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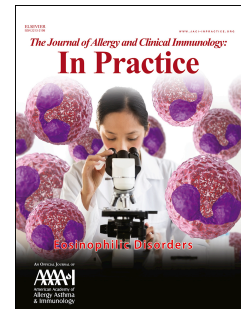
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A Practical Approach to Assist Asthmatics to Lose Weight

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List of Abbreviations:

aP2: Fatty acid binding protein 4
ACT: Asthma Control Test
BMI: body mass index
CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
GERD: gastroesophageal reflux disease
GLP-1: glucagon like peptide-1
ICS: inhalational corticosteroids
LAGB: laparoscopic adjustable band
LRYGB: laparoscopic Roux-en-Y gastric bypass
LSG: laparoscopic sleeve gastrectomy
MEN: multiple endocrine neoplasia
NIH: National Institute of Health
OSA: obstructive sleep apnea
PCOS: Polycystic ovarian syndrome
PO: by mouth
SQ: subcutaneous
T3: triiodothyronine
T4: thyroxine
TBW: Total body weight
TSH: thyroid stimulating hormone

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ABSTRACT

Treating patients with obesity, particularly asthmatics, is a complex challenge that requires a unique and individually tailored approach. Obesity, defined by the Centers for Disease Control and Prevention (CDC), is a body mass index (BMI) of 30.0 kg/m² or greater. It affects approximately 43% of adults and 19% of youth in America. It is a multifactorial disease and should be managed with the same intensity as any other medical problem, for it represents a risk factor for the onset and severity of asthma. Furthermore, it is a comorbid condition that exacerbates rhinosinusitis, gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), hypertension, anxiety, and depression. Being obese also increases morbidity for cardio/cerebrovascular diseases, metabolic syndrome, type 2 diabetes, breast and bladder cancer, and migraines. Osteoarthritis, in particular, of the knees and hips, is also associated with obesity, and that too will complicate asthma by hindering a subjects' mobility and ability to exercise. This paper reviews the epidemiology and pathophysiology of obesity, its effect on asthma, and practical strategies to achieve weight loss. Words:171

OVERVIEW

Obesity is primarily attributed to poor dietary quality, a sedentary life, and a variety of psychological and medical problems. For example, certain illnesses such as endocrinopathies and side-effects of medications can also contribute to weight gain. Therefore, to effectively treat obesity, it is important to comprehend its complexity and focus on a targeted approach that treats physiologic and emotional causes to ultimately help the subject lose weight. Wing and Hill suggest that sustained weight loss be defined as a 10% loss of initial body weight maintained for one year or more.¹ Studies show improvement in asthma with weight loss of 7-8% of initial BMI.²⁻⁵

ASTHMA AND OBESITY

According to the World Health Organization, the prevalence of obesity has almost tripled worldwide since 1975.⁶ Likewise, since the early 1980s, the prevalence of asthma also has increased and as of 2018, 25 million Americans have asthma, including 6 million children under 18 years of age.⁷ Excessive weight is associated with an increased incidence of asthma, e.g., subjects with BMIs of 25-29.9 have a 38% increased incidence of asthma and those with a BMI ≥ 30 have a 92% increased incidence of asthma.⁸ In fact, obesity is linked to 250,000 new asthma cases in the United States per year.⁹

Obesity is associated with an increase in inflammatory markers, such as pro-inflammatory cytokines, TNF-alpha, interleukins, and adipokines, derived from adipose, liver, gastrointestinal, pancreatic, vascular, and musculoskeletal tissues.¹⁰ Obesity also worsens airway hyper-responsiveness.¹¹ This leads to more severe asthma that is more recalcitrant to treatment.¹²⁻¹⁵ For example, adipokines, secreted by adipocytes, are linked to and directly exacerbate atopic

diseases, e.g., allergic rhinitis, asthma, and atopic eczema.^{16, 17} Higher levels of inflammation lead to the need for systemic glucocorticoids and high dose inhalational corticosteroids (ICS), which in turn, can exacerbate obesity by causing an increase in appetite, musculoskeletal wasting effects, and predisposition to metabolic diseases. Poor control of asthma can also lead to a more sedentary lifestyle.

Some dietary choices that lead to obesity may affect the health of asthmatics. Diets high in red meat, fat, dairy products, refined grains, foods high in sugar content, and highly processed foods may promote systemic inflammation through multiple mechanisms.¹⁸ For example, an increase in sputum neutrophils following a high fat meal resulted in increased airway inflammation and impaired bronchodilator response.¹⁹ Likewise, it is hypothesized that a “fast food” diet, low in antioxidants and high in saturated fats, can cause oxidative stress and stimulation of the NF-kB inflammatory cascade.¹⁸

A Mediterranean diet, high in fruits, vegetables, and whole grains, may decrease inflammation.²⁰ Fruits and vegetables may be protective against allergic diseases by decreasing Th2 inflammation and oxidative stress.²¹ These foods which are high in nutrients such as β -carotene, riboflavin, and vitamins A, C, D, and E are associated with decreased risk of wheeze and asthma in both adults and children.²¹ High fiber diets may do the same by activating free fatty acid receptors and inhibiting histone deacetylase.²² More information is needed to understand the importance of diet on airway inflammation and asthma.²³

Different psychological and medical illnesses and medications cause or are associated with weight gain and unsuccessful weight loss. Therefore, it is important to begin with a detailed history and physical examination. Secondary causes include psychological problems and medications, while primary causes include adrenal, thyroid and gonadal abnormalities.

