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Gastrointestinal System, Obesity, and Body Composition

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Obesity or overweight is arguably the most obvious physical feature of PWS. Perhaps for this reason, more than 80% of the over 1,600 publications to date regarding PWS mention, discuss, and/or explore the topic of obesity. Despite this attention, the diagnosis, pathogenesis, optimal treatment, monitoring, and outcome of this condition in PWS remain undefined. In addition, the paradox of the underweight infant with PWS evolving into an overweight child and adult has led to considerable speculation regarding pathophysiology.

In addition to the obvious physical feature of obesity/overweight and questions regarding optimal nutritional management, a variety of gastrointestinal (GI) disorders have been identified in PWS, with frequencies similar to respiratory disorders. A description of the GI system and related disorders in PWS will start this chapter, followed by a discussion of obesity and related nutrition and medical issues. Finally, a discussion of analytical methods for body composition analysis and their application in PWS is presented (see Chapter 5 for a complete outline of Part II).

Gastrointestinal System and Disorders

The primary function of the gastrointestinal system is to facilitate intake, digestion and absorption of nutrients. The elements of the system and their functions are as follows:

1. Oropharynx and Esophagus: sucking, mastication (chewing and softening of food), salivation, swallowing (deglutition), transfer of food to the stomach
2. Stomach and Intestines: digestion, production of regulatory hormones, absorption of nutrients and elimination of waste

Elements of these processes may be relevant to the pathophysiology of PWS. Therefore, each of the following sections begins with a very brief description of the relevant physiology, followed by a review of PWS-related pathophysiology and treatment.

Oropharynx

Physiology

In the resting state, in which a person is not eating or vocalizing, the oral cavity undergoes continual involuntary salivation and swallowing. Saliva is derived primarily from the parotid, submandibular, and sublingual glands in the oral cavity (90%); another 10% is derived from scattered salivary glands. An average adult produces 0.5 to 1.5 L per day. Saliva is composed primarily of water with dissolved proteins, enzymes, and minerals; the composition differs according to the source gland. The major functions of saliva include lubrication and cleansing of the oral cavity, neutralization of acids, inhibition of microbial growth, and protection of dentition.[133,157]

Taste, smell, and palatability are among the initial food qualities that determine intake and retention of substances in the oral cavity. After entry of solid or semisolid food into the oral cavity, a complex neuromuscular process of chewing (mastication), salivation, and swallowing (deglutition) follows. In the neonatal period, ingestion of liquid substances normally involves primarily deglutition (without mastication), and the physical mechanisms differ somewhat from that which occurs with solid food ingestion.

Mastication combines a number of processes, including reduction of food to smaller pieces suitable for deglutition. The teeth serve as passive tools for this process and are controlled by coordinated activity of the powerful jaw muscles.[102,187] The muscles of the tongue participate in churning and mixing of food in the oral cavity and movement of food toward the esophagus. Coordinated movement of the jaw, laryngeal, and pharyngeal muscles occurs both voluntarily and involuntarily, with neurosensory input and feedback.[119] Mastication may also play a role in feedback regulation of appetite,[163] although this has yet to be demonstrated in humans.

Increased salivation occurs in anticipation of food intake (e.g., via visual and olfactory inputs), during taste (gustatory stimulus), and during mastication. The neural inputs for this process have been summarized.[157] Gustatory input via cranial nerves VII (facial), IX (glossopharyngeal), and X (vagus) and masticatory input via cranial nerve V (trigeminal) to the brainstem salivary center is then relayed back to the salivary glands via cranial nerves VII (to the submandibular and sublingual glands) and IX (to the parotid glands), resulting in increased salivation. The stimulated parotid gland, which produces an amylase-rich saliva, can reach 50% of total production during mastication. During mastication, saliva has key roles in enhancing taste perception, solubilizing food products, initiation of starch and lipid digestion, and preparation of food boluses for swallowing.

The process of swallowing starts with movement of processed food toward the back of the oral cavity, accomplished primarily by voluntary movement of the tongue. The second stage involves a reflex elevation of the pharynx and peristaltic movement of the food into the esophagus. The larynx also elevates, with closure of the epiglottis, thereby protecting the airway during swallowing.[171] The final stage of

swallowing involves anterograde esophageal peristalsis, resulting in movement of the food bolus into the stomach. Swallowing is mediated by input via cranial nerves IX and X to the brainstem swallowing center, with output via cranial nerves V, VII, IX, X, and XII.[64,157] The entire process of swallowing is facilitated by saliva, which provides the necessary lubrication. In addition, saliva buffers the oropharynx and esophagus against acidic food and back leakage of gastric acid.

The human neonate relies exclusively upon the sucking reflex for nutrient ingestion.[70] The suck reflex develops relatively early during fetal life and involves intra- and peri-oral stimulation, leading to activation of brainstem centers interacting with the motor cortex, leading to rhythmic motor activity mediated by cranial nerves V, VII, and XII. Nonnutritive sucking (e.g., use of a pacifier) may have somewhat different dynamics and regulation from nutritive sucking (i.e., breast- or bottle-feeding),[70] the latter presumably involving additional coordination with swallowing. Although a sucking motor pattern can be identified in the 10- to 12-weeks' gestation fetus, coordination of sucking, swallowing, and respiration does not occur until after 35 weeks.[89,144] As with oral food intake after the neonatal period, the suck reflex is highly dependent upon oropharyngeal muscle tone and function.

Pathology in PWS

Generalized hypotonia in the neonate with PWS is manifested by an extremely weak suck reflex, lacking in both strength and endurance.[87] In addition, apparent lack of coordination between suck/swallow and breathing has been anecdotally observed in some infants. Although not yet studied in detail, hypotonia of the laryngeal, pharyngeal, and esophageal musculature could lead to further problems with swallowing, airway protection, and efficient movement and retention of liquid in the stomach.

Although the oropharyngeal hypotonia usually improves sufficiently to allow adequate oral nutrition by 6 to 12 months of age, the underlying problem probably continues throughout the life span. Older individuals with PWS are often noted to avoid meat and other foods that require a relatively high oromotor effort, which may in part account for the noted preference for carbohydrates over protein.[69] Micrognathia and microdontia (small lower jaw and teeth), noted in some individuals with PWS, may further compound the problem by providing less muscle bulk and surface area.

Perhaps even more problematic is the lack of adequate salivation. Unusually viscous saliva has been noted in the majority of patients with PWS,[22,105] and decreased volume of saliva is virtually universal. Saliva collection and analysis from 25 individuals with PWS (1 to 53 years old) showed an unstimulated salivary flow rate of 0.16 g/min, as compared with 0.54 g/min in controls.[94] Stimulation of salivary flow by mastication of paraffin increased the flow to only 0.38 g/min, as compared with 2.38 g/min in controls (it should also be noted that saliva could not be collected from an additional 15 PWS subjects due to inadequate flow and/or viscosity). PWS saliva was noted to be extremely viscous, with increased concentrations of all measured

solutes, including fluoride (165%), calcium (226%), phosphorous (157%), chloride (124%), sodium (154%), and protein (126%). No differences were noted between the 3 uniparental disomy and 17 deletion subjects (5 did not have detailed genetic studies). A similar, but not entirely identical, condition of decreased salivation and hyperconcentration of salivary fluid has been noted in non-PWS patients with denervation of the parotid gland.[130] However, a normal but prominent appearance of the three major salivary glands, despite decreased salivation, was noted in one subject with PWS.[204]

Decreased salivary secretion, or xerostomia ("dry mouth"), leads to decreased natural cleansing of the oral cavity, severe dental caries, enamel erosion, infection, and tooth loss.[7,11,94] These disorders are similar to those observed with xerostomia associated with other conditions.[133] Enamel erosion is due to inadequate salivary buffering of food-derived acids from citrus, acidic substances (including carbonated sodas, both regular and diet), and bacterial metabolism of dietary sugar and starch,[18,204] resulting in resorption of bone mineral in the acidic milieu.

In non-PWS patients, xerostomia has been associated with speech abnormalities (dysphonia), a sensation of thirst resulting in frequent sipping, oral discomfort, difficulty with mastication and swallowing, taste disturbances (dysgeusia), heartburn, and halitosis.[133,157] Several of these features are also noted in PWS, although direct cause/effect relationships have not been systematically studied.

Treatment

In neonates with PWS, hypotonic suck and lack of a coordinated feeding mechanism can often lead to a severe failure-to-thrive. Nasogastric tube-feeding is often used to meet nutritional needs,[79] and many infants require gastrostomy tube placement to facilitate feeding for the first few months of life.

The use of treatment strategies to improve oromotor strength and coordination of swallowing can significantly enhance feeding success. Such strategies may include early introduction of occupational and speech therapies, use of adaptive devices, positioning strategies, jaw-strengthening exercises, thickening agents for liquids, and use of low-calorie binding agents. These therapies reduce the need for parenteral (tube) feedings, as shown by our experience at Texas Children's Hospital (Figure 6.1). Infants with PWS who received supplemental oromotor therapy required nasogastric feedings for a mean of 40 days, as compared with 234 days for infants who did not receive this therapy ($p = 0.003$).

Occupational and speech therapy are often utilized after the neonatal period (see separate chapters); the efficacy of these treatments in relation to feeding behavior and food preferences has not been studied in PWS, and there is poor documentation of results in other forms of dysphagia associated with muscle disease.[101] Nonetheless, these therapies are generally recommended for individuals with PWS.

Nonpharmacologic treatment of xerostomia in non-PWS patients often involves the use of natural secretagogues (e.g., sour lozenges,

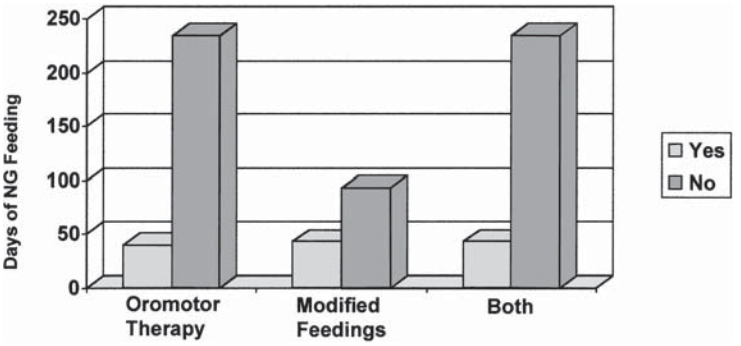

Figure 6.1. Impact of supplemental therapies on the duration of nasogastric tube feedings in infants with PWS (total N = 15). The y-axis is the mean number of days that nasogastric feedings were required. The x-axis shows supplemental therapies that were administered. (*Source:* A. Scheimann, unpublished data.)

sugarless chewing gum) to provide continuous salivary gland stimulation. This approach has been reported in some individuals with PWS,[204] but larger scale studies have not been conducted. Pharmacologic treatment of xerostomia has relied primarily upon topical application of artificial saliva, although the use of salivary secretagogues is increasing[161]; these modalities have not been studied in PWS.

