated IAP produced a significant increase in the pulmonary wedge pressure (Fig. 2) and hemodynamic changes characterized by decreased cardiac output, increased filling pressures, and increased systemic vascular resistance. Pulmonary effects were hypoxia, hypercarbia, increased inspiratory pressure, and elevated pleural pressure [15]. These changes were consistent with the pulmonary pathology characteristic of obesity hypoventilation syndrome.

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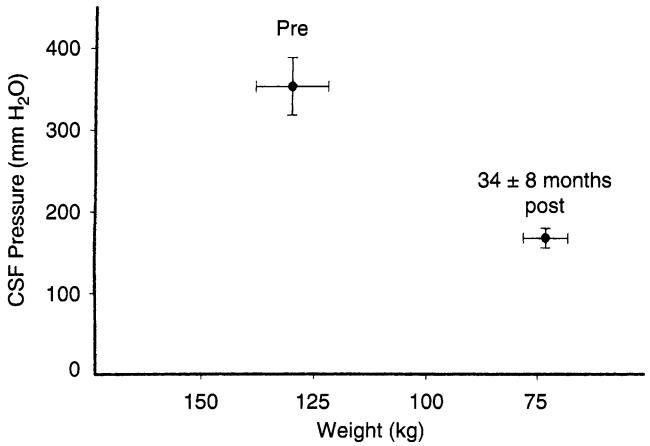

FIG. 1. Elevated cerebrospinal fluid (CSF) pressure prior to, and significant ($p<0.001$) decrease 34±8 months following, gastric surgery for severe obesity associated with pseudotumor cerebri (Sugerman et al. [9], with permission).

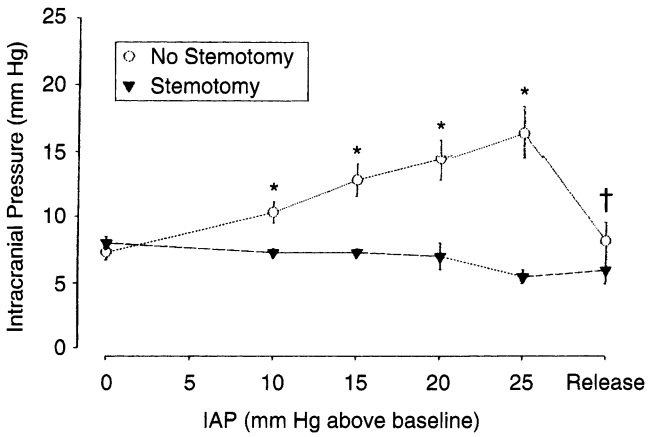

FIG. 3. Progressive increase in directly measured intracranial pressure with increasing intra-abdominal pressure associated with the intra-abdominal instillation of iso-osmotic polyethylene glycol in an acute porcine model and prevention of this increase in animals that had undergone a median sternotomy and pleuropericardiotomy (Bloomfield et al. [16], with permission).

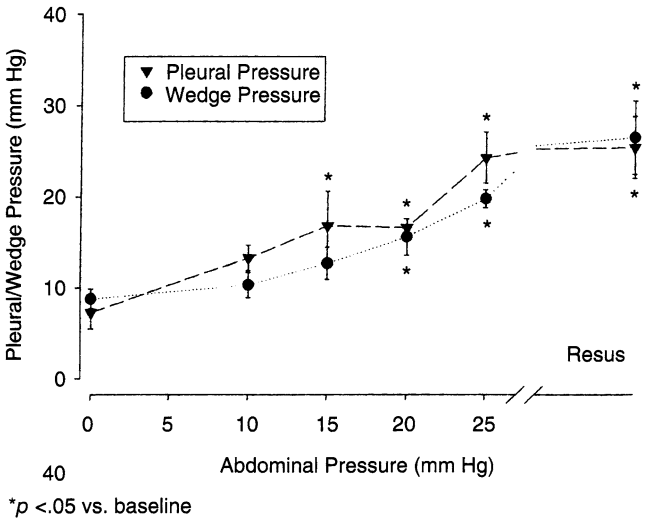

FIG. 2. Progressive increase in pleural pressure and pulmonary artery wedge (occlusion) pressure with increasing intra-abdominal pressure associated with the intra-abdominal instillation of iso-osmotic polyethylene glycol in an acute porcine model. Resus, resuscitation (Ridings et al. [15], with permission).