PRIMARY CAUSES OF WEIGHT GAIN (Table I)

Adrenal

Endogenous hypercortisolism or Cushing's syndrome is associated with weight gain. Subjects present with central weight gain associated with early onset of hypertension, hyperglycemia, and osteopenia/osteoporosis. Clinical signs include facial plethora, proximal myopathy, abdominal striae (deep, purple, ≥ 1 cm wide), and thin skin with easy bruisability. There is characteristic wasting of the musculature and fat of the upper extremities, particularly proximal muscles, leading to difficulty in standing from a sitting position. Other symptoms may include headache, depression, hirsutism, and amenorrhea.²⁴ The presentation is similar in children with the key characteristics of decreased growth velocity and stunted pubertal progression.

The laboratory tests to screen for hypercortisolism (Table I) include a elevated 24 hour urine to measure free cortisol, a midnight salivary cortisol (at least 2 separate measurements) or a dexamethasone 1 mg by mouth (PO) overnight suppression test.²⁴ For adults, if the first 2 tests yield high levels of cortisol and there is no suppression of cortisol after the dexamethasone (< 1.8 mcg/dL or 50nmol/L), a referral to an endocrinologist is recommended. Random cortisol levels may vary with time of day and reference ranges vary with age, so results of this test are not diagnostic. Morbid obesity, depression, and alcoholism can result in false positive test results and require repeat or additional testing.

Thyroid

Increased weight gain can be associated with both hyper and hypothyroidism.²⁵ However, it is unlikely that weight gain would be the only clinical sign or symptom of these diseases. Hypothyroid subjects are constipated, tired, fatigued, experience cold intolerance,

develop dry skin, and mentation problems. Hyperthyroidism is associated with increased anxiety, fatigability, insomnia, palpitations, and heat intolerance. There is a hereditary component to thyroid disorders, so a positive family history should increase suspicion for the same. A screening thyroid stimulating hormone (TSH) suffices to check for these diseases; however, obtaining a serum free thyroxine (T4), free triiodothyronine (T3), and thyroid antibodies should follow an abnormal TSH.²⁶ Abnormal or inconsistent results may require an endocrinology consultation.

Gonadal Causes

Hypogonadism in both genders can cause weight gain. Low testosterone in males can lead to anhedonia, low libido, and decreased muscle mass. A low 8 am fasting calculated free testosterone level (a calculation that takes into account total testosterone, Sex Hormone Binding Globulin (SHBG) and albumin) is indicated to rule out this disease. Total testosterone, though a reliable assay, can be falsely low in the obese population because of a preponderance of low SHBG levels. Unfortunately, the direct free testosterone assay is considered inaccurate hence the importance of getting a calculated free testosterone instead.²⁷ Levels below age appropriate ranges on two separate occasions indicate that further workup and potential treatment is necessary.²⁸

In females, peri-menopause and menopause are associated with climacteric symptoms, such as hot flashes, mood variation, insomnia, and alterations in weight distribution, e.g., an increase in abdominal fat.²⁹ The diagnosis is clinical, based on a patient's age and symptoms.³⁰ Menopause is defined to have occurred one year following the last menstrual cycle. An elevated follicle-stimulating hormone usually can occur in late menopause. A study supported by the National Institute of Health (NIH) shows a significant increase in BMI among post-menopausal

women who take at least one weight promoting medication compared to women who do not, indicating that some medications may drive postmenopausal weight gain.³¹

Polycystic ovarian syndrome (PCOS) is characterized by anovulatory cycles leading to irregular menses and cystic ovaries. Patients with PCOS gain weight easily and have trouble losing it. It can be present from the start of menses and is a diagnosis of exclusion. It requires ruling out other causes, e.g., thyroid disease and hypercortisolism, and 2 out of 3 Rotterdam criteria: clinical or biochemical hyperandrogenism, e.g., facial hair and/or male pattern hair loss, irregular menstrual cycles, and/or polycystic ovaries.³² Again, an endocrine consultation may be necessary.

Pregnancy is often accompanied by excessive weight gain, most commonly in those already obese. Gestational weight gain goals for women with a pre-pregnancy BMI ≥ 30 is 4.99-9 kg.³³ Losing weight following pregnancy is challenging, with as many as 20% of women retaining ≥ 4.99 kg postpartum.³⁴ Therefore, an appropriate weight loss plan is critical, in particular, in the postpartum period.

