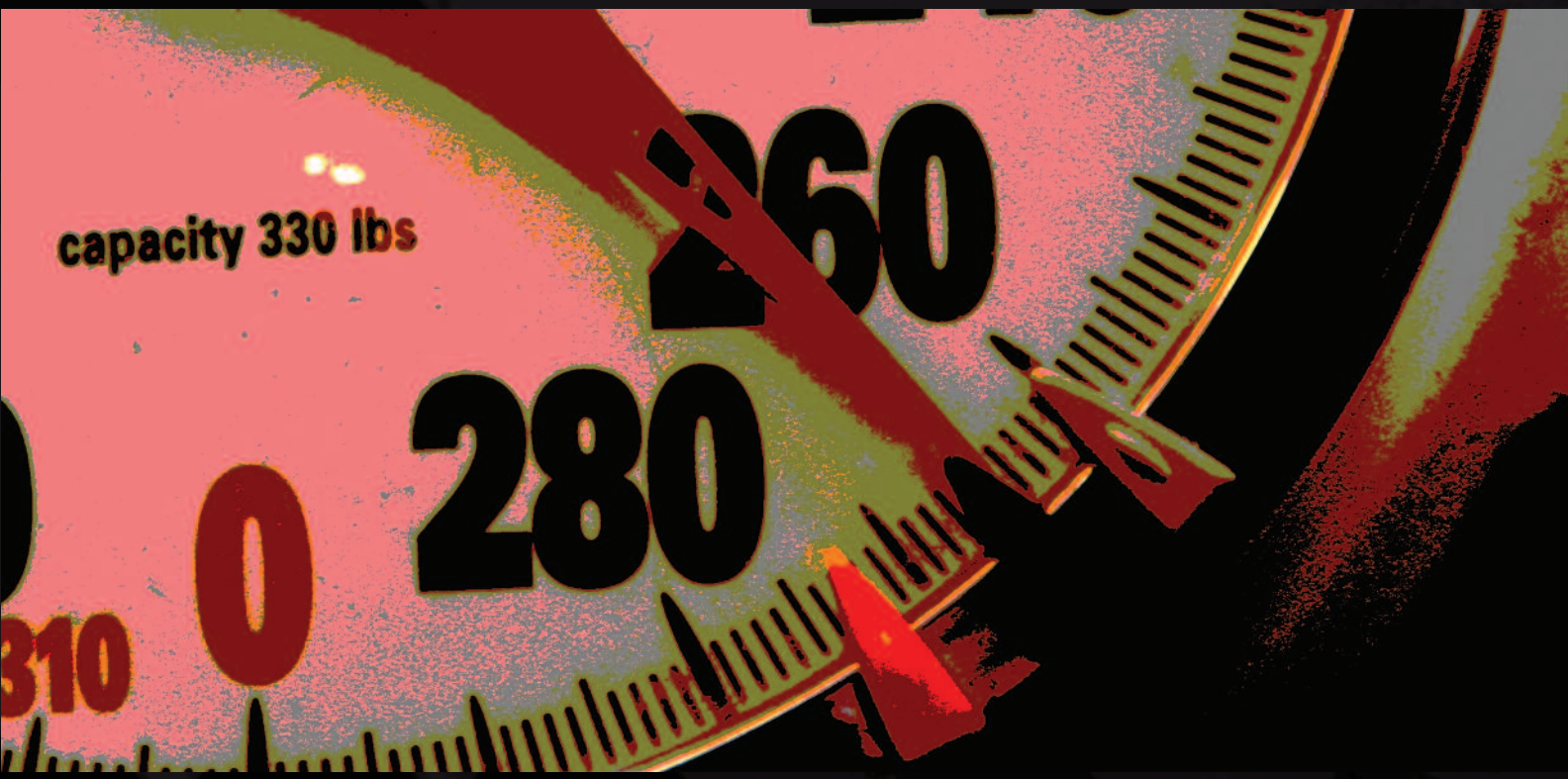
Special Edition 2011

OBESITY

IN SOUTH DAKOTA: AN EXPANDING EPIDEMIC



South Dakota medicine

SPECIAL EDITION

THE JOURNAL OF THE SOUTH DAKOTA STATE MEDICAL ASSOCIATION

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L to R: Luis A. Rojas, MD; Kelly McCaul, MD; Addison R. Tolentino, MD; Anwarul Haq, MD, FACP

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South Dakota medicine

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The Journal

Special Features

A very special thanks to Judith Peterson, MD, for providing the cover and inside photography for this special edition.

Obesity's Impact on South Dakotans

By Thomas J. Huber, MD
SDSMA President

It's impossible to overstate the concerns of the medical community on the topic of obesity. We see the impacts of the obesity epidemic on the people of our state every day.

This special edition of *South Dakota Medicine* highlights the very latest in screening, diagnosis and treatment of obesity in South Dakota. It's an issue that is expanding at a frighteningly rapid pace and has the potential to threaten to derail the progress we've made in increasing the longevity of humankind.

As a physician, I urge you to take these articles in this special issue into careful consideration to learn more about obesity and how we can continue to fight the battle of the bulge.

Thank you, and congratulations to the SDSMA staff, the South Dakota Department of Health and the contributing physicians and researchers who have worked so hard to create this special issue of *South Dakota Medicine*.

Sincerely,

Fellow South Dakotans:

On behalf of the South Dakota Department of Health, I am pleased to welcome you to this special issue of South Dakota Medicine.