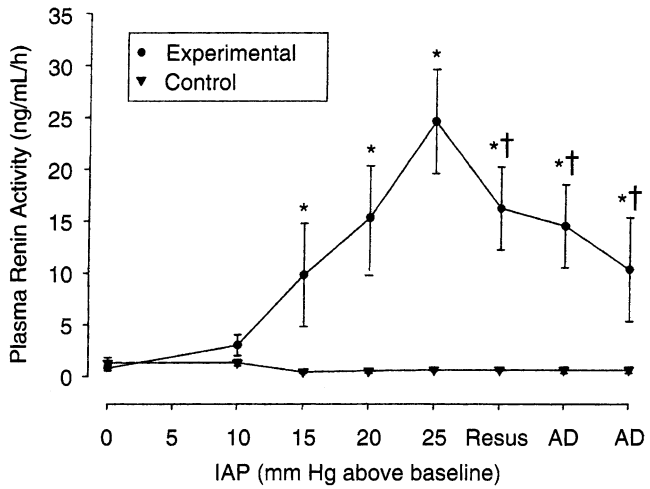

FIG. 4. Progressive increase in plasma renin activity with increasing intra-abdominal pressure (IAP) associated with the intra-abdominal instillation of iso-osmotic polyethylene glycol in an acute porcine model as compared to control animals that did not have their IAP increased; effect of volume expansion (resuscitation) and 30 and 60 min after abdominal decompression (AD). *$p<0.05$ versus baseline and control animals; †$p<0.05$ versus pre-resuscitation value (Bloomfield et al. [17], with permission).

As IAP increased, pleural pressure, central venous pressure, and intracranial pressure also increased (Fig. 3). When pleural pressure was prevented from rising by midline sternotomy and incision of the pleura and pericardium, the effects of rising IAP on the cardiovascular, pulmonary, and central nervous systems were all negated, except for the decrease in cardiac output [16]. Acute elevation of IAP caused increases (Figs. 4 and 5) in both plasma renin activity (PRA) and aldosterone levels [17].

Clinical Studies

During the course of this research, it was noted that conditions known to increase IAP such as pregnancy, laparoscopic pneumoperitoneum, and ascites are associated with pathologic consequences also encountered in the morbidly

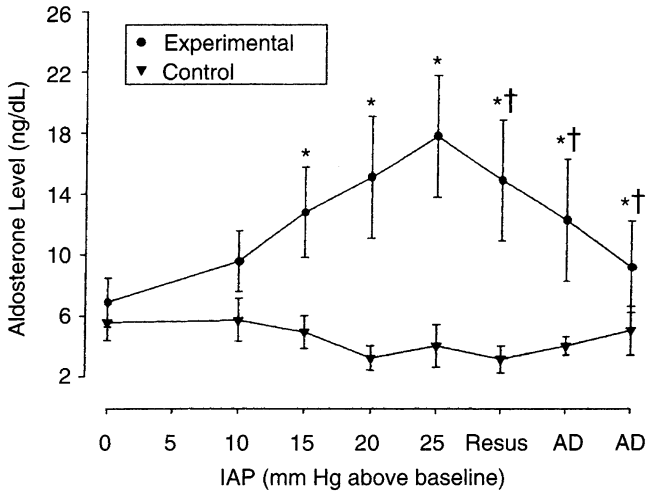

FIG. 5. Progressive increase in serum aldosterone levels with increasing IAP associated with the intra-abdominal instillation of iso-osmotic polyethylene glycol in an acute porcine model as compared to control animals that did not have their IAP increased; effect of volume expansion (resuscitation) and 30 and 60 min after abdominal decompression (AD). *$p<0.05$ versus baseline and control animals; †$p<0.05$ versus pre-resuscitation value (Bloomfield et al. [17], with permission).

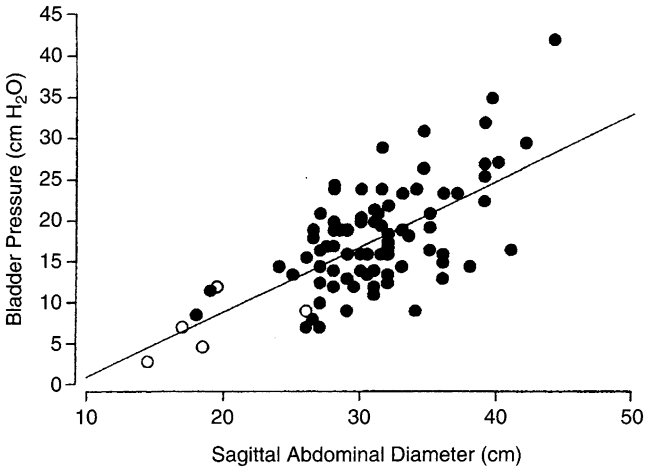

FIG. 6. Correlation between urinary bladder pressure and sagittal abdominal diameter in 84 morbidly obese patients (*filled circle*) and five control nonobese patients (0) with ulcerative colitis, $r=0.67$, $p<0.0001$) (Sugerman et al. [14], with permission).