Given the high risks for severe dental caries and infection, regular dental care must be established for all individuals with PWS. Oral hygiene should be instituted in infancy, even if dental eruption has not yet occurred, using soft foam toothbrushes and wetting solutions. This may be particularly important for infants on parenteral feedings, where there is virtually no stimulation of salivation or wetting from oral feeds. Fluoride treatment may also be recommended. For treatment of caries, adhesive dental techniques have been recommended.[18]

Avoidance of sugars, thick starchy foods, citrus, carbonated drinks, and other acidic foods is advisable. In addition, individuals with PWS should be encouraged to include copious amounts of water with each meal to facilitate mastication, swallowing, and oral cleansing.

Stomach and Intestines

Physiology[50]

After swallowing, esophageal peristalsis results in delivery of food boluses into the antrum of the stomach. In the resting condition, the lower esophageal sphincter, composed of specialized smooth muscle cells (not a true sphincter) maintains a positive pressure to prevent gastric contents from moving back into the esophagus. During swallowing, this pressure is released in response to local stimuli, including vasoactive intestinal peptide (VIP) and nitric oxide, thereby allowing food to enter the antrum of the stomach.

The stomach, which begins at the lower esophageal sphincter and ends at the pyloric sphincter, is composed of inner circular and outer longitudinal layers of smooth muscle which undergo rhythmic

contractions controlled by a pacemaker located in the main portion of the stomach. The stomach is lined by secretory cells, including parietal, chief, and mucus cells. In response to food-related stimuli (smell, visual, cerebral), the vagus nerve signals release of acid from the parietal cells; this effect is mediated by histamine and gastrin. The acid environment, in turn, inhibits further gastrin release and also stimulates local production of somatostatin, which inhibits histamine and gastrin release. The parietal cells also produce intrinsic factor, which is required for absorption of vitamin B_{12}.

Vagal stimulation also results in release of pepsinogen from the chief cells of the stomach. In the presence of gastric acid, pepsinogen is processed to pepsin, which is the major enzyme involved in the initial steps of protein digestion.

Neurons within the stomach produce a number of substances that participate in regulation of gastrin, histamine, acid, and somatostatin release. These include acetylcholine and calcitonin gene-related peptide from the vagus nerve and pituitary adenylate cyclase-activating peptide, VIP, gastrin-releasing peptide, galanin, and nitric oxide from enteric neurons. Some of these peptides are also postulated to affect normal eating behavior and are discussed in the section on obesity.

When liquid substances enter the stomach, vagal stimulation results in relaxation of the proximal stomach, where the liquid is retained until gastric emptying. Solid foods are mixed, digested, and reduced to small particles in the distal stomach. Gastric emptying is accomplished by both muscular contractions of the stomach and by alternate opening and closure of the pyloric sphincter, which is under sympathetic and vagal control, respectively.

After passing through the pyloric sphincter, partially digested material enters the duodenum, where the fat, protein, and gastric acid stimulate duodenal production of cholecystokinin (CCK) and secretin. These peptides are absorbed into the bloodstream and travel to the pancreas, activating vagal stimulation of pancreatic enzyme secretion into the intestinal lumen. Duodenal distention also leads to pancreatic enzyme secretion through direct vagal stimulation (enteropancreatic reflex). These enzymes include (1) pancreatic amylase, which digests carbohydrates to oligosaccharides; (2) lipase and colipase, which digest fat (triglycerides) to monoglycerides and fatty acids; and (3) trypsin, chymotrypsin, and elastase, which digest peptides (resulting from pepsin digestion of proteins in the stomach) to oligopeptides.

Further digestion into amino acids, fatty acids, monoglycerides, and monosaccharides occurs in the small intestine. These nutrients are absorbed into the bloodstream from the intestinal lumen. In addition, the small and large intestines are responsible for absorption of water and electrolytes. Finally, the large intestine and anal sphincter are responsible for the process of solid waste elimination, or defecation.

A number of peptides are released from the gastrointestinal tract and pancreas into the bloodstream during the process of food intake, digestion, and absorption. These include insulin, glucagon, and postulated appetite-regulatory hormones. Some of these peptides are discussed in the section on obesity.

Pathology and Treatment in PWS

Retrograde Movement of Ingested Substances: Normally, ingested nutrients move in an anterograde (forward) fashion from the mouth to stomach to intestines with minimal backflow. Retrograde movement of food from the stomach into the oropharynx may occur under two primary circumstances: (1) gastroesophageal reflux and (2) emesis. Voluntary regurgitation and reprocessing of food from the stomach, or rumination, may also occur. Retrograde movement of intestinal contents has been observed in cases of severe obstruction and constipation in patients without PWS, but these problems have not been reported to be a particular concern in PWS.

Gastroesophageal reflux is a passive phenomenon in which liquid and partially digested food moves up the esophagus from the stomach into the oropharynx. Gastroesophageal reflux is a relatively common finding in otherwise normal (non-PWS) infants, occurring in the majority of infants under 4 months of age[153] and usually resolving within the first year of life.[190] The severity may be increased in infants with hypotonia, prematurity, or other predisposing conditions. Contributory factors may include transient relaxation of the lower esophageal sphincter pressure and positioning after feeds. It has been postulated that reflux may trigger arousal, thereby being protective against sudden death in infants.[190] In addition, in non-PWS infants, it has been found that a nasogastric tube increases the frequency of reflux episodes.[160]

In severe cases, chronic reflux of gastric acid can cause esophagitis, esophageal stricture, and cellular dysplasia and carcinoma of the distal esophagus. In older children and adults, gastroesophageal reflux may be associated with symptoms of "acid reflux" or heartburn. Endoscopic evaluation and surgical treatment may be necessary.

Possible gastroesophageal reflux has been occasionally reported in PWS,[18] but systematic documentation of prevalence has not been performed. Anecdotal experience suggests that clinically significant reflux is not as commonly observed in infants with PWS as might be expected. In addition, typical symptoms and complications due to gastroesophageal reflux have not been reported. This may, in part, be due to the lower volumes per oral feed that are usually ingested by PWS infants.

There are concerns regarding the possibility that due to hypotonia, infants with PWS may be unable to adequately protect the airway during reflux episodes, thereby increasing the risks for aspiration pneumonia and respiratory compromise. As a safety measure, reflux precautions should be taken for all infants with PWS, especially if taking substantial volumes of oral bolus feeds, and continued until the child is ambulatory. Optimal precautions have not, however, been defined in infants with PWS. In non-PWS infants, a 30-degree incline post feeds (e.g., in an infant seat) has been traditionally recommended. Given the concerns that this may worsen reflux in some infants due to increased intra-abdominal pressure, the prone or left-lateral position has been recommended,[160,190] but the relative advantages of this positioning have not been tested in infants with PWS. In any case, a supine position should be avoided.

Gastroesophageal reflux and/or complications related to this condition have not been reported in older individuals with PWS. Since individuals with PWS have decreased pain sensation (see Chapter 5), typical symptoms of heartburn may not be a reliable indicator of acid reflux. In one case of a 27-year-old man with PWS, heartburn was reported, but no abnormalities were noted on endoscopic examination.[204]

Emesis is an active process that may be considered to be a normal protective reflex. When emetic agents and toxins enter the gastrointestinal lumen, mucosal chemoreceptors are triggered which then signal through the vagus nerve back to a brainstem emetic center.[107] Emetic toxins in the bloodstream signal directly to this same area through the area postrema of the brainstem. Processing of these signals results in sequential signaling through vagal and other motor neurons, resulting in retching (simultaneous, forceful contractions of the diaphragm and abdominal muscles) and expulsion (prolonged forceful contraction of the abdominal muscles in coordination with the rib cage and pharyngeal and laryngeal muscles). Retrograde intestinal contraction occurs with gastric relaxation. Emesis then results from sequential and coordinated increases in intra-abdominal and intrathoracic pressure. Active retrograde peristalsis of the stomach or esophagus is not thought to be involved in emesis. Hypothalamic release of vasopressin and oxytocin may also be essential elements of emesis.

A commonly reported feature of PWS is a decreased ability to vomit, with a complete absence of "natural" or induced (e.g., with syrup of ipecac) vomiting noted in a large proportion of individuals.[3,104] The reasons for this are not completely known. Hypotonia of the diaphragmatic, abdominal, and intercostal muscles may be contributory since forceful contractions of these muscles are required for emesis. A deficiency of oxytocin neurons[179] could play a role, although CSF oxytocin levels are reportedly elevated in PWS.[140] Vagal autonomic dysfunction is also a possibility, although, as reviewed in Chapter 5, the evidence for autonomic dysfunction in PWS is limited.

Caution has been advised regarding reliance on emetic agents, particularly syrup of ipecac, in the treatment of accidental poisoning for individuals with PWS since the response may be inadequate. The American Academy of Pediatrics no longer recommends routine supply or use of syrup of ipecac for home treatment of childhood ingestion[46]; therefore, this issue may be a moot point, at least in the U.S. Instead, parents and guardians are advised to call the local poison control center for guidance. However, healthcare practitioners and guardians should be aware of the decreased ability to vomit in the event that an emetic therapy is considered in the emergency room or other medical care facility.

Although most individuals with PWS have a decreased ability to vomit, others may have rumination, a condition characterized by *voluntary* regurgitation of gastric contents that are then rechewed and reswallowed. A survey study found that 10% to 17% of 313 individuals with PWS reported a history of rumination and that approximately half of this group had a history of emesis.[3] Rumination was also suspected

in a 17-year-old who was found to have gastric secretions in her pharynx despite fasting during preparation for general anesthesia.[174] Rumination may be a form of self-stimulation and, in the case of PWS, a means of obtaining food, albeit reprocessed.

Regurgitated food usually contains gastric acid, which may add to problems with dental enamel erosion. Therefore, in addition to behavioral treatment, the use of pharmacologic agents to block stomach acid secretion should be considered in patients who have rumination.

Gastric Dilatation: In 1997, Wharton et al.[197] reported six females with massive gastric dilatation; two died of gastric necrosis, one died of cardiac arrest, and three survived. Fever, abdominal pain, and distention were presenting signs, and vomiting was reported in two cases. These individuals had all had strict dietary control; the authors postulated that gastric muscular atony and atrophy may have occurred as a result of the dietary limitations, resulting in dilatation and necrosis following sudden ingestion of a large quantity of food. No additional cases have been published and the prevalence of this condition in PWS is unknown. However, aside from the usual recommendations for prevention of binge eating, caretakers should be vigilant for signs of acute onset of unusual abdominal distention, fever, and emesis.