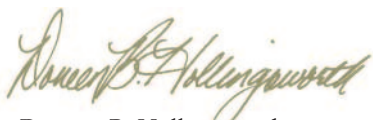
Obesity is a growing problem in our nation and unfortunately, South Dakota's numbers place us at the forefront of this epidemic. Thirty percent of adults in our state are obese, higher than the national prevalence, and that percentage is increasing at a faster rate than other states. The picture is much the same among our younger residents, with 16.4 percent of 2- to 5-year-olds and 16 percent of kindergarten through grade 12 students being obese.

Obesity prevention and treatment is a complex issue, and reversing the current trends will require the involvement of all segments of society. Individual responsibility plays a key role, but it's also important that society as a whole creates environments that make physical activity and healthful eating the easy choices for our citizens.

As South Dakotans seek advice and guidance on leading healthier lifestyles, physicians are a vital and trusted resource. The department and its Healthy South Dakota program are pleased to collaborate with the South Dakota State Medical Association and its member physicians in the effort to reduce obesity and its related chronic diseases.

Working together, we can reverse the obesity trend in our state and help South Dakotans lead healthier lives.

Sincerely,



Doneen B. Hollingsworth
Secretary of Health

Dear reader,

Obesity – adult and childhood – is epidemic in our country. This has been recognized for many years, and yet, the problem worsens. In 2001, the U.S. Surgeon General issued a "Call to Action" to reduce the prevalence of the disease in adults to 15 percent, an objective of Healthy People 2010. As of the most recent data, no state had reached this goal. South Dakota doesn't fare well, with a prevalence of obesity for adults of 29.6 percent (2009) and for children of 27.5 percent (2008) according to the most recent Centers for Disease Control statistics.

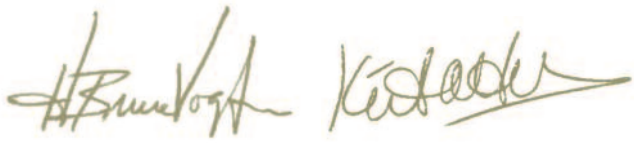
With this recognition, *South Dakota Medicine* elected to devote this fourth special edition of our journal to this growing problem. Editors and staff identified 15 topics and 23 authors or co-authors with the goal of providing our readership with a resource we hope will be of value to you in your practice.

The issue begins with an overview of the extent of the problem in our state and is followed by a series of articles addressing the genetics and hormones of obesity, specific medical conditions, various therapeutic modalities and the increasingly worrisome subject of childhood obesity. The issue concludes with further information on the latter topic, including the emerging epidemic of type 2 diabetes mellitus and final commentary on obesity in general.

The editors do wish to acknowledge an absence in this special publication. We are all aware of the high prevalence of obesity in and the great burden of this problem on our largest minority group in South Dakota, the American Indian population. Unfortunately, the author of a manuscript discussing the specific ethnic issues related to this population of South Dakotans was unable to produce the document by our printing deadline. We will work to publish a manuscript devoted solely to this topic in a future issue.

We wish to thank all the authors who contributed to this body of work. Finally, we want to thank the South Dakota Department of Health for sponsoring this special edition of *South Dakota Medicine* and Secretary Doneen Hollingsworth for her efforts as our chief public health officer in addressing this sobering problem.

Sincerely,



H. Bruce Vogt, MD, and Keith Hansen, MD
Co-Editors,
South Dakota Medicine

The Obesity Epidemic in South Dakota: How Big is the Problem?

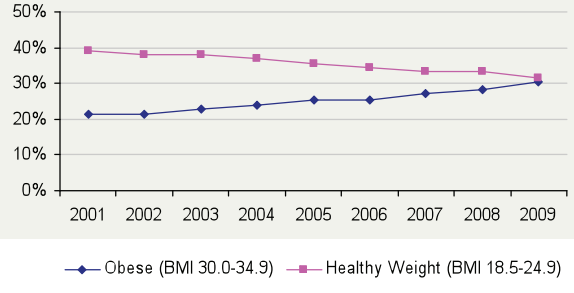
By Kristin Biskeborn, MPH, RD, LN; Matthew Christenson, PhD; Linda Ahrendt, MS

Abstract:
Obesity is an increasing problem both in the United States and South Dakota. Currently, 30.3 percent of South Dakota adults self-report being obese, which is higher than the national prevalence and also increasing at a faster rate than other states. The obesity rate for South Dakota 2- to 5-year-olds from limited-income households is 16.4 percent and above the national prevalence. Obesity prevalence among students Kindergarten through grade 12 was 16.0 percent for the 2009-2010 school year, not higher than national data.

Discussion

From 1995 to 2009, the rate of increase in adult obesity in South Dakota was third-fastest in the nation, behind Oklahoma and Mississippi. In 2009, 30.3 percent of South Dakota adults were obese, tied for 10th with Michigan for the most obese state. In 2007, South Dakota ranked 19th in obesity.1 During the past 15 years, the proportion of obese adults in the state more than doubled, when 13.9 percent of adults were obese in 1995. While the continued rising trend in obesity is alarming nationally, in South Dakota it is particularly concerning. The steep obesity trend in South Dakota is shown in Figure 1. Every five years, about 5 percent more of our adult population became obese. About 6,000 more South Dakotan adults became obese each year from 1995 to 2009. If the same trend continues 50 percent of adults will be obese in 2029.