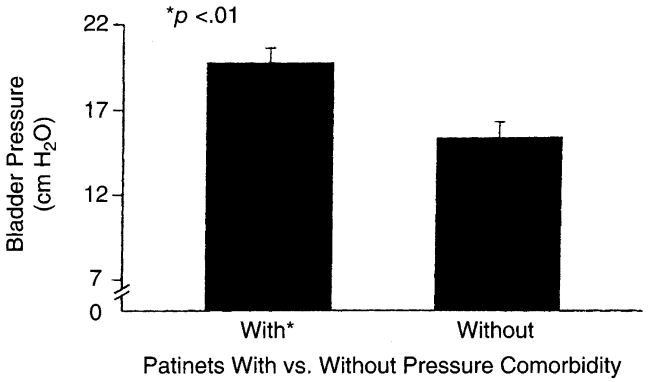

FIG. 7. Increased urinary bladder pressure in 67 patients with IAP-related morbidity and in 17 patients without IAP-related morbidity (Sugerman et al. [14], with permission).

obese, such as gastroesophageal reflux, abdominal herniation, stress overflow urinary incontinence, and lower limb venous stasis [18–20]. Furthermore, it was noted that these comorbidities significantly improved in conjunction with the marked decrease in IAP [21]. Thus, the comorbidities that are presumed to be secondary to increased IAP in obese patients include CHF, hypoventilation, venous stasis ulcers, GERD, urinary stress incontinence, incisional hernia, pseudotumor cerebri, proteinuria, and systemic hypertension [9, 10, 21–25]. In recent years, there have been a number of other confirmatory studies regarding the pulmonary and hemodynamic effects of an increased IAP [26–31]. There have also been several studies documenting the effects of a high IAP in relation to pelvic floor dysfunction [32–35], as well as studies regarding the relationship between a high IAP and GERD, pseudotumor cerebri, venous stasis disease, and systemic hypertension [36–42].

In a study of 84 patients with severe obesity prior to GBP surgery and five nonobese patients prior to colectomy for ulcerative colitis, it was found that obese patients had a significantly higher UBP (18 ± 0.7 versus 7 ± 1.6 cmH_2O, $p<0.001$) which correlated with the sagittal abdominal diameter (SAD, $r=0.67$, $p>0.001$, Fig. 6) and was greater ($p>0.05$) in patients with (compared to those without) morbidity presumed due to increased IAP (Fig. 7) [14]. The waist/hip ratio (WHR) correlated with UBP in men ($r=0.6, p>0.05$) but not in women ($r=-0.3$), supporting the concept that the SAD is a better reflection of central obesity than the WHR. In 15 patients studied before and 1 year after GBP, there were significant ($p>0.001$) decreases in weight (140 ± 8 to 87 ± 6 kg), body mass index (BMI) (52 ± 3 to 33 ± 2 kg/m^2), SAD (32 ± 1 to 20 ± 2 cm, Fig. 8), UBP (17 ± 2 to 10 ± 1 cmH_2O, Fig. 9), and obesity comorbidity with the loss of 69 ± 4 % of excess weight [15].

Discussion

The relationship of central obesity to the constellation of health problems known collectively as the metabolic syndrome appears well established [3, 7].

This has been presumed to be due to increased visceral fat metabolism. Increased UBP and its relationship to increased IAP have been used in postoperative patients as an indication for emergent re-exploration and abdominal decompression

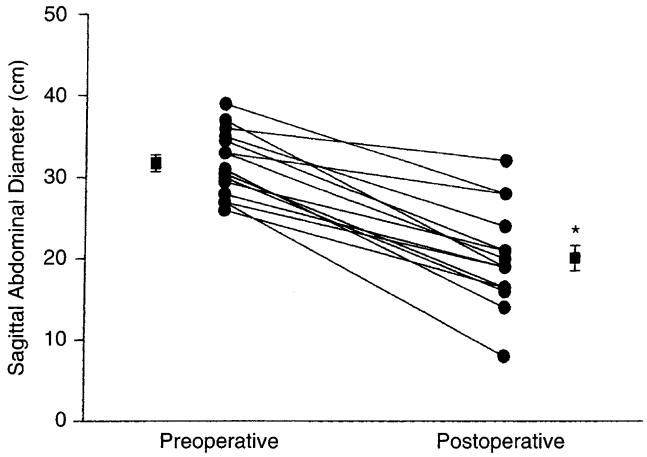

FIG. 8. Sagittal abdominal diameter before and 1 year after surgically induced weight loss. *Filled circle* = individual patient, *filled square* = mean ± standard error of the mean. *$p < 0.0001$ (Sugerman et al. [11], with permission).