SECONDARY CAUSES OF WEIGHT GAIN

Psychological

Subjects should first be questioned about psychological problems, such as depression, anhedonia, anxiety, and adjustment disorders. Likewise, once obese, there is a higher risk of psychosocial problems.³⁵ Eating disorders exist even in the obese. Binge eating disorders, for example, are more common in women than men and usually occur around 23 years of age.³⁶ Treatment consists of a multidisciplinary approach and may include psychotherapy, nutritional counseling, and the use of medications.³⁷

Medications (Table II)

Medications, such as anti-psychotics, anti-depressants, anti-epileptics, and anti-hyperglycemics can lead to an increased appetite and decreased satiety and activity leading to obesity.³⁸ Therefore, patients should be made aware of the potential side effect of weight gain when initiating such treatment.³⁹ A baseline weight should be obtained and monitored both at home and in the clinic. Weight gain of ≥ 2.0 kg/month, be it from a notable increase in appetite or without any alleged increase in food or lifestyle change, can indicate an iatrogenic cause and prompt additional counseling about dietary restrictions or, if possible, a change in medication.³⁸ If the patient is on several medications associated with weight gain, changing one at a time, to try to better identify the key offender, is indicated. For example, if a patient is on a sulfonylurea, glipizide, and atenolol, one can first try to switch the glipizide to a weight neutral antihyperglycemic like metformin. If this is not effective, and the antihypertensive is causing the weight gain, a switch to a weight neutral antihypertensive, such as an ACE inhibitor, may be indicated. Of course, if discontinuing or changing the medication is not an option, the patient should be encouraged to change their diet and/or increase physical activity. Adding a weight-control medication or other intervention also may be warranted, as discussed below.

A common iatrogenic cause of weight gain in subjects with asthma is the recurrent use of systemic glucocorticoids, exacerbated with prolonged treatment. Short term use, such as a 10-day course, is not commonly associated with weight gain.⁴⁰ When prescribed, systemic glucocorticoids should be discontinued or eliminated as soon as possible, when the asthma is controlled. High dose ICS also can be associated with weight gain, however, not to the degree of systemic glucocorticoids.

A study of 180 adults with asthma indicates that ICS used for 1 year can cause an average weight gain of about 1 kg in females.⁴¹ This same study also showed slightly decreased weight in males. Higher doses of ICS were associated with greater weight gain for females and greater weight loss for males. The mean $\pm$ SD of fluticasone propionate equivalent was $776 \pm 568 \mu\text{g}$ for women and $716 \pm 460 \mu\text{g}$ for men.⁴¹ This difference in weight change between genders may indicate a hormonal role in weight gain.⁴¹ Pediatric subjects with moderate to severe asthma on ICS also are at higher risk for weight gain, one of several reasons to use the lowest effective ICS dose.⁴²

TREATMENT

There are a variety of different reasons why patients gain weight but the primary one is that they consume more calories than they metabolize. In general, most foods are safe, if they are consumed in appropriate amounts not exceeding daily caloric needs. Once obese, it is extremely difficult to lose weight. Successful initial weight loss is just part of the challenge. Maintaining weight loss is just as difficult. The percent of people who can lose weight and maintain that weight loss is as little as 1-3%.⁴⁴ For some, it may be more difficult to lose weight than to stop smoking; 90-95% who attempt to stop smoking fail.⁴⁵ In the short term, a majority of patients will lose at least some weight. In a study of over 4,000 obese adults, 63% attempted weight loss in the past year, and of these, 40% lost $\geq 5\%$ and 20% lost $\geq 10\%$ of initial body weight.⁴⁶ Long term sustained weight loss is not as successful. A 2018 meta-analysis reviews 29 long term weight loss studies. More than half of the weight lost is regained at 2 years and 80% at 5 years.⁴⁷ There only may be a 5-10% average weight loss even with behavioral counseling and/or an optimally controlled diet and exercise program.⁴⁷ Using a team based

approach is the best way to achieve desired weight loss. The primary care physician as well as the specialists should work together to make sure all relevant issues pertaining to weight loss management are addressed and optimized. The ideal strategy to prevent obesity and its negative impact on health is to avoid weight gain in the first place.

HEALTHY EATING

Caloric restriction is the key (Table IV). The estimated caloric intake recommended depends on need, i.e., trying to gain, maintain, or lose weight and varies with age, gender, and physical activity. Most adult females need 1,600 to 2,400 and males 2,000 to 3,000 calories per day to maintain weight.⁴⁸ Young children require between 1,000 and 2,000 and adolescents 1,400 to 3,200 calories per day.⁴⁸ To lose weight, one has to eat less than the recommended calories necessary to maintain weight. Consuming a calorie deficit of 500 to 1,000 calories per day is a proven means to lose weight.⁴⁹ However, extreme calorie restriction is not recommended because it can potentially lead to malnutrition, fatigue, decreased cognitive function, depressed mood, and increased risk to develop eating disorders.⁵⁰

A formal diet program to lose weight can help the patient avoid excessive caloric intake. Several calorie calculators are available online or via popular phone applications e.g., MyPlate Calorie Tracker, Argus, Lose It!, and Diet Tracker.⁵¹ There are also a variety of different popular diet programs, e.g., Weight Watchers, Jenny Craig, Nutrisystem, and others, all of which are effective. Programs that supervise diet plans and include group attendance, offer social support, and focus on both diet and exercise, have the highest success rates.⁵² The fact is that any diet, regardless of the type, depends on the patient's adherence.⁵² Another alternative is to have a patient maintain a food diary. Once the reality of overeating is recognized, it is much easier to advocate for portioned food intake depending on need and preference. Portion

controlled eating is better than strict dietary restrictions, the latter of which can trigger an unintentional rebelliousness and an increased consumption of food. Nutrition literacy studies demonstrate a lack of understanding of nutrition labels.⁵³ Therefore, one of the most effective methods to achieve proportional eating is to have overweight subjects meet with a dietitian to learn about proper portion control.