Figure 1: Healthy Weight and Obese Percentages for South Dakota Adults, 2001-2009



Source: The Behavioral Risk Factor Surveillance System, South Dakota Department of Health, 2001-2009

Distribution of Obesity

The prevalence of adult obesity in the state differs along population demographics according to the Behavior Risk Factor Surveillance System (BRFSS).[1] A curvilinear relationship exists between obesity prevalence and adult age. Twenty-five percent of South Dakotans aged 18 to 24 were obese in 2009, compared to 36.8 percent of 55-to 64-year-olds and compared to 25.2 percent of those age 65 and older. Thirty-seven percent of the adult American Indian population in South Dakota was obese in 2009. Socioeconomic status plays a role in the differences in obesity risk, as 36 percent of adults in 2009 who were obese lived in households below $25,000 annual income, compared to 29 percent earning $25,000 and above. Differences between males and females in the state were also noteworthy. Seventy-six percent of adult males were obese or overweight, compared to 58 percent of adult females. Among the obese population in 2009 in South Dakota, 19.9 percent were considered class I obese, 7.2 percent class II obese, and 3.2 percent class III or extremely obese (Table 1).

Caution is warranted when interpreting self-reported height and weight estimates from the BRFSS. Compared to obesity estimates based on clinical measurements of height and weight from the 2007-2008 National Health and Nutrition Examination Survey (NHANES), obesity estimates from the BRFSS appear to be underestimates of the true prevalence of obesity. In 2007-2008, NHANES estimated that 33.8 percent of the nation's adult population was obese, compared to 26.9 percent from the BRFSS in 2009. Furthermore, NHANES estimated that 35.5 percent of the

adult female population was obese, compared to 26 percent from BRFSS. With self-report surveillance methods, it is understood that men overestimate their height and women underestimate their weight, and both lead to underestimates of population obesity prevalence. While NHANES data do not allow state-specific estimates for comparison, it is likely that the prevalence of obesity in South Dakota is higher than estimated by the BRFSS. Both population-based surveys rely on measuring weight status using height and weight data to calculate Body Mass Index (BMI) scores. Table 1 shows the BMI scores that correspond with healthy weight, overweight, and obese classifications.

Table 1. Weight Status Definitions.

	Children and Adolescents 2 to 20 years – BMI-for-Age	Adults 18 and over – BMI
Healthy Weight	>5th percentile to < 85th percentile	18.5-24.9
Overweight	≥ 85th percentile to < 95th percentile	25.0-29.9
Obese	≥ 95th percentile	30 and over
Class I		30.0-34.9
Class II		35.0-39.9
Class III		≥ 40

Does Obesity Matter?

Why is it a problem if obesity is sweeping across South Dakota and the nation? Obesity dramatically increases suffering, pain, disease, immobility, early death and health care costs. Complications linked with obesity include cardiovascular disease, type 2 diabetes, some cancers, cholelithiasis, fatty liver and cirrhosis, osteoarthritis, chronic inflammation, gall bladder disease, sleep apnea, reproductive disorders in men and women, infections from skin problems, psychological and social disorders, dementia and premature death. Obesity increases social, economic and psychological difficulties because of discrimination, prejudice, low body image and poor self-esteem. Obesity complications affect employment, personal and professional relationships and lifestyle.[2]

Metabolic syndrome is a cluster of metabolic risk factors that come together in a single individual leading to the development of type 2 diabetes, cardiovascular disease and stroke. Metabolic syndrome is most common among obese adults, but not all obese people develop metabolic syndrome. It is characterized primarily by insulin resistance, hypertension and increased abdominal fat. It is present in 65 percent of those that are obese, 30 percent of those overweight and about 7 percent of people with normal body weight.[3]

Obesity is the second-leading cause of preventable deaths in the United States and South Dakota, second only to tobacco use. It is expected to surpass tobacco as the leading cause of preventable deaths as obesity continues to rise and smoking continues to decline.[4,5] Furthermore, the estimated annual cost of treating obesity in the U.S. adult non-institutionalized population is $168.4 billion, or 16.5 percent of national spending on medical care.6 The annual health care costs of treating obesity in the U.S. have doubled in less than a decade.[7] The medical costs for an obese person are 42 percent higher than a person not overweight. This means $1,429 more per person per year, and the annual difference in costs for an obese person on Medicare is even greater.[7] It is estimated that Medicare prescription drug payments for an obese recipient are about $600 more a year than a recipient not overweight. These increased costs result almost entirely from treating the diseases that obesity promotes.[7]

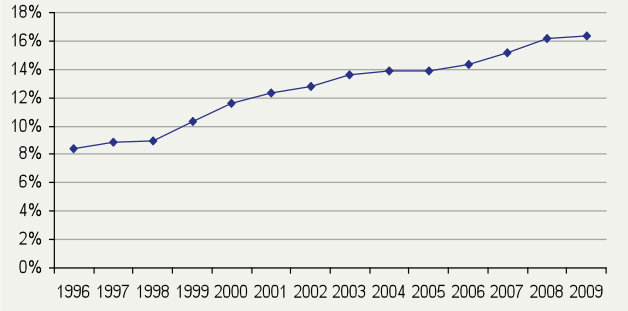
Children and Obesity

For the first time in American history, children could have a shorter lifespan than their parents because childhood obesity is rising. Obesity causes damage to many internal organs, including changes in the brain, hormones, lungs, heart, liver, gall bladder, pancreas and growth plates. In the U.S., about 32 percent of children and adolescents aged 2 to 19 are overweight or obese.[8] Excess weight can exert a profound and immediate effect on physical, mental, emotional and social development. For these reasons, childhood obesity is even more daunting than adult obesity.