Bowel Complaints: As indicated in Figure 6.2, complaints related to bowel function are frequently reported by individuals with PWS (data summarized from various sources). For the most part, these appear to

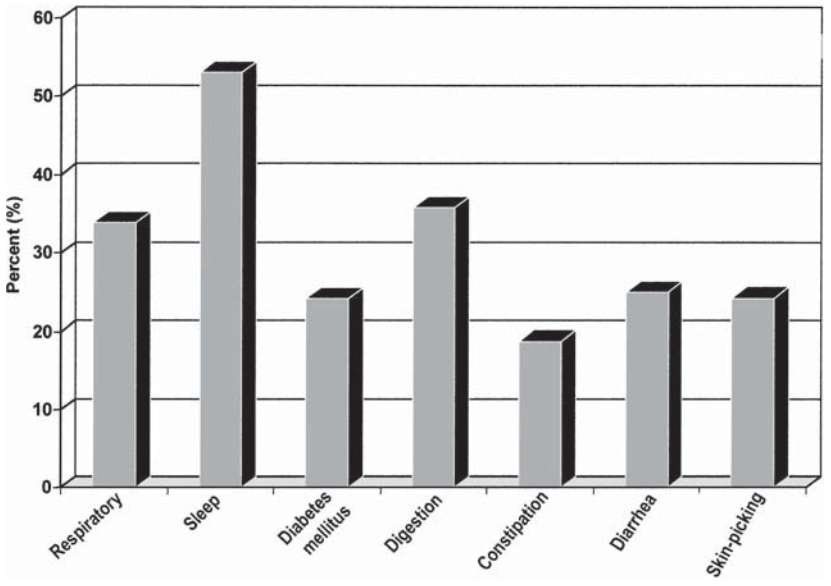

Figure 6.2. Symptom prevalence in adults with PWS (*Sources:* Butler et al.,[27] 2002, Holm et al.,[104] 1992, and personal communications from S.B. Cassidy and B.Y. Whitman.)

be secondary to factors related to eating. As of this writing, no intrinsic abnormalities in bowel anatomy or function have been associated with PWS.

Composite data indicate that 20% of individuals with PWS report constipation. Constipation can be defined as hard, dry bowel movements, usually occurring less than three times a week. Abdominal and rectal pain, rectal fissures, hemorrhoids, and rectal bleeding (bright red blood) may occur in association with the disordered defecation. In addition, affected individuals may have abdominal distention, bloating, and a general feeling of discomfort. Lack of dietary fiber and inadequate liquid ingestion may be contributory factors. Hypotonia of the pelvic floor and abdominal muscles can increase the difficulty of defecation. General physical immobility is also associated with constipation. Although hypothyroidism does not occur with increased frequency in PWS, it is fairly common in the general population and often presents with constipation.

Treatment of constipation involves provision of adequate dietary water and fiber, encouragement of physical activity, and thyroid hormone replacement, if deficient. In some cases, rectal stimulation, irrigation, suppositories, or enemas may be necessary to clear the rectal ampulla. Laxatives may be helpful in some cases; however, chronic use is not recommended.

Diarrhea, often thought of as the opposite of constipation, can be defined as loose, watery, and frequent stools. Diarrhea is reported somewhat more frequently than constipation in PWS. Noninfectious diarrhea can be caused by consumption of large amounts of poorly absorbed dietary sweeteners (e.g, sorbitol or fructose) or fat substitutes (olestra), use of antiabsorptive agents (e.g., orlistat), and food intolerance (e.g., lactose intolerance). Consumption of contaminated foods, not uncommon in PWS due to the foraging behavior, enhances the likelihood of acquiring infectious diarrhea. A careful history, examination of the stool and blood count, stool cultures (including cultures for *C. difficile*, if indicated), and parasite studies (including *giardia lamblia*) may be included in the evaluation.

Treatment of diarrhea is dependent upon the cause. Diarrhea, especially if copious, watery, and acidic, can cause perianal irritation, bleeding, and infection. These secondary conditions also require attention and treatment.

Rectal ulcers may occur as a result of a regional skin picking sometimes termed "rectal digging."[14,38,143] This behavior is often exacerbated by rectal irritation from constipation, diarrhea, or large stools. Symptoms may include mucoid rectal discharge, bloody stools, constipation, rectal pain, abdominal pain, and tenesmus. Behavioral and possibly psychotropic agent therapies are the recommended therapy for skin picking (see Chapter 12). Stool softeners and treatment of constipation and other contributory factors are also necessary to avoid further rectal irritation.

Treatment of bowel disorders in individuals with PWS often requires ongoing specialized treatment and monitoring. A multidisciplinary approach is often necessary to optimize therapy.

Other Gastrointestinal Organs

No intrinsic structural or functional abnormalities in pancreatic exocrine or endocrine function have been identified in PWS. Disordered serum levels of pancreatic secretions (e.g., insulin, pancreatic polypeptide) have been reported, as discussed elsewhere, but are not postulated to be due to primary pancreatic disease.

Nonalcoholic fatty liver disease (NAFLD) is a condition that typically occurs in obese individuals, particularly those with insulin resistance, characterized by lipid accumulation in the liver.[67] NAFLD may progress through the stages of fat accumulation (steatosis), fibrosis and inflammatory necrosis (nonalcoholic steatohepatitis), cirrhosis, and liver failure. The first stage is fairly common in the general obese population; subsequent progression is less common, but NAFLD is a major cause of nonalcoholic liver failure in the overall population. Diagnostic signs include elevated liver enzymes, liver enlargement, and ultrasound evidence of steatosis. Hepatic steatosis has been occasionally reported in cases of PWS,[99,203] but the overall frequency is not known. The treatment of NAFLD has not yet been delineated, although metformin may have beneficial effects in the early stages of disease.[112]

There are two case reports of childhood liver tumor in PWS, an adenoma and a hepatoblastoma.[95,180] It is not known whether these were specific or chance associations.

Obesity and Nutrition

Definitions

Obesity or overweight is both a major feature of PWS and a burgeoning problem in the non-PWS population. However, the recognition, diagnosis, and characteristics of obesity in PWS are very different from virtually every other population. In addition, while the terms *obesity* and *overweight* may be interchangeable in the general population, this may not the case in PWS. This is not merely a semantic argument; distinguishing obesity from overweight may have important pathophysiologic and treatment implications for PWS.

The derivation of the word obesity is somewhat obscure. An online dictionary of etymology (www.etymonline.com) has the following listing:

obesity—1611, from Fr. *obésité*, from L. *obesitas* "fatness, corpulence," from *obesus* "that has eaten itself fat," pp. of *obdere* "to eat all over, devour," from *ob* "over" + *edere* "eat." The adj. *obese* is attested from 1651.

Other sources trace the word to *ob* (Eng: toward) *ese* (Ger: eating).

In modern medical terminology, obesity is often defined as a condition characterized by excessive body fat. While some definitions include reference to overweight resulting from excess body fat, a more standard scientific definition refers to an excess proportion of fat to nonfat mass. This latter definition is probably most relevant to PWS.

In normal human physiology and with usual diet composition, as weight is gained, fat and nonfat (bone, muscle, water) mass increase in a nearly linear relationship, with fat increasing at a faster rate than nonfat mass.[75] This "companionship of lean and fat"[75] holds for a variety of human conditions in which total body weight is altered, including diabetes mellitus, anorexia nervosa, and "normal" obesity. In an underweight individual, there is a relatively higher proportion of lean mass. As body weight increases, the ratio of fat to nonfat mass gradually increases, but both compartments increase in a linearly correlated fashion.

Because of this relationship, a ratio of weight to height provides a reasonable estimate of total body fat, with weight (kg) divided by height squared (m^2), also known as body mass index (BMI), providing the best approximation of more direct measures of body fat (see Body Composition section in this chapter). For non-PWS populations, BMI provides a convenient noninvasive indicator of body fat. As defined by the Centers for Disease Control, obesity in adults is equated with a BMI of ≥25. However, it is possible to have a BMI in the obese range without actually being obese, as in the case of a body builder who has increased muscle mass.

Since the proportions of body fat to height change during human growth, childhood *overweight* is defined as a BMI ≥95th percentile as compared with the age-/sex-related norms; *obesity* is not defined by BMI alone. As with adults, overweight usually but not always equates with obesity. For instance, athletic adolescent males may have increased muscle mass, decreased fat mass, and a relatively high BMI.

PWS is one of the few conditions in which the companionship between fat and lean does not hold. Forbes noted that while individuals with a number of conditions showed a linear, superimposable relationship of lean mass and weight, individuals with PWS were clear outliers, with a marked deficit in lean mass for weight.[75,76] Other studies have shown an excess of body fat in individuals with PWS, including underweight infants.[20,40,54,55]

Therefore, in the natural history of PWS, while overweight invariably equates to obesity, normal and underweight are also accompanied by increased body fat. At least by the definition of increased fat to lean, all individuals with PWS, regardless of weight, may be considered obese. Distinction of obesity and overweight (total body mass) may be important in terms of defining related morbidity risks and treatment. In addition, total fat mass and fat distribution may have different pathophysiologic implications from obesity and overweight.

Pathogenesis

Given the above discussion, the pathogenesis of the increased fat mass in PWS can be separated into two considerations, which may or may not be related to one another:

1. What causes the apparent violation of the "companionship rule"; i.e., why does fat mass increase in an abnormal proportion to lean mass as weight increases?

2. What causes the apparently insatiable appetite and the consequent unlimited weight (primarily fat) gain?

Knowledge of the pathogenesis of these conditions could be crucial to designing adequate treatment protocols.

The inappropriate proportion of fat to nonfat mass probably begins *in utero* and is accompanied by an absolute deficit in muscle and bone mass. This could result from either (1) inappropriate preferential shuttling of nutrients into fat, thereby causing a deficit in lean (bone and muscle) mass, and/or (2) inappropriately low utilization of nutrients by bone and/or muscle, leading to a default deposition of fat.

The mechanisms by which the human body normally shuttles ingested substrate (glucose, amino acids, fatty acids) into fat, muscle, and bone have not been completely defined[72,98,115] and a discussion of this topic is beyond the scope of this chapter. There is evidence that hormones and neuropeptides that may regulate appetite (e.g., leptin, neuropeptide-Y (NPY), adiponectin, Agouti-related protein) may also affect substrate partitioning[98,115]; however, much of the data has been collected in rodents and may not apply directly to humans. In addition, no specific defects in the physiology or action of these substances have been reported in PWS, and none are coded within the PWS gene region. Therefore, it is not known at this time whether the primary body composition abnormality in PWS is excess lipogenesis, decreased formation of muscle and/or bone, or a concomitant dysregulation of both fat and nonfat mass accretion.

The propensity for insatiable appetite and weight gain in PWS is likewise not completely understood. Normal eating behavior has been separated into three components: (1) an initial, relatively acute "drive to eat," or *hunger*; (2) an immediate postmeal feeling of fullness, or *satiety*; and (3) a longer-lasting feeling of satisfaction, or *satiation*. The control mechanisms for each of these stages are likely to be different. On a theoretical basis, environmental stimuli and voluntary control are more likely to influence hunger, whereas satiety and satiation may be more dependent on intrinsic physiologic control. Studies indicate that the primary deficit in PWS involves the third stage, satiation.[131]

Satiation may be controlled by endogenous appetite suppressants and stimulants (orexins). Theoretically, the balance between these two components is maintained by peripheral metabolic and/or neurogenic signals. Many of the characterized appetite-regulatory pathways in rodents and humans have been localized to the arcuate nucleus of the hypothalamus. A primary hypothalamic defect has been postulated to drive the hyperphagia in PWS, although no relevant functional or structural abnormalities have been identified thus far.[81,82,85,86] The possibility exists that the primary disorder may involve a defect in peripheral satiety signaling, perhaps related to the defective nutrient cycling and body composition abnormality. This latter model would agree with the clinical observation that the eating behavior in PWS more closely resembles nutritional deprivation or starvation rather than normal hunger.[103,127]

As of this writing, the study of appetite regulatory peptides in the general population and in PWS is actively developing.[50,56,199,201] The following list summarizes current knowledge of several postulated appetite regulatory peptides in relation to PWS. In general, the current model of appetite regulation includes peptides generated within the gastrointestinal system or body tissues that are released into the bloodstream (endocrine) or nervous system (neurocrine). These peptides then feed back to specific receptors in the hypothalamus, resulting in generation of signaling within the central nervous system and back to the body tissues.