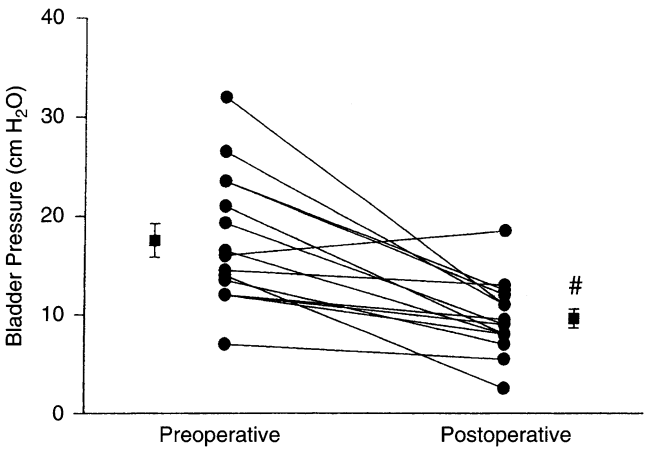

FIG. 9. Urinary bladder pressure before and 1 year after surgically induced weight loss. *Filled circle* = individual patient, *filled square* = mean ± standard error of the mean. *$p < 0.0001$ (Sugerman et al. [11], with permission).

for an acute abdominal compartment syndrome to correct oliguria and increased peak inspiratory pressures with mechanical ventilation [11–13]. The decision to perform emergency abdominal decompression is usually taken when the UBP is ≥25 cmH_2O. In the study of obese patients prior to GBP surgery, 11 patients had UBPs ≥25, four ≥30, and one ≥40 cmH_2O [14]. It became apparent after our previous study where we found very high UBPs in severely obese women with stress overflow urinary incontinence [10] that centrally obese patients may have a chronic abdominal compartment syndrome. We have also found a significantly higher ($p < 0.001$) risk of incisional hernia following open surgery for obesity (20 %) than after colectomy in mostly nonobese patients with ulcerative colitis (4 %) where two-thirds of the colitis patients were taking prednisone and had a much larger incision [23]. Four of the seven incisional hernias in the colitis group occurred in patients with a BMI ≥30. Presumably, this increased risk of incisional hernia was due to an increased IAP in the obese patients.

UBPs were significantly higher in patients with comorbid factors mechanistically presumed to be associated with an elevated IAP than in patients with obesity-related problems that are not considered to be secondary to an increased IAP. The abdominal pressure-related morbidity factors chosen have been documented in pregnancy and cirrhotics with ascites, as well as obese patients, and included hypoventilation, venous stasis disease, GERD, urinary incontinence, pseudotumor cerebri, and incisional hernia. In another report we have found that obese women with pseudotumor cerebri have increased SAD, thoracic pressures as measured transesophageally, and cardiac filling pressures [24]. In addition, hypertension was considered to be probably related to IAP through one or more of the following mechanisms: (1) increased renal venous pressure, (2) direct renal compression [24], and (3) an increased intrathoracic pressure leading to a decreased venous return and decreased cardiac output. Each of these may lead to activation of the renin-angiotensin-aldosterone system, leading to sodium and water retention and vasoconstriction. The increased renal venous pressure could lead to a glomerulopathy with proteinuria. It is currently hypothesized that the hypertension seen in the morbidly obese is secondary to insulin-induced sodium reabsorption. However, systemic hypertension in the morbidly obese may not be associated with hyperinsulinemia, and these patients have been noted to have a decreased renal blood flow (RBF), glomerular filtration rate (GFR), and proteinuria [39]. This was confirmed in a porcine model where a cinch was placed around the right renal vein after left nephrectomy which was associated with a decreased GFR, increased aldosterone and renin, as well as proteinuria [43]. In another study, we found that chronically elevated IAP in a canine model led to the progressive development of systemic hypertension which resolved with restoration of a normal IAP [44]. Others have suggested that the increased ICP with central obesity and increased IAP is responsible for hypertension via the central nervous system [42]. Regardless of cause, surgically induced weight loss is associated with significant decreases in systemic arterial pressure [45].