Obese children and adolescents suffer disproportionately from diabetes, asthma, high blood pressure, high cholesterol, atherosclerosis, bone/joint problems and sleep apnea.[9,10] They often experience intense social stigmatization. Childhood obesity is associated with low self-esteem, social withdrawal, increased loneliness, sadness, nervousness and increased use of alcohol and tobacco.[9,10] Severely overweight children are more than five times as likely as their non-overweight counterparts to have a lower health-related quality of life (i.e., ability to move around, play sports, perform in school, levels of fear and sadness and quality of relationships with peers).[11] About 70 percent of obese adolescents and older children become obese adults. People that experience obesity during childhood are at elevated risk for chronic diseases and premature death during adulthood.[9,10]

Figure 2 shows obesity trends of 2- to 5-year-olds in limited-income families in South Dakota from 1996 to 2009.

Figure 2: South Dakota 2-5 Year Olds Who are WIC Participants, BMI-for-Age 95th Percentile and Above

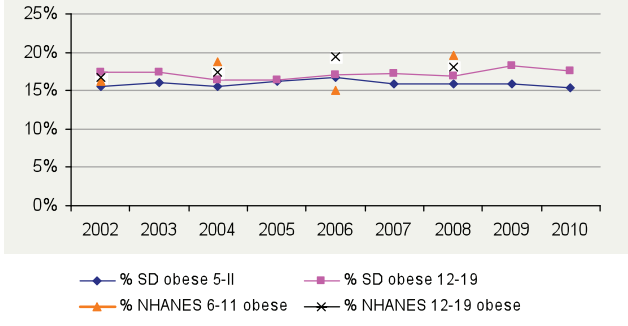


Source: Pediatric Nutrition Surveillance System (PedNSS), South Dakota Department of Health, 1996-2009

Similar to adults, obesity prevalence has doubled for these young children. Data comes from in-clinic measurements of children enrolled in the South Dakota Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). In 2009, 16.4 percent were obese, and an additional 19.9 percent were overweight.[12] Nationally, 14.7 percent were obese in 2009.13 Young children living in limited-income families in South Dakota are more likely to experience their first years of life overweight and obese compared to the national average.

Obesity prevalence among older children and adolescents in South Dakota was usually not higher than national averages as shown in Figure 3. Furthermore, obesity trends are relatively flat for these age groups. These data come from in-school measurements taken by school nurses or health and physical education teachers. In the 2009-2010 school year, 16 percent of all students were obese, and 16.7 percent were overweight, for a combined total of 32.7 percent. Native American obesity and overweight prevalence was higher than whites (26 percent vs.14.5 percent for obesity; 19.6 percent vs. 16.2 percent for overweight). The 2007-2008 NHANES obesity estimates for 6- to 19-year-olds was

Figure 3: Prevalence of Obesity Among SD and US Children and Adolescents



Sources: School Height and Weight Report for South Dakota Students, South Dakota Department of Health, and National Health and Nutrition Examination Survey (NHANES), Centers for Disease Control

18.7 percent. In South Dakota and the nation, more males were obese than females. The National Survey of Children's Health (NSCH) further corroborates the in-school height and weight data collected by South Dakota schools by showing that the prevalence of obesity among 10- to 17-year-olds in the state was also not above the national average for that parental report survey.

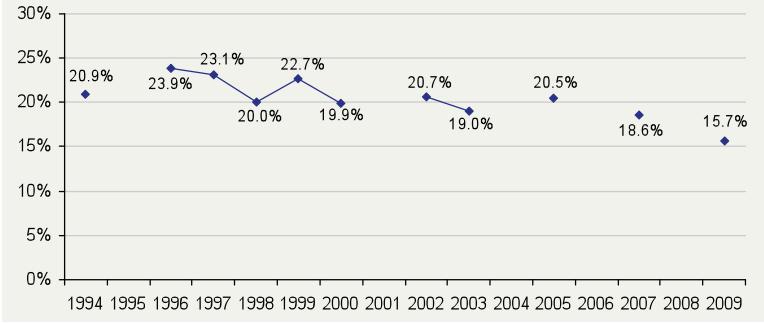
Obesity Risk Factors

Obesity is caused by many interacting factors. In general, obesity is a result of one's genetic predisposition interacting with the environments in which an individual lives, works and plays. Genetic susceptibility cannot be changed, but lifestyle behaviors still have a strong influence on weight status. Social, physical and economic environments have a strong influence on shaping lifestyle behaviors.[14] Therefore, the primary risk factors of interest to reduce or prevent obesity can be grouped into two broad arenas: personal lifestyle behaviors/choices and environmental influences. Since it is unlikely that changes in genetic susceptibility across the population have caused the obesity epidemic, it is reasonable to examine changes in lifestyles and environments to develop effective obesity prevention strategies. Physical activity and nutrition behaviors are widely accepted as the most direct pathway to manage and control a person's calorie intake and calorie expenditure. Less well-known and understood is how the broader social, physical, and economic environments shape a person's physical activity and nutrition choices.

Fruits and Vegetables

Results from the BRFSS show that South Dakota is well below the national average when it comes to fruit and vegetable consumption. South Dakota was cited in the September 10, 2010, U.S. Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report as having the lowest intake of vegetables of any state in the union.[15] Moreover, Sioux Falls specifically was recognized as the city with the lowest consumption of fruits and vegetables in the nation.[15] Trends in the consumption of fruits and vegetables show decreases in recent years with only 15.7 percent of adults in the state reporting eating the minimum of five servings of fruits and vegetables per day in 2009. Figure 3 shows trends of fruit and vegetable consumption. Current recommendations are that adults need seven to 10 servings of fruits and vegetables per day (1.5 to two cups fruit plus two to three cups of vegetables). In 2009, only 25.2 percent of South Dakota adults aged 18 and over consumed the minimum two servings of fruit per day, compared to 32.5 percent nationally.