1. Cholecystokinin (CCK)

CCK is produced by the endocrine I cells in the duodenum and jejunum in response to fat, amino acids, and gastric acid. Actions include stimulation of pancreatic enzyme secretion, gallbladder contraction, intestinal motility, insulin secretion, and pancreatic polypeptide secretion. CCK delays gastric emptying and inhibits release of gastric acid. In the brain, high concentrations of CCK are present in the cerebral cortex. CCK is postulated to be responsible for initiating satiety during a meal.[201] In PWS, fasting levels of CCK are normal but unlike in non-PWS controls, fasting CCK is not correlated with free fatty acid levels.[31] In response to a protein meal, CCK levels rise normally in individuals with PWS.[183]

2. Pancreatic Polypeptides

The pancreatic polypeptides PP, PYY (peptide YY), and NPY (neuropeptide Y) are produced in the pancreatic islets of Langerhans (PP), the large and small bowel (PYY), and peptidergic neurons of the stomach, small intestine, and central nervous system (NPY). PP secretion is primarily stimulated by protein intake and cholinergic activity. PYY secretion is stimulated by mixed meals and oleic acid. NPY functions as a neurotransmitter, with high concentrations in the arcuate nucleus of the hypothalamus. PP and PYY are postulated to play a role in satiety.

PP secretion in response to a protein meal has been reported to be deficient in PWS.[183,209,210] Short-term infusion of PP was initially reported to cause a mild inhibition of food intake in females with PWS[13]; however, a more detailed investigation indicated no effect.[208]

PYY levels have been reported to be low in non-PWS obese individuals, and PYY infusion causes a reduction in food intake.[9] PYY levels are reportedly low in PWS[29]; however, infusion studies have not been reported.

NPY activity in the hypothalamus is postulated to stimulate food intake.[199] Hypothalamic NPY neurons appear to be normal in PWS.[85] Serum levels of NPY are reported to be low-normal in adults with PWS and do not change with GH therapy.[108,109]

3. Hypocretins (orexins)

Hypocretins are neurocrine peptides that are postulated to stimulate feeding. Hypocretin-containing neurons in the lateral hypothalamus

are stimulated in response to hypoglycemia. Hypocretins are also postulated to play roles in regulating energy expenditure and sleep/wake cycles. In a study of hypocretin levels in relation to sleep disorders,[142] cerebrospinal fluid hypocretin levels were found to be normal in a 16-year-old with PWS. However, cerebrospinal fluid hypocretin levels were reported to be low in four patients with PWS, in association with daytime sleepiness.[154]

4. Agouti-Gene-Related Protein (AGRP)

AGRP production is co-localized with NPY in the hypothalamus. AGRP stimulates food intake by inhibiting the actions of melanocortin, an anorexigenic neurocrine peptide. AGRP expression was reported to be decreased in the neonatal mouse model of PWS, in which there is failure to gain weight (as with human PWS).[80] However, AGRP neurons appear to be normal in older individuals with PWS.[85]

5. Ghrelin

Ghrelin is a peptide released from cells in the stomach. The normal function of ghrelin is not completely defined. In both rodents and humans, serum ghrelin levels rise progressively during fasting and it is postulated that ghrelin provides a signal to initiate food intake. In agreement with this theory, pharmacologic administration of ghrelin to mice results in increased food intake. However, the ghrelin knockout (deficient) mouse has no apparent defect in appetite or any other body function.[178] Recent studies indicate that the hyperphagic effect of exogenously administered ghrelin in mice is mediated by NPY/AGRP neurons.[44]

Serum ghrelin levels have been reported to be elevated in individuals with PWS[29,48,51,84,92,109] and are postulated to contribute to the hyperphagia. However, examination of the data reveals that levels are not increased in all individuals with PWS (although hyperphagia is virtually universal) and mean levels are not significantly different from normal in some studies.[16] In addition, serum ghrelin levels appear to decrease appropriately in response to meals and somatostatin administration in PWS.[16,93] Therefore, as of this writing, the role of ghrelin in PWS pathophysiology is not known.

6. Opioids (endorphins)

Opioid peptides produced within the central nervous system function as neurotransmitters. In some cases, opioids may enhance intake of foods, particularly sugary foods, perhaps by inducing positive sensations.[199] Opioids have been postulated to play a role in various types of eating disorders, including PWS.[116] However, serum levels of beta-endorphin were found to be normal in children with PWS,[138] and administration of opioid inhibitors had no effect on food intake.[207,211]

7. Leptin

Leptin is produced by fat and appears to signal adequacy of energy storage back to the brain.[26,37,39,41,132] Except in those conditions involving genetic defects in leptin or leptin receptor expression, serum leptin

levels correlate directly with body fat.[202] In cases of genetic defects in leptin synthesis, the hyperphagia and other physiologic abnormalities are alleviated by leptin administration. However, it is not clear at this point whether pharmacologic administration of leptin to normal obese individuals, who have high leptin levels, will lead to significantly decreased food intake. It has been postulated that leptin functions primarily to signal energy deficiency rather than adequacy.

In PWS, leptin levels are increased and appear to be directly correlated with body fat.[26,37,39,158] Molecular defects of the leptin gene have not been identified in PWS.[33] Growth hormone therapy may decrease leptin levels in PWS; this effect is probably related to decreased absolute body fat.[59,111,148,205]

Energy Expenditure

Previous studies have described alterations in metabolic rate in individuals with PWS. Schoeller et al.[169] noted problems with use of common mathematical formulae to predict the basal metabolic rate (BMR) in adults with PWS and advocated use of the Cunningham BMR formula to adjust for the deficit in lean mass (FFM). Subsequent studies[100,188] have demonstrated a low basal metabolic rate with varied interpretation of data dependent upon the technique of body composition analysis. However, although resting energy expenditure may be normal or near-normal for lean mass, lean mass is deficient, leading to deficient expenditure for total body mass.[12,82,169]

Despite differences in body composition, energy expenditure during physical activity is similar to that of controls[151,152] when corrected for lean mass. However, individuals with PWS are less active than controls.[49,189] The combination of diminished BMR and activity level necessitates lower caloric intake or a significant increase in physical activity to avoid excessive weight gain.

Associated Morbidities

Body fat itself is rarely a direct cause of morbidity or mortality. Fat embolism is an example of direct fat-related morbidity, but this condition is not reported to occur with increased frequency in PWS. In PWS, the increased *proportion* of fat to lean mass (regardless of weight) is largely the result of decreased muscle mass. The resultant hypotonia is a major contributor to morbidity and mortality, as discussed in previous sections. As body weight increases above normal in PWS, the fat mass itself becomes problematic.

Body fat can contribute indirectly to pathophysiology in two ways: (1) complications due to a mass effect, i.e., in morbidly obese individuals, and (2) via metabolic complications related to fat.

The detrimental effects of excess body mass are well recognized. In particular, increased fat is associated with respiratory impairment and obstructive apnea. The sheer weight of excess fat in the presence of low muscle mass also contributes to impaired physical mobility and difficulty with daily tasks. Many adults with PWS adopt a typical hypotonic posturing, with both arms folded across the upper abdomen,

while others become wheelchair-dependent in young adult life. Increased fat mass may also theoretically exacerbate scoliosis and fragility fractures involving weight-bearing bones and joints (vertebrae and hips), but, on the other hand, increased weight may augment bone mineral density, as shown in non-PWS populations.[129]

Metabolic effects of increased body fat have been well defined in the general population. In non-PWS children, early puberty (particularly adrenarche),[163] accelerated linear growth, and advanced bone age can occur; final adult height is usually not adversely affected despite the accelerated physical development. Adrenarche is the portion of sexual development characterized by increased production of adrenal androgen precursors, which, in the peripheral tissues, are converted to testosterone and dihydrotestosterone. In normal puberty, adrenarche is responsible for secondary sexual hair growth in females; the effect of adrenarche is usually less notable in boys due to testicular production of testosterone. The hormones produced during adrenarche also cause acceleration of bone growth and epiphyseal closure. The physiologic control of the timing of adrenarche has not been defined; however, insulin resistance and hyperinsulinemia are associated with earlier onset.

In children with PWS, premature adrenarche occurs in a relatively small subset of cases[121,126,167] and is manifested by early (before age 8 to 9 years) appearance of pubic hair. Anecdotal experience suggests that the frequency of premature adrenarche is less than might be expected in a similarly overweight non-PWS population. In affected children, the increased linear growth rate due to adrenarche often replicates a normal, non-PWS growth rate (which is actually accelerated for PWS). Unfortunately, the end result is often extreme short stature due to premature epiphyseal closure, which is quite different from the normal stature attained by non-PWS children with obesity-related premature adrenarche. Therefore, "idiopathic" premature adrenarche cannot be considered to be a benign condition in PWS.

In older children, adolescents, and adults, obesity can lead to metabolic syndrome, also known as dysmetabolic or insulin-resistance syndrome (defined by various criteria, but generally including insulin resistance, overweight/obesity, dyslipidemia, and hypertension; all associated with increased cardiovascular risk), polycystic ovary syndrome, and Type 2 diabetes mellitus.[58] In non-PWS populations, insulin resistance and consequent morbidities have been specifically associated with increased abdominal visceral fat (as opposed to subcutaneous fat).

Glucose intolerance and Type 2 (also known as non-insulin-dependent) diabetes mellitus (T2DM) can occur in patients with PWS.[27,42,78,91,113,123,150,162,170,172,203] The usual case of T2DM in PWS is indistinguishable from non-PWS obesity-related diabetes, which is occurring with increasing frequency worldwide.[198] Unlike Down and Turner syndromes, there does not appear to be any unique risk for Type 1 (insulin-dependent) diabetes mellitus (T1DM) in PWS. In addition, no specific metabolic abnormalities have been identified in PWS to

suggest a unique predisposition to T2DM except for obesity.[21,136] A reduced amount of insulin receptors was noted in one report, but the clinical significance of this finding is uncertain.[120]

Recent data indicate that individuals with PWS may have a lower risk for insulin resistance and T2DM than would be expected based on the degree of overweight. Average fasting insulin levels are reported to be low in children and adults with PWS and there is a relative lack of clinical signs consistent with insulin resistance,[57,111,145,156,181,206] although some reports have found elevated fasting insulin,[125,155] and others have reported elevated fasting but decreased 2-hour postprandial insulin.[128] However, the bulk of evidence suggests that insulin levels are relatively low in most individuals with PWS, arguing against an increased frequency of insulin resistance. In addition, serum levels of adiponectin, a protein secreted by adipocytes that is thought to increase insulin sensitivity, are unexpectedly high in PWS,[110] whereas low levels are usually observed in non-PWS patients with obesity and insulin resistance.