What diet program is best? A systematic review of several clinical trials compares the most popular diets in the United States. Seven diets were evaluated: Atkins, Dietary Approaches to Stop Hypertension (DASH), Glycemic-Index, Mediterranean, Ornish, Paleolithic, and Zone. Of these, the Atkins Diet (Table III) provides the most substantial evidence for meaningful weight loss at 6 months and 1 year.⁵⁴ Regardless of the diet proposed, such programs should be individualized and dietary counseling included, as necessary. Protocols that utilize an appropriate diet and exercise program are generally more successful than hypocaloric diets alone.⁵⁵ A weight loss study compared the effects of diet and exercise, alone or combined and demonstrated an average weight loss of 8.5% from baseline in the diet group, 2.5% in the exercise group, and 10.8% in the diet plus exercise group.⁵⁶

EXERCISE

Most physicians who advocate weight reduction have heard the patient reply, “But doctor, I don’t eat that much” or “I have to begin to exercise”. Most studies on weight loss indicate that dieting is more important than exercise. However, both are appropriate and better than one or the other alone. A 24-week randomized controlled trial showed that exercise intervention improved asthma control by 23% measured by Asthma Control Test (ACT) scores and reduced shortness of breath by 30.1%.⁵⁸ Developing an exercise plan must be individualized and realistic.

Guidelines recommend 150 minutes of moderate to vigorous physical activity per week or 30 min. of activity 5 times a week to lose weight.⁵⁹ Levels of activity are measured in metabolic equivalents (METs), with moderate activity defined as 3.0-6.0 METs and vigorous activity as greater than 6.0 METs.⁵⁹ Examples of moderate activity include mowing the lawn, walking briskly, or cleaning a home. Examples of more vigorous activity include backpacking, jogging, or aerobic dancing. Weightlifting fits into both categories depending on its intensity. Typically, the faster the heart rate, the more vigorous the workout and more calories burned (Table IV). Asthmatics especially may benefit from a pulmonary rehabilitation program as many patients need assistance understanding the difference between dyspnea on exertion from their obesity vs. bronchial hyperresponsiveness. High-intensity pulmonary rehab provides better exercise capacity and asthma control in obese asthmatics and should be considered in the treatment plan for these patients.⁶⁰

Vigorous exercise with high energy expenditure can result in increased appetite. Therefore, it is important to create a reasonable balance between food intake and exercise. The type of exercise is dependent on age, physical condition, and must be safe to avoid injury, the latter of which can be a setback to attaining weight loss goals. Jogging and running causes stress to weight bearing joints, particularly of the lower extremities.⁶¹ Using a stationary bike, swimming, or water aerobics are examples of low impact exercises. Various behavior modification tools are available to track weight loss and calorie intake. So too are free or subscription-based training program phone applications, e.g., Sworkit Fitness and Workout App, The 7 Minute Workout, and StrongLifts 5x5.⁶²

WEIGHT LOSS MEDICATIONS (Table V)

Patients become frustrated when they do not see weight loss occur despite efforts. They may benefit from a prescribed weight loss medication with the caveat that no medication substantially or sustainably results in continued weight loss without parallel lifestyle efforts. Cost can be a major hurdle to prescribe these medications, and often insurance coverage is inadequate or lacking. Many manufacturers do offer coupons and discounts. Once prescribed, gauging success is important. If the patient does not lose at least 5% of baseline weight in 3 months, the medication should either be increased, if indicated, discontinued, or an alternative therapy prescribed. Of note, no weight loss medication is recommended at conception or during pregnancy.⁶⁵

Phentermine

Phentermine is both an inexpensive and widely used medication for weight loss. It is a sympathomimetic stimulant that reduces appetite via the hypothalamus and the release of norepinephrine and other catecholamines. Theoretically, catecholamines increase metabolism and also decrease neuropeptide Y, a principal appetite stimulator.⁶⁶ It is a schedule IV controlled substance in doses of 8, 15, 30, and 37.5mg. The Food and Drug Administration (FDA) recommends that it be used at 3-month intervals to avoid dependency. However, it is commonly used beyond 3 months when the patient shows benefit. Higher doses can be associated with tachycardia and uncomfortable anxiety, therefore, 8-15mg PO daily should be prescribed initially and increased accordingly. The drug should be used with added caution in the elderly, especially with heart disease and hypertension.