Figure 4: Percent of South Dakotans Who Eat 5 Servings or More of Fruits and Vegetables Per Day, 1994, 1996-2000, 2002-2003, 2005, 2007, and 2009



Source: The Behavioral Risk Factor Surveillance System, South Dakota Department of Health, 1994-2009

Low consumption of fruits and vegetables was also reported by high school students. Nationally, 33.9 percent of high school students reported eating five or more servings of fruits and vegetables a day in 2009, compared to 14.7 percent of South Dakota high school students.[16] For those consuming three or more servings of vegetables, South Dakota high school students reported 11.3 percent, compared to 22.3 percent nationally.

The Centers for Disease Control and Prevention (CDC) has identified policy and environmental indicators that support improved fruit and vegetable consumption. While the availability of farmers' markets in the state is similar to national levels (1.9 versus 1.7 nationally per 100,000 population), no farmers' markets in the state accept electronic benefits transfer (EBT), and 6.7 percent accept WIC Farmer's Market Nutrition Program coupons. The availability of healthier foods in schools is below national rates. Only 7.9 percent of South Dakota middle and high-schools offer fruits (not juice) and non-fried vegetables as competitive foods, as compared to 20.9 percent nationally. Nor does South Dakota have a state-level farm-to-school policy.[17]

Physical Activity

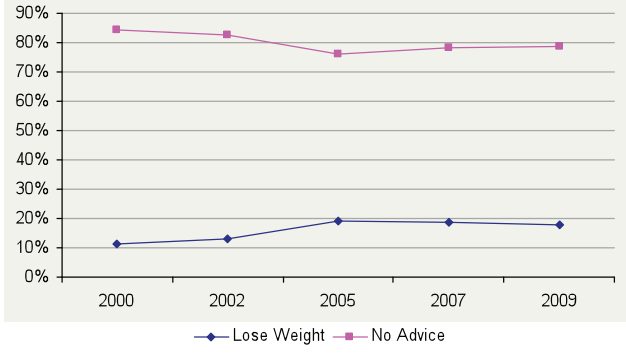
The 2008 Physical Activity Guidelines for Americans recommends adults complete at least 150 minutes a week of moderate-intensity aerobic physical activity or 75 minutes per week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. While the physical activity of adults in South Dakota does not meet the Healthy People 2010 goal, it is close to the national average. In 2009, 62.7 percent of South Dakota adults met the physical activity guidelines as compared to 64.5 percent nationally.[18]

In 2009, 46.7 percent of South Dakota high school students reported they were physically active for a total of at least 60 minutes per day during five or more of the past seven days.[16] This compares to 37 percent nationally. Our high school students are some of the most active in the nation. This reported physical activity does not come from participating in physical education classes, as only 29.1 percent of South Dakota high school students report attending physical education classes on one or more days in an average week. This is the lowest of any state in the union. The average is 56.4 percent nationally. However, 64.4 percent of South Dakota high school students report playing on one or more sports teams during the past 12 months, which is the highest in the U.S.[16]

The CDC has identified policy and environmental indicators that support individual physical activity behavior. South Dakota is lower than the national average in the percent of census blocks with a park within one half-mile of its boundary (5.3 percent versus 20.3 percent) and the percent of census blocks with a fitness center within one half-mile of its boundary (7.2 percent versus 16.6 percent) While this may be due to our rural state, it does affect access to places for physical activity. South Dakota does not require elementary schools to provide a scheduled recess, while 20 states do require it. South Dakota does not require physical activity in child care centers. South Dakota does not have any state-level enacted, community-scale urban design and land use policy requirement, while 23 states do have such requirements. We also do not have a state-level enacted transportation and travel policy, while 36 states do have such policies. Such policies promote active transportation like walking or biking.[17]

Though obesity continues to increase, the vast majority of South Dakota adults reported that their physician has not given them any advice about their weight. Figure 5 shows

Figure 5: Doctor's Advice about Weight for Those Who Have Been to the Doctor for a Routine Checkup in the Past 12 Months



Source: The Behavioral Risk Factor Surveillance System, South Dakota Department of Health, 2002, 2005, 2007, and 2009

that less than 20 percent of adults in South Dakota have been told to lose weight by their doctor going back to 2000. About two-thirds of the adult population is overweight and obese in South Dakota and would receive health benefits from weight loss.

Breastfeeding

Having been breastfed is associated with subsequent weight status in childhood. Breastfeeding initiation and duration rates have improved in the state in recent years. For infants born in 2007, 76.9 percent of South Dakota infants were ever breastfed as compared to 75.0 percent nationally.19 Both meet the Healthy People 2010 goal of 75 percent for breastfeeding initiation.