In non-PWS individuals, insulin resistance syndromes and T2DM are part of a spectrum of disorders related to increased body fat and, in particular, intra-abdominal visceral fat[73,165] (as distinguished from subcutaneous fat). Lipid deposition in muscle and other body tissues may also be contributory.[114] However, in obese individuals with PWS, subcutaneous but not visceral fat has been found to be increased[83,182]; the mechanisms for this occurrence have not been defined. In addition, visceral fat characteristics for individuals with PWS and insulin resistance have not yet been reported.

Monitoring for signs and symptoms of insulin resistance and T2DM should be a routine element of care for all individuals with PWS. Some cases of T2DM may present with the classic symptoms of diabetes mellitus: polyuria, polydipsia, and, in some cases, unexpected weight loss despite continued hyperphagia. Ketoacidosis, obtundation, and disordered consciousness may occur in the most severe cases.[203] However, most individuals with insulin resistance or T2DM will be asymptomatic. A classic, but not universal, physical sign of insulin resistance is acanthosis nigricans: hyperpigmented, velvet-textured skin in the nuchal, axillary, inguinal, and other folds of the body thought to be due to direct or indirect effects of hyperinsulinemia on keratinocytes.[184]

Individuals suspected of having insulin resistance should be screened for associated morbidities, including dyslipidemia (fasting lipid panel) and hypertension. Diagnosis of impaired glucose tolerance (IGT) and T2DM should be made according to criteria of the American Diabetes Association[2]:

1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. FPG ≥ 126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 hours.

or

3. Two-hour post-load glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

Since criteria 1 and 3 do not require an elevated fasting glucose, and a 2-hour oral glucose tolerance test may not always be feasible, some practitioners utilize a random glycated hemoglobin or hemoglobin A1c measurement to screen for clinically significant glucose intolerance and diabetes mellitus.

Treatment

Nutritional management of PWS can be separated into four major areas of concern:

1. Control of under- and overweight
2. Optimization and conservation of lean mass
3. Special nutritional considerations
4. Treatment of obesity-related morbidities

Evolving clinical needs for the individual with PWS requires adaptation of nutritional support. During infancy, diminished muscle tone affects the volume of caloric intake during feedings. A variety of techniques are available for nutritional support of the infant with PWS including adaptive feeding bottles and nipples (e.g., Haberman feeder, cleft palate nurser, adaptive nipples), thickening agents (Thick-It, cereal), formula concentration, and nasogastric tubes. The feeding therapy utilized is determined by the adequacy of swallowing skills, and nutritional status.

Nasogastric and gastrostomy feedings are commonly used to meet the nutritional needs of infants with PWS. Gavranich et al.,[79] reported use of tube feedings for a mean of 8.6 weeks among 67% of infants with PWS in New South Wales. Since gastrointestinal absorption and motility are essentially normal, intravenous total parenteral nutrition is usually not required. In infants receiving feedings primarily through a non-oral route, oral feedings as tolerated and non-nutritive sucking should be continued to encourage development of oromotor strength and coordination.

Intake parameters during infancy can be patterned along guidelines from the Nutrition Committee of the American Academy of Pediatrics.[47] During the first 6 months of life, breast milk and infant formula should serve as the primary nutritional source and should be given in usual amounts. Solids are generally introduced at 5 to 6 months of age and advanced in texture, dependent upon oral motor skills. Higher-calorie solids, desserts, and juices are commonly avoided. Through close monitoring of growth data over the first 2 years, oral intake can be appropriately adjusted to maintain weight for height between the

25th and 80th percentiles. Caloric restriction under the guidance of an experienced nutritionist or other health care provider is required, with supplementation of deficient vitamins and minerals, if weight gain becomes excessive.

Nutritional strategies beyond the toddler years focus on avoidance of overweight. Limited studies[106,159] have evaluated the caloric requirements for individuals with PWS. Weight maintenance has been reported with intakes of 8 to 11 kcal/cm/day (non-PWS children require 11–14 kcal/cm/day; cm = height); weight loss has been documented with intakes of 7 kcal/cm/day. Sample calorie guidelines, adapted from guidelines published by PWSA (USA) [17] are listed in Table 6.1. It should be noted that while these guidelines are based on logical criteria, there are no prospective data regarding efficacy. In addition, these guidelines may be excessive for children who are unusually inactive and, conversely, inadequate for children with PWS receiving growth hormone therapy.

Similar guidelines have not been specifically formulated for adolescents and adults with PWS, although a general recommendation has been 800 to 1,000 kcal/day for weight loss. These calorie guidelines are a significant reduction from usual food intake in the general population; therefore, the individual with PWS will probably need to have different food preparation and provision from the rest of the household.

A typical approach to a calorie-restricted weight control treatment plan is to introduce a "balanced" calorie reduction, with maintenance of the usual carbohydrate-protein-fat proportions (i.e., 60%-15%-25%, respectively). Emphasis on low-glycemic-index carbohydrates (i.e., slowly-absorbed complex carbohydrates rather than, for instance, high sugar foods) may also reduce insulin secretion, facilitate optimal nutrient utilization and have a positive effect on satiety,[135] although these effects have not been studied in individuals with PWS.

Adherence to a calorie-restricted diet requires intensive and continuous monitoring of intake and regular dietary counseling, including analysis of food histories and attention to possible associated nutrient

Table 6.1. Sample Calorie Guidelines

Age (yr)	Average Height (cm)	Weight Maintenance (kcal/d)	Weight Loss (kcal/d)
Female			
3	**89**	**700–980**	**630**
5	**102**	**800–1120**	**720**
7	**112**	**880–1232**	**790**
9	**135**	**1060–1484**	**954**
Male			
3	**94**	**740–1036**	**660**
5	**107**	**840–1176**	**760**
7	**119**	**940–1316**	**845**
9	**122**	**960–1344**	**864**

deficiencies. Behavioral aspects of this plan require attention to all potential sources for intake including cafeterias, school buses, classroom activities ("life skills"), vending machine access, neighbors, and convenience stores as well as home access (e.g., pantry, garbage cans, refrigerator, tabletop). Locks on kitchen doors and refrigerators are often recommended elements of this plan. More detailed discussions of behavioral and environmental management strategies appear elsewhere (see Chapters 12 and 18).

There is no doubt that total calorie restriction will achieve weight maintenance or loss if completely implemented; however, it remains unresolved as to whether this approach is justified in view of the physiology. As mentioned above, there is growing consensus that the food foraging and apparently insatiable appetite in PWS may be triggered by internal mechanisms that more closely resemble true starvation than non-PWS pre-meal hunger or eating behavior. If this is true, then the intentional restriction of all intake could have detrimental effects on overall behavior and well-being and may, in fact, augment foraging and food-sneaking behavior. This hypothesis has not been tested, although it appears to hold some validity on review of anecdotal patient experience.

An equally important issue relates to adverse effects on body composition. Although increased body fat and overweight is a major visible morbidity in PWS, a more crucial functional morbidity is the lack of lean mass. In non-PWS individuals, induction of an energy deficit (e.g., fasting, total calorie restriction) and weight loss using a balanced nutrient intake results in loss of not only fat mass, but also lean mass. In addition, the lower the total calorie intake, the higher the proportion of lean mass lost. In non-PWS individuals, excess body fat will provide a relative protection against loss of lean mass (i.e., thinner individuals lose proportionately more lean mass than obese individuals during weight loss).[77]

As stated by Dr. Gilbert Forbes, a pioneer in this field of research, "There is no level of reduced energy intake that will completely spare LBM [lean body mass] when significant amounts of body weight are lost."[75] In individuals with PWS, where total lean mass is deficient even in the presence of overweight, there is no reason to suspect that a balanced calorie restriction diet will result in preservation of absolute lean mass.

However, lean mass can be at least relatively preserved during calorie deficit by preferentially preserving protein intake. The initial observations of this phenomenon preceded the currently popular low-carbohydrate, increased protein diets.[75] In a short-term metabolic unit study in four patients with PWS, a protein-sparing (1.5 gm of meat protein per kg body weight), ketogenic, modified fast preserved positive nitrogen balance and lean body mass in the presence of significant weight reduction.[15] A similar nutritional approach in an obese ventilator-dependent adolescent with PWS apparently facilitated weight management and weaning from the ventilator.[45]

In addition to potential effects on preservation of lean mass, protein may have a greater positive effect on satiety than carbohydrates or fat,

as demonstrated in both short- and long-term human studies.[5,25] Although this effect has not been investigated in individuals with PWS, it was postulated to occur in outpatient follow-up of patients involved in the previously mentioned study using a protein-sparing fast.[15]

A ketogenic protein-sparing fast is probably not practical for most individuals with PWS. However, several other approaches to high-protein, lower carbohydrate meal planning are available. Popular diets using this approach typically result in 28% to 35% calories from protein, 8% to 40% from carbohydrate, and the remainder from fat.[5] One of the authors (PDKL) has prescribed modified lower-carbohydrate, lower-fat guidelines in his PWS clinics for several years, an approach which is similar to other, perhaps more stringent regimens.[5,146,147] The basic five-step approach is as follows: (1) elimination of sugar and all packaged foods containing >5 g sugar per serving, (2) limitation of complex carbohydrates to one to two servings three times daily, with one serving = 15 gm of carbohydrate, (3) avoidance of fried and fatty foods, (4) encouragement of lean protein intake, and (5) provision of "free foods"—i.e., carb-free, low-fat, low-calorie—for ad lib snacking and/or foraging. In addition, an exercise guideline of 30 minutes sustained activity, three to five times weekly is recommended. This regimen is provided as a one-page guideline and reviewed during clinic visits. For most individuals, adherence to this simple plan results in a substantial reduction in total calories. This approach has the advantages of being easy to learn (requires teaching of food label readings and basic carbohydrate counting), relatively straightforward implementation, and possible integration into usual household eating patterns. More structured dietary regimens can be added to this basic program for individual patients.

Whatever dietary approach to weight control is taken, it is important that it be logical, consistent, easily implemented, emphasized at each clinic visit, and carefully monitored. Modifications should be made for individual patients, and in children developmental changes should be taken into account.

Pharmacologic agents for weight management should be considered as adjuncts and not primary treatment modalities. None of the appetite suppressant or antiabsorptive agents marketed for obesity treatment have shown efficacy in PWS, and systematic studies have not been published. Some of the psychotropic agents commonly used in PWS have been anecdotally reported to control food-foraging behavior, but exacerbation of overeating has also been observed.[118] Anecdotal reports indicate that growth hormone therapy may have a beneficial effect on eating behavior, but this has not been demonstrable in objective studies. In a short-term uncontrolled trial, the anti-epileptic medication, topiramate, was reported to improve eating and other behaviors in seven patients with PWS, resulting in weight loss in three[175]; however, several of the subjects were on concomitant medications and the overall results were not entirely conclusive.