Orlistat (OTC)

Some over-the-counter weight loss medications are available. Orlistat inhibits gastrointestinal and pancreatic lipases, thereby decreasing dietary fat absorption by approximately 30%.⁷⁹ Low dose orlistat (Alli[®] manufactured by GlaxoSmithKline, Brentford, United Kingdom) 60mg should be taken with each fatty meal but not more than once every 8 hours.⁷⁸ It is advertised on Amazon for 40 US dollars for a bottle of 60 capsules. Orlistat (Xenical[®] manufactured by Roche, Basel, Switzerland) is prescribed at a higher dose, 120mg q8 hours, and is indicated for subjects with a BMI ≥ 30 with or without hypertension, diabetes mellitus, and hyperlipidemia.⁷⁹ Each prescription of 90 capsules costs about 600 US dollars.⁸⁰ The most common side effects are gastrointestinal, e.g., steatorrhea, diarrhea, bloating, and abdominal pain.⁶⁸

Phentermine/topiramate

Qsymia[®] (manufactured by Vivus, Campbell, CA in the United States) is the brand name of this combination drug. It results in more weight loss than either drug alone and is recommended for overweight and obese subjects with diabetes, hyperlipidemia, and hypertension.⁷⁴ It comes with simplified titration instructions that make dose adjustments easy to follow. A monthly prescription of Qsymia[®] is around 200 US dollars, significantly more than the cost of each individual generic prescription.⁷⁵ However, it must be noted that topiramate alone is not approved for weight loss. Any female of childbearing age needs to be on proper contraception as it may lead to birth defects and cannot be used in pregnancy or while breastfeeding.

Naltrexone/bupropion sustained release

Naltrexone/bupropion sustained release (Contrave[®] manufactured by Currax Pharmaceuticals, Morristown, NJ in the United States) contains both a dopamine and norepinephrine reuptake inhibitor and opioid receptor antagonist, respectively. It increases pro-opiomelanocortin producing hypothalamic cell secretion of α -melanocyte-stimulating hormone causing anorexia and thereby weight loss.⁷¹ It is approved for those who are obese with related comorbidities. Naltrexone, 8mg, and bupropion, 90mg, once daily is the initial dose, increased over three weeks to two 8mg/90mg tablets twice daily.⁷¹ A one-month supply of 2 tablets twice a day costs around 200 US dollars.⁷³ Its use is linked to an increase in suicidal ideation in younger adults and possible cardiovascular side effects and is not considered a first-line medication.⁶⁸

Liraglutide

Liraglutide is a glucagon like peptide-1 (GLP-1) receptor agonist. It induces weight loss by slowing gastric emptying, increasing satiety, and thereby suppressing appetite. For weight loss, it is marketed as Saxenda[®] (manufactured by Novo Nordisk, Bagsvaerd, Denmark) with a target dose of 3.0mg subcutaneous (SQ) daily. This product is available for diabetes management as Victoza[®] (manufactured by Novo Nordisk, Bagsvaerd, Denmark) with a max dose of 1.8mg SQ daily. The injectable device used is analogous to an insulin pen and requires a separate prescription for pen needles. Begin with the lowest dose, 0.6mg SQ daily, and escalate by 0.6mg one week at a time until the target dose is reached.⁷⁶ Proper titration decreases gastrointestinal side effects, e.g., abdominal discomfort, nausea, diarrhea, and constipation.⁶⁸ Pancreatitis is a rare side effect. It has a black box warning for families with a history of medullary thyroid cancer or multiple endocrine neoplasia (MEN) type 2 because of an increased

incidence of medullary thyroid cancer in rats.⁸¹ A one-month supply of Saxenda[®] costs approximately 1,300 US dollars.⁷⁷

Herbal Medications

Herbal medications are not regulated or approved by the FDA. There is no evidence that they help lose weight.⁸² Therefore, they are not recommended.

Bariatric surgery

Bariatric surgery results in more weight loss and higher remission rates for type 2 diabetes and metabolic syndrome compared to non-surgical treatment.⁸³ Its effectiveness varies depending on the type of bariatric surgery. The two most common include the laparoscopic Roux-en-Y gastric bypass (LRYGB) and the laparoscopic sleeve gastrectomy (LSG). Both are more effective in causing weight loss than the third most common procedure, a laparoscopic adjustable band (LAGB).⁸⁴ A systematic review and meta-analysis compares these three surgical procedures with a mean reduction in BMI of 14.4, 13.5, and 10.6 for LSG, RYGB, and LAGB, respectively.⁸⁴

Sending a patient for bariatric surgery does not necessarily mean that surgery occurs. The process from start to finish can take months: first, reinstituting a dietary program, second, evaluating the patient for medical and psychological problems, and third, performing appropriate laboratory work. This journey to possible surgery has value and is meant to increase post-operative success or perhaps determine necessity for surgery. There are three indications: first, a BMI (kg/m^2) ≥ 40 ; second, a BMI ≥ 35 -39.9 with one or more associated comorbid conditions, and third, a BMI ≥ 30 -34.9 with diabetes or metabolic syndrome.⁸⁵ Asthma is an accepted comorbid condition to qualify (Table VI).⁸⁶

402 LRYGB is more complicated than the other options. The stomach is divided and a small
403 pouch created from the proximal portion of the stomach is used for gastrojejunal anastomosis.
404 Pouch contents drain directly into the small intestine diverting nutrients and effectively bypass
405 the body of the stomach, duodenum, and proximal jejunum. Less calories are absorbed and the
406 small residual stomach results in early satiety. No bowel is removed. There also may be some
407 effect on gastrointestinal hormones and peptides, such as ghrelin, Peptide YY, and GLP-1, which
408 also may help with weight loss.⁸⁷ Ghrelin is a peptide which stimulates appetite and is primarily
409 produced in the oxyntic glands of the stomach. It decreases following bariatric surgery.⁸⁷
410 Peptide YY and GLP-1 are released by the gastrointestinal tract and also increase after bariatric
411 surgery, inhibiting gastric emptying and increasing satiety.⁸⁷ Malabsorption of vitamin B12,
412 iron, and calcium are possible side-effects.⁸⁸