The obesity-fighting benefits from breastfeeding are impacted by both dose and duration. For South Dakota infants born in 2007 48.5 percent were still breastfed at 6 months of age, compared to 43.0 percent nationally, and 22.7 percent were breastfed at 12 months of age, compared to 22.4 percent nationally. None of these rates met the Healthy People 2010 goals, though 14 and 15 states respectively did meet these goals. Maternity care practices have been shown to improve breastfeeding rates. According to the 2007 CDC administered Maternity Practices in Infant Nutrition and Care (mPINC) survey,[20] while South Dakota has strengths in the documentation of mothers' feeding decisions and the availability of prenatal breastfeeding instructions, there were several hospital practices that needed improvement to support breastfeeding:

- Only 16 percent of hospitals in South Dakota adhere to the clinical practice guidelines of the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists against routine supplementation with formula, glucose water or water.
- Only 26 percent of South Dakota facilities have adequate assessment of staff competency as demonstrated by lack of annual assessment of basic breastfeeding management and support.
- No South Dakota facilities follow the recommendations of medical and public health groups against distributing formula company discharge packs.

Conclusion

The adult population in South Dakota is becoming obese at one of the highest rates in the nation. In conjunction, the amount of fruit and vegetable consumption in the state is one of the lowest in the nation. If obesity trends in South Dakota continue, our state will soon be at the forefront of the obesity epidemic in terms of disease, suffering and overwhelming health care costs.

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The Influential Role of Genes in Obesity

By Quinn P. Stein, MS, CGC; Amelia R. Mroch, MS, CGC; Kristen L De Berg, MS; Jason D. Flanagan, MS, CGC

Abstract:
Obesity risk is amplified in the presence of obese relatives yet does not usually follow classic Mendelian inheritance patterns. A combination of gene mutations, deletions and single nucleotide polymorphisms are all known to contribute to obesity. Most cases are polygenic, the result of multiple genes interacting with a changing environment. Each "obesity gene" only makes a small contribution to phenotype, but collectively, inherited genetic variations play a major role in determining body mass and how the body responds to physical activity and nutrition. While obesity is most commonly associated with polygenic inheritance, there are other instances in which the cause is monogenic or syndromic. Monogenic obesity typically is caused by a single gene mutation with severe obesity as the main symptom. Syndromic obesity, on the other hand, has many characteristics, of which obesity is one symptom.

Introduction

Is it nature or nurture, genes or environment, Grandma's genes or Grandma's homemade pork-and-beans? Just what is it that makes some people overweight, while others can seemingly eat forever without gaining a pound? Years of research have pointed to obesity as a multifactorial genetic condition, involving a complex interface of genetic components and environmental influences. Within the past decade, however, strides have been made in understanding not only how genes interact with the environment, but also how genes interact with each other. In this article, we review complex (polygenic) obesity, monogenic obesity, and a handful of genetic syndromes associated with increased body habitus. By examining each of these causal factors of obesity, we can begin to understand the role genes play in weight gain.

Syndromic Obesity

Many syndromes, previously thought to be controlled by single genes, are conversely controlled by multiple elements. Prader-Willi, Bardet-Biedl and Cohen syndromes are all illustrative examples. For these genetic syndromes, obesity is just one of many identifiable characteristics, yet studying genetic syndromes for which obesity is a major complication can lead to a greater understanding of the genes involved.

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a relatively common, generally sporadic, genetic disorder with a recognizable pattern of dysmorphic features and major neurologic, cognitive, endocrine and behavioral/psychiatric disturbances.[1] Infants with PWS have hypotonia, poor suck, decreased arousal, and failure to thrive, often requiring tube feedings for several weeks to months.[2] This period is followed by progressive obesity beginning at 1 to 6 years of age. Additional characteristics include developmental and intellectual disability, hypogonadism, hyperphagia leading to morbid obesity if uncontrolled, short stature and a characteristic facial appearance. Children with PWS have a typical behavioral phenotype that includes temper tantrums and compulsive traits.[1]

PWS has a general prevalence of one in 15,000 to 30,000 people. It was the first recognized human disorder related to genomic imprinting and the first shown to be caused by uniparental disomy. It results from failure of expression of paternally inherited genes in the PWS region of chromosome 15.[3] Large interstitial deletions of paternal origin on chromosome 15q11–q13 are the cause of PWS in approximately 70 percent of cases. Most remaining affected individuals have maternal uniparental disomy 15, and some have imprinting defects. A number of paternally expressed genes mapping within this critical region have been suggested to have a role in the pathogenesis of PWS.[4]

The genetics of PWS are complex; several candidate genes have been implicated including the *SNURF-SNRPN* gene (encoding small nucleolar RNAs), *NECDIN* (encoding NECDIN protein), and *MAGEL2* (a NECDIN-related protein). It is clear that the genes disrupted in PWS play vital roles in the regulation of body fat and metabolism.[5] Individuals with PWS demonstrate a state of relative hypoinsulinemia despite profound obesity.[1,6] Fasting insulin concentrations are lower in those with PWS compared with body mass index (BMI)-matched children.[5] The causes of hypotonia, muscle weakness and motor problems in PWS patients are not clear. It is presumed, however, that contributing factors include abnormal body composition, with an increase in fat mass and a decrease in muscle mass, and possibly some degree of neuromuscular abnormality. [7]

Ironically, the energy requirement for people with PWS is lower than average, further predisposing to obesity. Because of this, affected individuals need a low-calorie diet, supervision to minimize food stealing and regular exercise to prevent obesity. In many instances, growth hormone treatment can be used to normalize height, increase lean body mass, decrease fat mass and increase mobility.[6]

Bardet-Biedl

While obesity is associated with Bardet-Biedl syndrome (BBS), it is not typically the presenting symptom or biggest factor contributing to morbidity and mortality. However, BBS should be considered in the differential as a syndromic cause of obesity when certain other clinical findings are present. The challenge to making a diagnosis of BBS is that it is highly variable and has major diagnostic criteria that present after infancy, and the molecular testing is not straightforward.