Personal experience and one report[42] indicate that metformin may have efficacy for weight control in PWS when coupled with dietary management, particularly with carbohydrate limitation. Similar results

have been reported in treatment of non-PWS obesity.[6,146,147] The mechanism(s) of action for metformin in weight management have not been completely elucidated, although an anorectic effect has been demonstrated in animal studies.[112]

Surgical options for weight management are not generally recommended in PWS. Bariatric surgery causes weight loss through either a diminished capacity for food intake and/or via reduced digestion and absorption of food. In non-PWS obesity, studies in adolescents and adults show efficacy in promoting weight loss, although surgical risks, gastrointestinal problems, and malabsorption are a concern.[71]

Experience with bariatric surgery in PWS has been less encouraging, as summarized in Table 6.2, although relatively long-term success has been reported in selected patients.

There is no apparent effect of bariatric surgery on hyperphagia in PWS. Therefore, the need for dietary intervention and monitoring is not eliminated. Over the long-term, weight gain may recur after the patient develops compensatory dietary strategies. At the current time, bariatric surgery should be considered only in severe cases in which serious obesity-related morbidities are present and rapid weight loss is considered to be potentially beneficial.

Special Nutritional Considerations

Vitamin and mineral supplementation is highly recommended for individuals with PWS and particularly for those on a balanced, calorie-restriction diet. For example, the sample calorie guidelines from PWSA (USA)[17] listed in Table 6.1 are deficient in calcium, iron, vitamin D, vitamin E, biotin, pantothenic acid, magnesium, zinc, and copper; multivitamin and mineral supplementation is recommended in the publication. In addition, many individuals with PWS have limited sun exposure, especially those affected with hypopigmentation. Since a large proportion of the body stores of vitamin D are synthesized in response to sunlight, lack of sun exposure can result in vitamin D deficiency and an increased risk for osteoporosis.

As a general rule, it is recommended that all patients with PWS receive daily multivitamin and mineral supplementation in consideration of their individualized meal plan and sun exposure. An over-the-counter preparation may be adequate for many patients. Others may require additional monitored supplementation with calcium, trace minerals, and vitamins. Trace mineral, iron, and fat-soluble vitamin supplementation should be carefully monitored to avoid overload.

Obesity-Related Morbidities

Premature Adrenarche

In children without PWS, premature adrenarche is usually a benign condition that does not require specific therapy; indeed, specific therapies have not been proven to have efficacy.[163] In some cases, premature adrenarche may be associated with early central puberty, which may require treatment. As mentioned previously, premature adrenarche in

Table 6.2. Bariatric Surgery in Prader-Willi Syndrome

Reference	Type of Surgery	No. of Patients	Median Age	Median Weight	Success Rate	Complications
Soper et al. (1975)[176]	Gastroplasty	7	15 yrs	92.5 kg	43%?	57% required revisions due to inadequate weight (wt) loss
Anderson et al. (1980)[4]	91% Gastric bypass 9% Gastroplasty	11	13 yrs	85 kg		• 54% required revision due to inadequate wt loss • 1 (9%) wound infection • 1 dumping/diarrhea • 1 death from uncontrolled wt gain
Fonkalsrud and Bray (1981)[74]	Vagotomy	1	17 yrs	120 kg	29 kg initial wt loss, followed by 20 kg gain	20-kg weight gain
Touquet et al. (1983)[185]	Jejunoileal bypass	1	24 yrs	181 kg	62 kg (1 yr)	• Postoperative wound infection • DVT/pulmonary embolus • 4–5 stools/day
Laurent-Jacard et al. (1991)[124]	Biliopancreatic diversion	3	27.6 yrs	84.5 kg	Significant wt loss 1st year, followed by wt gain (2½–6 yrs)	• Diarrhea • Vitamin D, vitamin B_{12}, folate, and iron deficiency

Dousei et al. (1992)[53]	Vertical banded gastroplasty	1	21 yrs	57.4 kg	Initial improved DM control	Short-term wt loss followed by break of staple line and wt gain
Chelala et al. (1997)[43]	Laparoscopic adjustable gastric band	1	?	?		Death 45 days postoperatively from GI bleeding
Grugni et al. (2000)[88]	Biliopancreatic diversion	1	24 yrs	80 kg	Initial wt loss, but wt gain without restriction	Diarrhea, severe osteopenia, anemia, hypoproteinemia
Marinari et al. (2001)[139]	Biliopancreatic diversion	15	21 yrs	127 kg	56%–59% wt loss at 2–3 yrs, then regained 10%–20% of wt lost	2 deaths from unrelated causes (no vitamin levels or bone density data provided)
Braghetto et al. (2003)[19]	95% gastrectomy with Roux-en-Y, hypocaloric diet	1	15 yrs	BMI = 57.7	70 kg weight loss over 1 yr; BMI = 30	No surgical complications reported
Kobayashi et al. (2003)[117]	Roux-en-Y gastric bypass	1	30 yrs	146 kg	54-kg weight loss over 18 mos, improved lipid profile	No complications

children with PWS is not a benign condition since it is associated with severe short stature and an inadequate increase in height velocity.[126,167] Although obesity is thought to be pathogenetic for this condition, there is no evidence that intensive weight control after onset will slow the progress of the adrenarche. Prevention of predisposing factors for premature adrenarche via weight management beginning in very early childhood is the best recommendation at this point. In cases where the process has already started, growth hormone therapy should be considered even if current height is normal in order to optimize final adult height.

Insulin Resistance and Type 2 Diabetes Mellitus

The treatment of insulin resistance and T2DM in PWS should follow current standard-of-care guidelines for these conditions in the non-PWS population. A comprehensive discussion of this topic is beyond the scope of this chapter; the reader is referred to the current literature and healthcare organizations for more detailed protocols (e.g., American Diabetes Association, American Association of Clinical Endocrinologists).

In general, the first-line approach should include diet and exercise, as described above for treatment of obesity and overweight; in milder cases, these therapies may lead to complete resolution of the disorder. Metformin should be considered a first-line pharmacotherapy for insulin resistance, especially if T2DM is present.[42,112] Insulin may be necessary in cases where there is evidence of insulin deficiency (ketoacidosis, unexplained weight loss) but should be avoided in all other cases since it may augment increases in body fat. Sulfonylureas and PPAR-agonists also have a tendency to increase body fat, and the efficacy of these agents in individuals with PWS and T2DM has not been shown. The authors' anecdotal experience suggests that diet, exercise, and metformin are sufficient for treatment of most individuals with PWS and insulin resistance and/or T2DM.

Monitoring of patients with insulin resistance and T2DM should include periodic evaluation of fasting lipid profiles and blood pressure. Fasting insulin levels can be checked periodically, but the clinical utility of this measurement, which can be highly variable, is not defined. Clinically, weight, calculated body mass index, waist circumference, and status of acanthosis nigricans (if present) can be useful.

Individuals treated with metformin should have routine annual monitoring of liver and kidney function tests; an elevated serum creatinine level is a contraindication to therapy. With T2DM, routine home monitoring of fasting and postprandial glucose levels and periodic glycated hemoglobin measurements are necessary, with an optimal goal of achieving normal levels for both parameters.

There have been surprisingly few reports of diabetes-related complications in PWS.[8,192] However, individuals with diabetes mellitus should be routinely monitored for evidence of retinopathy, nephropathy, hypertension, and cardiovascular disease, with institution of appropriate therapy as needed as per general standard-of-care practice guidelines.

Measurement of Body Composition

The measurement and monitoring of body composition has become an essential element in clinical research and management of individuals with PWS. In particular, body composition measurements may be used to diagnose decreased bone mineral density (osteopenia, osteoporosis) and monitor changes in total body fat and nonfat mass.

Anthropometry

Anthropometry refers to body measurements, such as length or height, weight, circumferences, and skinfold thickness. Although anthropometric techniques (weight-for-height indices, skinfold thickness, waist-to-hip ratio) have been used for many years to indirectly estimate body composition, these techniques are less commonly used for that purpose today. Instead, if detailed body composition analysis is needed, more sophisticated models and techniques are used, as discussed below.

Height growth is an essential feature of human development and should be measured for all children at regular intervals. The measurements should be plotted to the nearest fractional age on charts compiled from the background normal population. Such charts are available for the U.S. pediatric population from the U.S. Centers for Disease Control (www.cdc.gov). Standards for most other industrialized countries are available. Children under 2 years of age should be measured using recumbent length, which is the basis for these standards. Height velocity charts are also available. Procedures for accurate measurement and calculation of height and velocity are also described on the CDC Web site.

Height growth is basically a measure of long bone (leg, spine) growth, which in turn is dependent on a number of genetic, hormonal, structural, and mechanical factors. Abnormal height growth in children can be the first sign of a systemic abnormality. As mentioned previously, height growth in children with PWS is highly variable but usually abnormally low starting at or before the toddler stage. As shown in several population studies, the average final adult height in PWS is at approximately 2 standard deviations below the mean for the background population.[1,22,36,97,123,149] Scoliosis, if present, may also account for loss of height growth.

Weight is basically a measure of total body mass, regardless of composition. As a stand-alone measurement, it has little intrinsic utility, even if plotted on normative curves. However, the clinical value of a weight measurement is increased when analyzed in conjunction with height, that is, in determination of weight-for-height or body mass index. Assuming that fat and lean mass are present in a predictable proportion (see previous discussion regarding "companionship rule" above), these ratios can provide a measure of body fatness (normative charts available on www.cdc.gov). However, in conditions where there is an excess proportion of lean mass (e.g., body building) or deficient lean mass/excess fat mass (e.g., PWS), these ratios do not provide an accurate estimation of body fat.

Anthropometric measurements for head circumference, hand and foot length, and other body parts have been published for PWS[28,32,34–36,65,141,196] (see Appendix C). Head circumference measurements are primarily used as an indicator of brain growth in infants and toddlers under 3 years of age. Careful monitoring of head growth is also important for detection of craniosynostosis, premature closure of the cranial sutures resulting in severe neurologic sequelae. One such case in PWS has been published,[66] and the authors are aware of other cases.

Waist circumference and waist to hip circumference ratios have been used to indicate visceral fat and consequent risks for T2DM and cardiovascular disease in non-PWS adults. However, this correlation is likely to be less reliable in PWS since visceral fat may not be increased.