413 LSG is the less invasive procedure in which 75-85% of the stomach is removed leaving
414 behind the lesser curvature and creating a tubular gastric sleeve. This results in less room for
415 food, thus less caloric intake and absorption. There may be hormonal effects as well which
416 affect both satiety and hunger as occurs with LRYGB. Side effects are similar to LRYGB. Total
417 body weight (TBW) loss with LRYGB ranges from 12% to 45% within 3 years of surgery
418 comparable with LSG.⁸⁸

419 Less gastrointestinal rearrangement and manipulation from surgery is associated with
420 substantially lower perioperative and long term risks.⁸⁸ Serious complications from bariatric
421 surgery did occur in 4.1% of patients, 4.8% with laparoscopic bypass, 7.8% with open gastric
422 bypass, and 1.0% with LAGB in a multicentered study funded by the NIH.⁸⁸ Those at highest
423 risk have the highest BMIs, obstructive sleep apnea, a smoking history, the inability to walk 200
424 feet because of severe shortness of breath, and/or a history of deep vein thrombosis.⁸⁸ Long and

midterm complications include hernia formation, marginal ulcer formation, and intestinal obstruction.⁸⁸

Bariatric surgery can result in profound weight loss, increase asthma control, and decrease inflammation linked to decreased inflammatory markers.⁹¹ For example, following bariatric surgery, adipokine imbalance, levels of leptin, and inflammatory cytokines such as IL-6, all pro-inflammatory molecules, decrease, while levels of anti-inflammatory adiponectin increase.⁹¹ Decreased inflammation and improvement in airway physiology results in better lung function. Likewise, asthma control and quality of life improve.¹¹ One study demonstrates decreased airway inflammation which correlates with a decreased BMI.⁹¹ This study also shows that obese, asthmatic subjects, following weight loss, require less asthma medications.⁹¹ Patients who lose at least 20% of their BMI have better asthma control and higher ACT scores.⁹¹ Subjects after bariatric surgery have a decreased risk for asthma exacerbations resulting in decreased emergency department visits and hospitalizations.⁹² Following bariatric surgery, asthmatics have nearly a 60% reduction in the risk of having an asthma exacerbation.⁹³ GERD and OSA, also comorbidities of asthma, may improve or resolve.⁹¹ Following such surgery, it is important to continue appropriate medical follow up, psychological counseling, a vigorous dietary program, and appropriate exercise.

The Future

There are many common risk factors for the development of both asthma and obesity. Some evidence exists for shared genetics between the two and common environmental factors such as smoking, are also linked to the development of obesity and asthma.^{94, 95} Targeting the causative commonalities between asthma and obesity is an

evolving topic and further study is needed to shed light on future prevention and treatment strategies.

Research on hormones dually related to obesity and asthma is a continuously evolving field that could result in future treatment options for the obese asthma phenotype. Fatty acid binding protein 4 (aP2) is a hormone released by adipose tissue and is elevated in both the lungs and systemically in obese subjects, particularly in individuals with asthma.⁹⁶ Levels of aP2 may impact asthma pathogenesis and airway hyperreactivity and be a pathological link between obesity and asthma. It could be a potential target for future treatment.⁹⁶

The microbiome in obese asthmatic subjects may also impact asthma control and inflammation. The lung microbiota differs in asthmatic vs. non-asthmatic subjects.⁹⁷ Lung dysbiosis is present across multiple asthma phenotypes, including the obese.^{98,99} Gut microbiota is altered by obesity and this change causes the formation of molecular metabolites, such as short chain fatty acids.⁹⁹ These metabolites, elevated in obese patients, may affect the lung tissue and function and play a significant role in obese asthmatics disease.⁹⁷ Microbe based therapies could be a future preventive measure and treatment.¹⁰⁰

CONCLUSION

Physicians and other healthcare professionals need to help patients, both with and without asthma, to lose weight. Just like asthma, so too, obesity is a treatable medical condition. First, the physician or the healthcare professional must determine why a patient is overweight. Is it metabolic or functional? A physician guided diet and exercise program should be prescribed and followed for at least 3 months. If unsuccessful, reevaluation of adherence is necessary with reinstitution of a revised program. Medications may be helpful, in particular, to initiate weight

loss. If such approaches are unsuccessful, bariatric surgery should be considered. Treating obesity using the strategies mentioned above can help the patient lose weight, reduce asthma risk, improve asthma control, and decrease the sequelae from other diseases associated with obesity.