BBS has a general prevalence of one in 100,000 to 160,000 with reports of one in 13,500 to 17,500 in certain population isolates such as the Bedouins and those of Newfoundland extraction. Inheritance is autosomal recessive, indicating that parents of an affected child have a 25 percent recurrence risk with a subsequent pregnancy. There are 14 genes reported in association with BBS and likely others not yet described.

Typically, children with BBS have a normal birth weight and develop truncal obesity within the first year of life. Retinitis pigmentosa affects essentially all children with BBS, presenting first as night blindness, and occurring most often by age 7 or 8. Other primary features include postaxial polydactyly, hypogonadism in males or various genital abnormalities in females and renal anomalies. The renal involvement can be significant and lead to end stage renal disease.

BBS is part of a group of disorders that trace their cause to the function of cilia.[8] Cilia are present in a wide variety of cell types within the body and are, therefore, highly susceptible to genetic mutations that affect structure or function.[8]

Other ciliopathies include polycystic kidney disease, Alstrom syndrome, nephronophthisis and Joubert syndrome. The overlap of these diseases, especially with regard to retinal and kidney function, is intriguing.[9] This clinical overlap, in combination with the presence of multiple causative genes within each disorder, led to the recognition of the many proteins involved in forming ciliary complexes or that have ciliary-associated interactions.[9]

Several of the molecules associated with ciliary function have been implicated in the underlying mechanism leading to obesity in BBS.[8-9] There are mouse models that reflect the various genes involved in BBS and the multiple pathways through which obesity can occur.[8] One current thought is that dysfunction of the cilia of the hypothalamic neurons in the brain leads to misinterpreted signals from visceral organs regarding hunger.[8-9] It has also been found that several of the BBS genes are expressed during the generation of fat tissue, suggesting that they may have a more direct role in this process.[8] Further work is being done to more fully understand the role of the BBS genes in obesity.

Cohen Syndrome

Cohen syndrome was first described in 1973 by Cohen, et al. when they reported three children with a characteristic facial appearance in association with mental retardation, hypotonia, joint laxity, obesity of mid-childhood onset and ocular anomalies.[10] A 1984 report further outlined the phenotype to include microcephaly, neutropenia, high myopia and retinal dystrophy.[11] Since then, over 100 cases have been reported worldwide, with a cohort in Finland having a more confined phenotype.[11-12]

Cohen syndrome is highly variable, especially in those of non-Finnish descent. It is thought that the initial association of Cohen syndrome with obesity may have been overstated.[13] Obesity, if it develops, tends to do so in late childhood or adolescence.[11] Half of the patients are overweight, but only one-fifth are obese. The obesity is predominantly truncal; it seems that generalized obesity is uncommon.[11, 13]

Inheritance is autosomal recessive and, in 2002, mutations in the *COH1* gene were found to be associated with the phenotype. *COH1* maps to chromosome 8q22.[14] It encodes a potential transmembrane protein presumably involved in vesicle-mediated sorting and intracellular protein transport.[13] The relationship between *COH1* mutations and obesity is not yet understood.

Chromosomal abnormalities

On occasion, obesity presents as part of a syndromic chromosome abnormality, especially chromosomal deletions. Such deletions cause contiguous gene syndromes resulting in a complex phenotype. Examples include deletions of chromosomes 1p36, 2q37, 6q16 and 9q34. Deletions in these gene rich areas affect more than just body habitus and will typically also affect learning and development. Interestingly, all of the chromosome deletions named here show some overlap with Prader-Willi syndrome in that affected individuals are likely to have childhood obesity, hyperphagia, learning disabilities/developmental delay, hypotonia, neonatal feeding difficulties and characteristic eye shape.[15]

An additional case in point of a chromosome abnormality resulting in obesity can be seen in uniparental disomy for chromosome 14 (UPD 14). UPD 14 occurs when a child gets two copies of chromosome 14 from the same parent and no copies from the other parent, instead of getting the usual one copy from each parent. Like the chromosome deletions described above, UPD 14 has a phenotype that overlaps with Prader-Willi syndrome; namely: obesity, short stature, mild developmental delay and neonatal feeding difficulties.[15]

Testing for chromosome deletions and uniparental disomy can now be done simultaneously using a Single Nucleotide Polymorphism (SNP)-based, but not an oligo-based, microarray. SNP-based arrays are able to detect very small chromosome deletions or duplications, and can also tell if both copies of a chromosome have come from a single parent.

Monogenic Obesity

Monogenic obesity is both severe and rare, and can be defined as obesity resulting from a mutation or deletion of a single gene. The phenotype entails a variety of neuroendocrine issues like hyperphagia and hypogonadism in addition to morbid obesity. Significant developmental delays, however, are not commonly seen.[16]

The genetic causes of monogenic obesity tend to be related to the leptin-melanocortin pathway. This pathway is critical for energy balance and food intake, with a disruption in this pathway leading to severe obesity. Mutations in the melanocortin-4 receptor gene (*MC4R*) and the leptin receptor gene (*LEPR*) have been reported in about 2.5 percent and 1.5 percent of children with severe obesity.[17] An additional 0.5 percent of cases can be attributed to a chromosome 16p11.2 deletion where a gene known as *SH2B1* is deleted.