Skinfold thicknesses, measured using calipers at selected body sites, are sometimes used to estimate body fat and non-fat mass. Skinfold thickness is basically a measure of subcutaneous fat. Using assumptions and validated algorithms regarding the proportions of subcutaneous fat to other body compartments, fat and lean mass can be estimated. Although skinfold thickness measurements have been used in several key studies of PWS,[30,54,96] inter-observer variability and lack of validated disease-specific (including PWS) standards and algorithms are major limitations to routine clinical use.[193]

Body Composition Modeling

The first step in determining body composition is to select a model that provides clinically relevant measurements (Figure 6.3). The most extreme form of body composition analysis, elemental or chemical

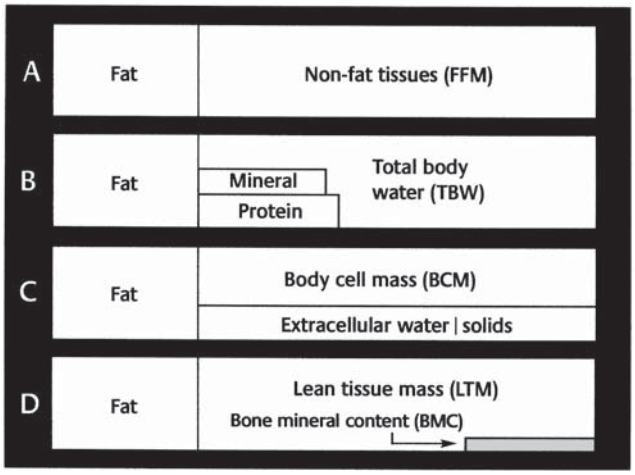

Figure 6.3. Multicompartment models of body composition. **A.** Basic 2-compartment model, weight = Fat + FFM (fat-free mass). **B.** Water, protein, and mineral subcompartments of FFM. **C.** Body cell mass and extracellular water and solids subcompartments of FFM. **D.** 3-compartment dual-energy X-ray absorptiometry (DXA) model.

analysis after ashing, is primarily of research interest since it is not feasible in an individual living organism. Elemental analysis can be also performed *in vivo* using isotope counting and neutron activation methods[62]; these measurements currently have limited clinical utility and will not be discussed.

The simplest clinically useful model of body composition, the 2-compartment (2-C) model, divides total body mass or weight (Wt) into fat mass (FM) and fat-free mass (FFM). Body fatness, in turn, can be defined as the FM/Wt ratio, expressed as a percentage. The basic 2-C model requires only one measurement to be made and is the easiest to use when the assessment of body fatness is the primary aim.

More detailed clinical models,[194,195] particularly for considering issues related to nutrition or growth, separate the FFM into components, creating a multicompartment model (Figure 6.3). A useful multicompartment model separates FFM into water and/or protein (muscle) and mineral (bone) subcomponents. Direct assay of FFM components is difficult but has been facilitated by recently developed imaging techniques. These sophisticated techniques, such as dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI), allow us to view the components of the living body.[52]

In the following sections of this chapter, the various methods that are available will be described in the context of their application in 2-, 3-, and 4-compartment models of body composition.

Methods Based on the 2-Compartment (2-C) Model

Underwater Weighing: For the 2-C model, Wt = FM + FFM, and $Vol_{TB} = Vol_{FM} + Vol_{FFM}$ (Total body volume = FM + FFM volumes). An accurate measurement of body weight is relatively easy to achieve, i.e., using a weight scale; the measurement of body volume is more challenging.

The classic technique of measuring body volume, underwater weighing (UWW, or hydrostatic weighing) relies on Archimedes' principle, which states that a body immersed in a fluid is buoyed up by a force equal to the weight of the displaced fluid. The procedure involves measuring body weight while totally submerged underwater, after exhalation of air from the lungs. The body volume is calculated by subtracting the underwater weight from the regularly measured body weight, the weight differential being equal to the weight of displaced water, and dividing the difference by the density of water. This number is adjusted for the measured residual lung volume.

The density of the body (ρ_{TB}) is the ratio of body weight (Wt) to body volume (Vol_{TB}). The classic UWW relationship between body fatness (%FM) and body density (ρ_{TB}) for a 2-compartment model is

$$\%FM = 100 \times \{(k_1/\rho_{TB}) + k_2\}$$

where the constants (k_1, k_2) are determined by the values selected for ρ_{FM} and ρ_{FFM} (densities of the fat and fat-free mass).[24,173] The density of fat can be assumed to be constant (0. 9004 g/cc), whereas the density of FFM is not constant, changes with growth,[134] and is altered by diseases and medications. Since body water is the major contributor to the

mass and volume of the FFM, changes in the relative water content (hydration) will have significant effects on ρ_{FFM}. Other components of the FFM can also change, but these have a secondary impact compared with hydration.

For short-term longitudinal studies in healthy subjects, using age- and gender-adjusted constants, the 2-C model is adequate for the assessment of changes in body fatness. However, it does not provide information about components of the FFM.

Air-Displacement Plethysmography: There can be several reasons why the underwater weighing technique cannot be used, e. g., lack of necessary equipment, fear of water, difficulty breathing underwater, too buoyant to be easily submerged. An alternative technique called air-displacement plethysmography (ADP) can also be used to measure body volume. The advantage of ADP is that the problems related to water are eliminated, although the subject still needs to wear a tight-fitting bathing suit and cap to cover scalp hair. The objective is to determine the volume of air that is displaced by the subject's body.[68,134] At present, there are only two commercial ADP instruments available (BODPOD for adults and PEAPOD for infants, Life Measurements Inc., Concord, Calif.).

The ADP technique is based on Boyle's Law for gases: pressure multiplied by volume is constant if temperature does not change. Poisson's Law for gases is also used in order to adjust for the subject's breathing (heated moist air coming from the lungs) and for the isothermal effects of air in contact with the subject's skin and body hair.

For the BODPOD measurement, the subject sits on a bench in a small test chamber that is about the size of a telephone booth. This chamber is connected via a diaphragm to a reference chamber behind the bench. The door (which has a large window) is closed, the diaphragm is oscillated at a low frequency, and the pressure difference between the two chambers is measured. The BODPOD instrument also has a built-in spirometer system that can be used to measure the subject's residual lung volume. It should be noted that without preliminary training, the spirometer procedure can be difficult for some subjects to perform correctly.

ADP estimates of body volume are highly correlated with those for UWW, and the two results are virtually interchangeable for healthy adults.[68] Additional studies with children may be needed, especially where body composition may be abnormal. However, it is reasonable to expect that the ADP technology may replace the underwater weighing technique for 2-C analysis in adult and pediatric populations.

Total Body Water and Potassium: Two alternate methods can be used in a 2-C model to estimate body fatness by measuring body water and cellular components of the FFM. The body composition parameters that are measured for these methods are total body water (TBW) or total body potassium (TBK), respectively.[60,62]

For these two assays, the simple 2-C equations for body fatness are as follows:

$$\%FM_{TBW} = 100 \times (Wt - TBW/k_3)$$

$$\%FM_{TBK} = 100 \times (Wt - TBK/k_4)$$

where the values for k_3 and k_4 are assumed to be relatively constant at a given age for a healthy subject. However, during infancy and childhood, the relative hydration and potassium content of the total FFM are not constant, and they may also be altered by disease and/or medications.[60] That is, the same limitations that were possible for the 2-C UWW or ADP models are also present for the 2-C TBW and TBK models. This is an inherent limitation of the 2-C model and not the methods. An advantage of the TBW and TBK assays, compared with UWW or ADP, is that these assays provide useful information on their own about the composition of FFM.

For the TBW assay, the subject drinks a small amount of isotope-labeled (non-radioactive) water. Several hours later, a body fluid sample (blood, urine, or saliva) is collected and stored for later analysis using isotope-ratio mass spectroscopy (MS) or Fourier-transformed infrared spectroscopy (FT-IRS). Since the amount of the tracer given to the subject is known, and its concentration in the water part of the fluid sample is measured, the total volume of the dilution space can be easily calculated.[168] The value for the conversion constant (k_3) that is used most often is 0.732 for older children and adults, gradually increasing to 0.83 for infants. That is, FFM contains, on average, about 73.2% water for healthy children and adolescents. This percentage, however, may be altered with diseases, such as severe malnutrition or edema, and by some drugs. A clear advantage of the TBW technique is that bulky instrumentation is not needed at the times of isotope administration and sample collection, thus making it a suitable choice for field studies. The MS or FT-IRS analysis could be performed immediately, but the usual practice is to collect multiple samples for batched analysis, thus the TBW results are often delayed until some time after the actual procedure.

The results of the TBK assay, on the other hand, can be obtained immediately. This assay takes advantage of a natural signal that is being constantly emitted from the potassium in the human body. A small fraction of natural potassium is radioactive (^{40}K), emitting characteristic gamma rays (1.46 MeV) at the rate of about 200 gammas per minute per gram of potassium. This signal can be detected external to the body using a whole-body counter,[63] usually a whole-room shielded counting chamber. Based on numerous studies over the past 40 years, the values for the conversion constant (k_4) are estimated at 59 to 61 mEq/kg for adult females and 62 to 64 mEq/kg for adult males. For infants, the ratio is reduced to ~43 mEq/kg because of increased hydration.[60,61] A major limitation with this assay is that the measurement instruments are not portable, and the number of available instruments and facilities is very limited. However, it is well recognized that the TBK assay is the best choice for monitoring body cell mass (BCM), the active metabolizing tissues of the FFM.[60] In many diseases, knowledge of the patient's BCM status has a higher priority than knowledge of body fatness.

Bioelectrical Impedance: The bioelectrical techniques for assaying body composition were developed as alternatives to the isotope dilution assay of total body water. The attractiveness of this technology is that the instruments are small in size, relatively inexpensive, don't require extensive operator training, and the results are immediately available. The principle of the bioelectrical impedance technique is that the body has general electrical properties, which primarily reflect the volume of the FFM and its electrolyte content.[90] Three approaches have been developed for human use: (1) single frequency (50 kHz) bioelectrical impedance analysis (BIA), (2) multifrequency (5–1000 kHz) bioelectrical impedance spectroscopy (BIS), and (3) total body electrical conductivity (TOBEC).

For the BIA and BIS procedures, pairs of electrodes are attached at the hand and foot. A weak electrical current is passed between the electrodes, and resistance (R) and reactance (Xc) are measured. The BIA assay uses a single frequency (50 kHz), while the BIS technique varies the frequency (5–1000 kHz). The basic BIA and BIS theory results in the assumption that the Ht^2/R ratio is directly proportional to TBW or FFM.[10] Some BIA instruments have been designed to measure only the upper body (electrodes placed on the hands) or lower body (subject stands in the electrodes), while other investigators have chosen to perform segmental BIA measurements (placing multiple electrodes at many sites on the body).

There are at least 30 single-frequency BIA devices commercially available. Unfortunately, there are almost an equal number of algorithms to choose from for the calculation of TBW, FFM, or %FM. Furthermore, some investigators have suggested that disease-specific calibrations of BIA should be used.[191] Although this approach may, at first, appear attractive, this type of "work around" simply avoids the more difficult issues related to the limited accuracy of the basic BIA theory and algorithms.

For the total body electrical conductivity (TOBEC) assay, no electrodes are placed on the body. Instead, the body passes through a large diameter electrical coil. The free charge particles in the body will attempt to align with the external magnetic field within the bore of the coil, causing a small measured perturbation in the coil current. The procedure takes only a few minutes to perform, and can be repeated as frequently as needed without risk to the subject.

Similar to the BIA and BIS assays, the TOBEC technique is a secondary assay, which means that the measured value (called the TOBEC number) must be calibrated with a more direct assay of FFM or TBW. A limitation with the TOBEC instrument is that it is very large compared with the BIA and BIS devices; hence it is not portable, and its initial cost is substantially higher. Thus, the number of TOBEC instruments worldwide is extremely limited, as with those based on the TBK technique.