Although the UBPs were measured supine in anesthetized, paralyzed patients and these pressures could be altered by the upright position, we believe the data to be clinically relevant. First, in the stress incontinence study, the pressures rose even further when the patient assumed a sitting or standing position [10]. Second, these pressures likely would be even higher in the absence of muscle paralysis. Third, most individuals spend 6–8 h sleeping in a supine or lateral decubitus position. Many severely obese patients, especially those with sleep apnea and hypoventilation, have found that they must sleep in the sitting position, presumably to lower the effect of the increased IAP on their thoracic cavity. It is also for this reason that patients with pseudotumor cerebri have more severe headaches in the morning upon awakening.

Although an increased WHR is a recognized measurement of central obesity and metabolic complications, we found a poor correlation between the WHR and UBPs in women but a good correlation in men. This is probably the result of the diluting effect of peripheral obesity, commonly present in women, on the estimate of central obesity. The greater problem of central obesity in men was reinforced by the finding of a greater SAD and UBP in men compared to women despite an equal BMI [14]. Unlike the WHR, the SAD provided good positive correlations with UBP in both men and women, corroborating the computed tomography (CT) scan data reported by Kvist et al. [46, 47] that the SAD is a better reflection of central obesity than the WHR.

In the study of UBP in patients following GBP surgery, significant weight loss was associated with a marked reduction in both pressure-related and non-pressure-related comorbidity, except for incisional hernias and the need for cholecystectomy. Several studies have documented improvement following surgically induced weight loss in conditions presumed to be caused by an abnormally high IAP, such as urinary incontinence [10, 32–35], respiratory insufficiency including sleep apnea and hypoventilation [8, 22–30], GERD [31, 48, 49], pseudotumor cerebri [9, 24, 41, 42], hypertension [45], and cardiac dysfunction [8, 45].

These possible pathophysiologic consequences of an increased IAP (hypertension, peripheral edema, proteinuria, increased CSF pressures, increased cardiac filling pressures, and increased hepatic venous pressures) suggest that the chronic abdominal compartment syndrome could be responsible for toxemia of pregnancy. This hypothesis is supported by the increased association of preeclampsia in primiparas (where the abdomen has never been stretched before), twin pregnancies, morbid obesity where an increased IAP is predictable, and its correction with parturition. Furthermore, there is no clinical animal model of preeclampsia, presumably because animals carry their fetuses in the prone position. The hypothesis is that an increased IAP compresses and reduces blood flow in the abdominal venous system which leads to fetal/placental ischemia, systemic hypertension, proteinuria, hepatic ischemia, platelet consumption in the spleen and liver, pulmonary insufficiency, and intracranial hypertension [50]. The placental/fetal ischemia is thought to cause an increased release of sFlt-1, endoglin, placental growth factor and a decreased VEGF.

Review Questions and Answers

Questions

1. Increased intra-arterial pressure is related primarily to the:
   (a) Hip circumference
   (b) Waist circumference
   (c) Waist:hip ratio
   (d) All of the above
2. Animal studies have shown that pseudotumor cerebri is a result of:
   (a) An increased thoracic pressure
   (b) An increased intra-abdominal pressure
   (c) An increased intracranial pressure
   (d) All of the above
3. Increased intra-abdominal pressure is associated with:
   (a) Urinary incontinence
   (b) Pseudotumor cerebri
   (c) Venous stasis disease
   (d) Obesity hypoventilation
   (e) All of the above
4. Roux-en-Y gastric bypass for severe obesity is associated with:
   (a) A significant decrease in body weight
   (b) A significant decrease in spinal fluid pressure
   (c) A significant improvement in arterial blood gases
   (d) All of the above

Answers

1. (b)
   The increased intra-abdominal pressure is secondary to an increased fat mass within the abdomen (i.e., central obesity). This is best measured by either the waist circumference or the sagittal abdominal diameter. Large lower abdominal obesity produces a large hip circumference; this reduces the waist:hip ratio, and therefore makes this ratio misleadingly low.
2. (d)
   The increased intra-abdominal pressure pushes the diaphragm cephalad and increases intrathoracic pressure. This decreases venous return from the brain, which leads to vascular engorgement and an increased intracranial pressure and severe headaches. It is called pseudotumor cerebri because there is no mass within the brain. It is also called "idiopathic intracranial hypertension."
3. (e)
   All of these obesity-related comorbidities are a result of an increased intra-abdominal pressure and all improve significantly after surgically induced weight loss.
4. (e)
   Surgically induced weight loss is associated with significant weight loss, decreased spinal fluid pressure and relief of severe headache associated with pseudotumor cerebri, improved respiratory function with a decreased $PaCO_2$ and increased PaO_2, and healing of venous stasis ulcers.

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