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TABLE I: Screening for Endocrinopathies

	Pathology	Clinical presentation	Tests
ADRENAL	Hypercortisolism (Cushing's)	Facial plethora, proximal myopathy, abdominal striae (deep, purple, $\geq 1\text{cm}$ wide), thin skin with easy bruising, hirsutism, depression, amenorrhea. May also have hyperglycemia, hypertension, or osteoporosis. Children have decreased growth velocity and stunted pubertal progression.	Rule out endogenous hypercortisolism: 1- 1mg dexamethasone suppression test a. At 11 PM at night have patient take 1 mg dexamethasone PO. b. 8 AM next morning, check cortisol (normal $< 1.8\text{mg}$) 2- 24-hour urine collection for free cortisol 3- Midnight salivary cortisol test
THYROID	Hypothyroidism	Constipated, tired, fatigued, experience cold intolerance, develop dry skin, and mentation problems.	If low suspicion: TSH If high suspicion or abnormal TSH: repeat TSH, Free T4, Total T3
	Hyperthyroidism	More frequent bowel movements, anxiety, fatigability, insomnia, palpitations, heat intolerance and tremors. Weight gain can be seen in milder forms when poor sleep and anxiety lead to polyphagia.	- Thyroperoxidase (TPO) antibodies to rule out Hashimoto's thyroiditis - Thyroid Stimulating Immunoglobulin (TSI) to rule out Graves disease
GONADAL	Low testosterone in male	Anhedonia, low libido, and decreased muscle mass	Check 8 AM calculated free testosterone
	Menopausal female	Climacteric symptoms such as hot flashes, mood variation, insomnia, and alterations in weight distribution.	Clinical diagnosis: 1 year from last menstrual cycle. FSH levels can be elevated in menopause but may be normal in perimenopause or early menopause.
	Polycystic ovarian syndrome (PCOS)	Hirsutism, obesity, hyperglycemia (diabetes), irregular menstrual cycles.	Diagnosis of exclusion Suspect if patient has 2 of the following 3: hyperandrogenism (elevated testosterone in labs or

			clinical signs), irregular menstrual cycles or polycystic ovaries
Sources for table: Adrenal: ²⁴ Thyroid: ²⁶ Gonadal: ^{27, 30, 32}			

Table II: Example medications known to cause weight gain (list not all inclusive):

Antipsychotics and mood stabilizers
Chlorpromazine, clozapine, lithium, valproic acid
Antidepressants
Mirtazapine, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclics
Antihyperglycemics
Sulfonylureas, insulin, pioglitazone, repaglinide
Antihypertensives
Atenolol, clonidine, diltiazem, valsartan
Glucocorticoids
All glucocorticoids e.g., dexamethasone, hydrocortisone, methylprednisolone, prednisone, etc.
Sources for table: ^{38, 43}

TABLE III: The Atkins Diet

Phases of the Atkins Diet	Examples of Acceptable Foods*
Phase 1: Induction Consume under 20g of net carbs daily for a minimum of 2 weeks. Foundation vegetables should account for 12-15g of daily net carbs for each phase.	Foundation vegetables (ex. asparagus, broccoli, celery, spinach), fish, fowl, shellfish, meats, eggs, fats and oils, cheeses, salad garnishes, salad dressings, herbs, and spices
Phase 2: Balancing Start by consuming under 25g of net carbs daily and slowly add back some nutrient-rich carbs in 5g per week increments as long as you are continuing to lose weight. Remain in phase 2 until you are 10 lbs. from goal weight.	Phase 1 foods plus: Dairy (ex. milk, yogurt, cream), nuts and seeds and their butters, fruits (ex. berries, cantaloupe, honeydew), juices (ex. lemon, lime, tomato), and legumes
Phase 3: Pre-maintenance Add about 5-10g of net carbs per week and continue until you have lost your target amount of weight and have kept it off for at least a full month. Reduce daily net carbs by 10g for at least one week if weight loss stops and you have exceeded your net carb tolerance needed for weight loss.	Phase 1 and 2 foods plus: Starchy vegetables (ex. carrots, peas, squash), fruits with higher carb content (ex. figs, cherries, watermelon), and grains (ex. wheat, quinoa, oatmeal)
Phase 4: Lifetime maintenance This phase is ongoing and is reached when you have maintained your goal weight and have established your net carb tolerance to maintain desired weight. Adjust carb intake if tolerance changes or weight is regained.	Phase 1, 2, and 3 foods plus: Starchy vegetables with higher carb content (ex. corn, potatoes, parsnips), fruits with even higher carb content (ex. bananas, dates, oranges), and grains with higher carb content (ex. rice, barley, grits)
*Examples of acceptable foods is not all inclusive Source for table: ⁵⁷	

TABLE IV: Calories Burned After 30 Minutes of an Activity

	If your weight is 68 kg (~150 lbs)	If your weight is 90 kg (~200 lbs)
Baseball, playing catch	85	113
Basketball, shooting baskets	153	204
Bicycling – moderate	272	363
Bowling	102	136
Dancing	153	204
Gardening	136	181
Golf, riding in cart	119	159
Pushing baby stroller	85	113
Running (5mph or 12min per mile)	272	363
Swimming, leisure, no laps	204	272
Vacuuming	119	159
Walking a dog	102	136
Walking 3mph or 20min per mile	109	145
Washing car	102	136
Calories in certain foods (for perspective)		
1 chocolate chip cookie	50	
12 ounce can of soda	125-180	
1 scoop vanilla ice cream	137	
1 bag (8oz) (227g) potato chips	150-240	
1 brownie (2 inch square)	112	
1 glazed donut	240	
Source for table: ^{63, 64}		