Methods Based on the 3-Compartment (3-C) Model

Body Density + TBW: As pointed out for the 2-C density models (UWW and ADP), the major limitation was the assumption that TBW was a

fixed percentage of the total FFM. This constraint can be overcome by using a 3-compartment (3-C) density model where the measurement of TBW is included. In this case, the %FM equation becomes:

$$\%FM = 100 \times \{(2.118rTB) - 0.78\ TBW/Wt - 1.354\}$$

where the density of body fat and solids are 0. 9004 g/cc and 1.565 g/cc, respectively. The advantage of this model is that the hydration state of the FFM can be variable, without introducing additional error in the estimate for body fatness. The disadvantage is that two assays (UWW or ADP *and* TBW) are needed, which increases the complexity and decreases feasibility of the procedure.

Dual-Energy X-ray Absorptiometry: Absorptiometric techniques were developed in the 1960s to examine bone because of the concerns that astronauts would experience significant bone loss during space flight. Over the last 40 years, significant advances have been made with this technology, evolving into the current technique, called dual-energy X-ray absorptiometry (DXA).[62] DXA assays of the hip and spine have become the clinical standards for the assessment of bone mineral density, used to screen for the increased risk of bone fractures, especially in postmenopausal women. In addition, a whole body DXA can be obtained in approximately 3 minutes with a very low total radiation dose (<10 μSv).

During a DXA procedure, the subject lies supine on the exam table, clothed but with removal of metal objects. An X-ray scanning arm passes over the selected body parts or the whole body. The X-rays are attenuated during passage through body tissues. The net signal is detected, converted into pixels, and analyzed using algorithms. For diagnosis and monitoring of osteoporosis, the scan is usually limited to the hip and/or lumbar vertebral spine, which are sites that are prone to osteoporotic fragility fractures. For more complete body composition analysis, a whole body scan is obtained.

In order for DXA to provide a quantitative measure of bone, the physics requires that the density of the overlying soft tissue must be known. This is accomplished by analyzing the nonbone pixels in the image next to the bone-containing pixels for their relative fat-to-lean content. Thus, a whole-body DXA scan can be used to produce a quasi-3-compartment (3-C) model: bone mineral content (BMC), fat mass (FM), and nonbone lean tissue mass (LTM). The sum of the bone-containing pixels provides a measurement called the bone area (BA), and areal bone mineral density (BMD) is defined as BMC/BA. It is to be noted that the DXA-derived BMD (g/cm^2) value is not true bone density (g/cm^3) but a projection of the total body mass onto a 2-dimensional or plainer image of the body.

A clear advantage of whole-body DXA is that the body scan image is divided into 10 general regions (head, arms, legs, trunk, pelvic, spine, etc.) with BMC, BMD, fat, and LTM calculated for each region. Thus, not only can the body FM be examined but also its regional distribution. Although this information is useful, it does not, for example, distinguish between subcutaneous fat and visceral fat stores in the body.

Methods Based on Body Imaging Techniques

To obtain precise body composition information, anatomical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are used. The CT technique uses collimated beams of X-rays that are passed through the body, and an array of detectors is positioned on the opposite side of the body to detect the transmitted signal.[62] The X-ray source and detector assembly are rotated as a single unit around the body, and the data are collected and reconstructed to generate a cross-sectional image or "slice" of the body for each rotation. The physics of the CT procedure makes it a quantitative assay, i.e., the relative density (g/cc) of each pixel in the cross-sectional image can be obtained. Thus, anatomical regions such as the subcutaneous adipose tissue (SAT) layer, muscle, skin, internal organs, bone, and visceral fat deposits (VAT) can be identified. A disadvantage with routine CT imaging is that the radiation exposure is higher than that needed for a DXA scan, and whole body or extensive regional scans are not feasible.[23] The image requirements for a clinical CT scan can be relaxed when it is used for body composition analysis, such as for determination of VAT and SAT, which reduces the dose significantly.[177]

Magnetic resonance imaging (MRI) also provides internal images of the body, which tend to be superior in anatomical quality to those obtained using CT. One can easily identify the subcutaneous and visceral fat areas, for example, in an abdominal MRI image. However, the quantitative quality of the MRI image is much less than that obtained with the CT scan, and a whole body MRI can take up to 10 times longer to perform than a DXA. On the other hand, the MRI technique has several advantages, including the ability to distinguish VAT and SAT, and the system can be tuned to respond specifically to lipids contained within the lean tissues.[137,166] This may help to better understand the association of excess adiposity with some chronic diseases, such as T2DM.[114]

Methods Selection

The pathogenesis of PWS involves alterations in body composition that are atypical for human physiology and pathophysiology. In particular, there is an inherent increase in fat mass that is disproportionate to lean mass regardless of weight. The distribution of this fat mass could be relevant to defining cardiovascular risk. Lean mass is extremely deficient, as reflected in the hypotonia and decreased spontaneous activity. Finally, bone mineral density tends to be low, particularly in older individuals with PWS, increasing the risks for osteoporosis and fragility fractures. Given these considerations, body composition monitoring is an important element of clinical care for individuals with PWS. However, the selection of methods can be confusing.

As discussed above, there are a number of techniques that can be used to examine human body composition,[62] each with its own sets of advantages and disadvantages. Two-compartment (fat, nonfat) and 3-compartment (fat, bone, nonbone lean) models have been the most

popular and clinically feasible. Higher-level models may provide a more complete picture of body composition, but multiple assays are required, some of which are not routinely found in most institutions.

In terms of 2-compartment models, the BIA technique has become widely available partly because it is relatively easy to perform, requires minimum investment, and is portable (for field studies or bedside use). Unfortunately, the body composition results are often not much better than those obtained using anthropometric measurements, such as body mass index calculations or skinfold measurements.

For more accurate 2-compartment modeling, air displacement plethysmography (i.e., using the BODPOD instrument) offers an attractive alternative to the more difficult underwater weighing technique.[68] However, the feasibility of this procedure in PWS has not been tested. In addition, although the methods for 2-compartment modeling are designed to measure fat-free mass (with fat mass calculated as the residual), they have the disadvantage of not providing additional information regarding the nonfat component (i.e., bone and nonbone lean mass).

Table 6.3 summarizes key considerations for body composition measurement methods, classified by the measured component. Costs are based on 2004 U.S. estimates. Precision and accuracy of each method are listed, as well as the minimal detectable change.

For practical purposes, the DXA procedure has become the reference method for the clinical assessment of bone mineral. This clinical acceptance of DXA, and its accessibility at many institutions, is also driving the use of this technique as a reference for the measurement of body fatness and lean mass. For patients with PWS, the DXA procedure has the additional advantages of rapidity, minimal patient cooperation requirements, and provision of measurements for all three clinically relevant body compartments. The 1% to 3% analytical precision of the DXA method allows detection of relatively small longitudinal changes in bone, fat, and nonbone lean tissues. However, there are significant differences in the calculation of %FM by DXA versus more sophisticated techniques; therefore, further improvements in DXA may be needed before a consensus can be reached[186] regarding the utility of DXA in estimating FM and nonbone lean mass. In addition, DXA methodologies differ according to manufacturers; results are not directly interchangeable; and pediatric, age-related, and ethnic normal ranges have not been widely accepted.[9,62,122,200] A minor disadvantage of DXA is that an exposure to X-rays is required; however, the dose is very small (>10 μSv) and carries minimal risk. From a practical standpoint, the DXA platform has body weight limitations; scans cannot be performed on individuals over 300 pounds on some commonly used DXA machines.

Single-slice abdominal CT and MRI methods are excellent choices when information about the distribution of body fat in the abdominal region is important. This information could have relevance to defining cardiovascular risk; however, these methods have not yet been validated for monitoring of individual patients, PWS or otherwise. In addition, these methods do not provide information about whole body tissue status.

Table 6.3. Comparison of Body Composition Methodologies

Measured Compartment	Method	Instrument Cost (US$)	Procedure Charge (US$)	Precision %	Accuracy %	MDC[i] Amt. (%)
Total Body Water	Deuterium dilution[a]	25–70 K	50–100	1–2	2–3	2 L (5)
	BIA/BIS[b]	3–7 K	30	2–4	3–7	4 L (10)
	QMR[c]	100 K	—	1	—	1 L (3)
Fat-Free Mass	UWW[d]	25–35 K	45	1–2	2–3	2 kg (4)
	ADP[e]	30–80 K	45	1–2	2–3	2 kg (4)
	BIA/BIS	3–7 K	30	2–4	2–8	4 kg (7)
	DXA[f]	125 K	150	2	1–2	1 kg (2)
Fat Mass	DXA	125 K	150	2–3	3–5	2 kg (11)
	CT[g]	800 K	350	3–4	3–4	— (10)
	MRI[h]	1500 K	600	3–4	3–4	— (10)
Bone Mineral Density	DXA	125 K	150	1	2–3	0.04 g/cm^2 (4)[j]
	CT	800 K	175	1	1	1.2 mg/cc (1)[k]

[a] Requires baseline body fluid sample, such as plasma, and 2–4 hours post-dose sample. Can be assayed using infrared spectroscopy or mass spec.; results are not "immediate," 2nd assay must be delayed 15–30 days to allow for initial dose to clear. Use of ^{18}O instead of deuterium results in 5–10-fold increase in assay cost.

[b] Single (BIA) and multifrequency (BIS) bioelectrical impedance analysis. At least 30 commercial instruments, with equal number of prediction equations. Can be repeated as needed.

[c] Quantitative magnetic resonance has only been used with small animals, but has been shown to be more accurate than dilution method and can be repeated as needed without harm. Magnetic field strength is about 1/200 of routine MRI instruments.

[d] Underwater weighing, requires subject to be totally submerged in water while air is exhaled from lungs. Classic method in use for more than 50 years, limited use for infants and older adults.

[e] Air-displacement plethysmography replaces underwater weighing method. Easily tolerated by subjects, can be repeated as frequently as needed, and both adult and infant-sized instruments are available.

[f] Dual-energy X-ray absorptiometry. Often considered as "gold standard" for *in vivo* bone mineral measurement. Gives regional information about body fat distribution.

[g] Computed tomography gives information about internal distribution of fat. Most frequently used to assay subcutaneous and visceral fat components of abdominal fat. Scan times in seconds, but frequency of repeat scans is limited by the radiation dose.

[h] Magnetic resonance imaging gives information and image of internal distribution of fat. Can be repeated as needed, but requires substantially longer time than CT.

[i] Minimum detectable change (MDC) for an individual. Value in parenthesis is the change expressed as a percent based on body composition of a 79-kg male with 25% fat. For CT and MRI, a 10% change in either fat subcompartment should be detectable.

[j] Values are for areal bone mineral density; similar values for total body, spine, or hip DXA.

[k] True density of bone, usually performed only for the spine.

In summary, with the various techniques that are available today, it is possible to obtain an accurate *in vivo* assay of the human body and to monitor the changes with growth or treatment of diseases. DXA is currently the most useful procedure for assessment of body composition in individuals with PWS; however care should be exercised in the proper interpretation of results.

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