806 Table V: Weight Loss Medication Chart (see discussion):

Weight Loss Medication	Recommended Dosing	Mechanism of Action	Common Side Effects	\$\$\$\$
Adipex-P [®] Lomaira [®] (phentermine hydrochloride) Controlled - IV	For Adipex-P [®] , patients can be started on either 8mg or 15mg daily and increased to the recommended maximum dose of 37.5mg once daily based on patient tolerability and efficacy. ^{66, 67}	This acts as an indirect sympathomimetic stimulant that reduces appetite by inhibiting neuropeptide Y and increases the release of norepinephrine and other catecholamines. ⁶⁶	Tachycardia, palpitations, dizziness, headache, insomnia, fatigue, hypertension and xerostomia ^{68, 69}	\$ ⁷⁰
Contrave [®] (naltrexone HCl and bupropion HCl)	Dosing is one 8mg naltrexone/90mg bupropion tablet per day and increase over three weeks to a target dose of two 8mg/90mg tablets twice a day. ⁷¹	This acts as a dopamine and norepinephrine reuptake inhibitor and as an opioid receptor antagonist. Its effects increase melanocortins which regulate energy balance and have an anorectic effect. ^{71, 72}	Headache, insomnia, dizziness, xerostomia, nausea, vomiting, diarrhea, constipation, increased heart rate, and blood pressure ^{68, 71, 72}	\$\$ ⁷³
Qsymia [®] (phentermine and topiramate extended-release) Controlled - IV	Start with one 3.75mg/23mg capsule daily for 14 days, then increase to the recommended dose of one 7.5mg/46mg capsule once daily. Max dose is one 15mg/92mg capsule once daily. ⁶⁷	This acts synergistically, combining the effects of norepinephrine and other catecholamines with modification of voltage-dependent sodium/calcium channels, activation of GABA receptors, and other mechanisms, possibly causing appetite suppression and an increase in metabolism. ^{72, 74}	Tachycardia, dizziness, paresthesia, headache, insomnia, xerostomia, constipation, and nasopharyngitis ^{68, 72}	\$\$\$ ⁷⁵
Saxenda [®] (liraglutide)	Start with one 0.6mg SQ injection daily and increase by 0.6mg weekly, up to the recommended target dose of one 3.0mg SQ injection daily. ⁷⁶	This acts as a glucagon like peptide-1 (GLP-1) receptor agonist and causes insulin secretion, increases satiety, and delays gastric emptying. ^{72, 76}	Tachycardia, headache, nausea, vomiting, diarrhea, constipation, and abdominal pain. Pancreatitis is rare (<1%). Contraindicated in patients with concern for medullary thyroid cancer ^{68, 72}	\$\$\$\$ ⁷⁷
Xenical [®] Alli [®] [OTC] (orlistat)	For Xenical [®] , take one 120mg tablet q8 hours with each meal containing fat. ⁶⁷ For Alli [®] , take 60mg three times a day with each meal containing fat. ⁷⁸	This acts to inhibit gastrointestinal and pancreatic lipases and reduces the absorption of dietary fat. ^{72, 79}	Steatorrhea, gas, leakage of oily stools, abdominal pain, and headache ^{68, 72}	\$\$\$ ⁸⁰

Notes (details of chart not all inclusive):

Relative price for a one month supply in US dollars as of August 2020:

0.00-100.00 = \$, 101.00-300.00 = \$\$, 300.00-1,000.00 = \$\$\$, >1,000.00 = \$\$\$\$

Adipex-P[®] manufactured by Teva Pharmaceuticals, Parsippany, NJ in the United States

Lomaira[®] manufactured by KVK Tech, Newtown, PA in the United States

Contrave[®] manufactured by Currax Pharmaceuticals, Morristown, NJ in the United States

Qsymia[®] manufactured by Vivus, Campbell, CA in the United States

Saxenda[®] manufactured by Novo Nordisk, Bagsvaerd, Denmark

Xenical[®] manufactured by Roche, Basel, Switzerland

Alli[®] manufactured by GSK, Bretteville, Middlesex in the United Kingdom

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827 Table VI: Comorbid Conditions of Obesity

Premature Mortality
Cardiovascular - Hypertension - Atherosclerotic cardiovascular disease, myocardial infarction, stroke - Congestive heart failure - Cardiac arrhythmias
Metabolic - Type 2 Diabetes, prediabetes - Dyslipidemia - Non-alcoholic fatty liver disease/steatohepatitis - Inflammation
Pulmonary - Obstructive sleep apnea - Asthma
Gastrointestinal - Gastroesophageal reflux disease - Gallbladder disease
Musculoskeletal - Degenerative arthritis - Immobility - Pain
Reproductive - Polycystic Ovarian Syndrome (PCOS) - Infertility - Sexual dysfunction
Genitourinary - Impaired renal function - Nephrolithiasis - Stress urinary incontinence
Central Nervous System - Impaired cognition - Headache - Pseudotumor cerebri
Psychosocial - Impaired quality of life - Depression - Other psychopathology
Cancer - Breast - Colorectal - Endometrial
Sources for table: ^{88, 89, 90}

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