Mutations in *MC4R* are the most common cause of monogenic obesity.[18] The gene encodes a receptor that plays a role in the regulation of food intake and energy homeostasis. *MC4R* mutations occur in 1 in 1,100 people, making it one of the most common autosomal dominant conditions in humans. Subjects exhibiting homozygous mutations have a more severe phenotype. *MC4R* is sometimes referred to as a "major gene defect" rather than a monogenic disorder, since having a mutation predisposes an individual to obesity but extrinsic factors such as diet and exercise are still crucial.[19] Interestingly, genetic variations in *MC4R* can lead to either loss or gain of function. In fact, a specific polymorphism in *MC4R* known as V1031 may have a protective effect. This polymorphism is negatively associated with serum triglyceride levels, BMI and obesity.

After *MC4R*, *LEPR* is the next most common gene linked to monogenic obesity. Unlike mutations in *MC4R*, however, mutations in *LEPR* act in an autosomal recessive manner. Children inheriting one mutation from each parent demonstrate severe obesity, hyperphagia, hypogonadotropic hypogonadism, and in some cases, central hypothyroidism.[17]

The most recent discovery of a genetic defect leading to monogenic obesity in children has been the observation of chromosome 16p11.2 deletions. There are nine known genes in the region, but the most significant is the *SH2B1* gene, which is known to be involved in insulin signaling.[20] When missing, it affects the brain's ability to respond to leptin, and as a result children have a hard time controlling their food intake and constantly feel hungry. About 40 percent of the time the deletion is *de novo*, occurring for the first time in an individual. About 60 percent of the time, it runs in the family.[20]

Clinical evaluation of severely obese children is becoming increasingly complicated. Careful clinic analysis does not easily detect obesity stemming from single gene mutations or deletions because of the lack of an obvious phenotype. Additionally, because of the number of obese patients in the world, it is simply not possible to perform DNA testing for everyone, which can be between $500 and $2,000 per gene tested. In the future, it would be useful to identify particular phenotypes, or clinical characteristics, for which additional genetic screening is warranted. For now, the presence of severe obesity in a young child (under age 5) with extreme hyperphagia, severe insulin resistance disproportionate for the degree of obesity and a positive family history of early-onset obesity may support a genetic analysis.

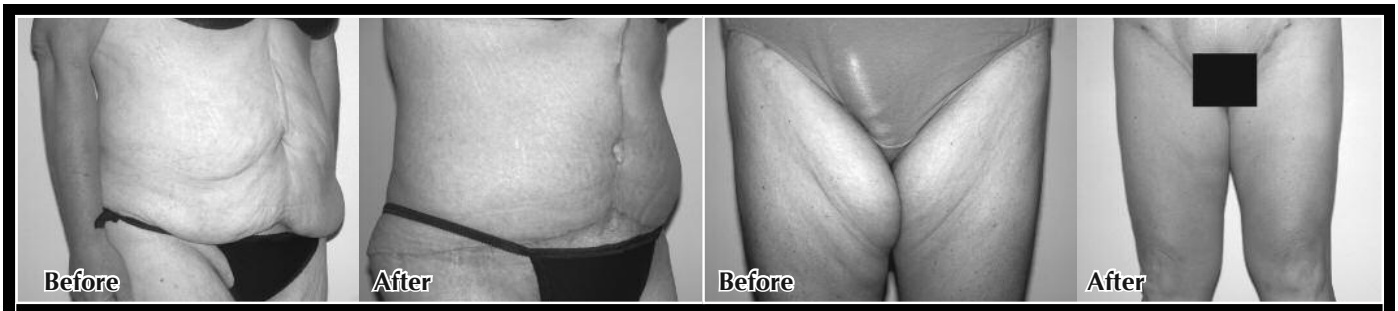
Complex/Polygenic Obesity

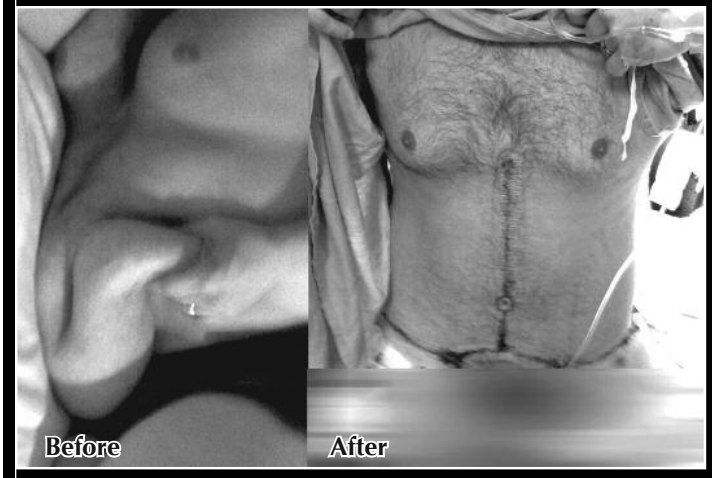
While monogenic obesity helps us better understand the biology and mechanism of obesity in general, it accounts for only about 5 percent of obesity overall.[17] The epidemic of obesity in the general population is much more complicated than a single gene explanation, and rather is the result of multiple genes interacting with a changing environment. In other words, the majority of obesity is a polygenic, multifactorial condition. Polygenic, or common, obesity arises when an individual's genetic makeup is vulnerable to an environment that encourages energy consumption over expenditure. Most Western societies have an environment that favors weight gain rather than weight loss because of an abundant food source and lack of physical activity.

Even though obesity is influenced by both genetic and environmental factors, it is easy to blame lack of exercise and unscrupulous food intake as the main culprit for the population's slide into obesity. The harder question is "how does genetic makeup also contribute to obesity?" One common hypothesis is the "thrifty genotype" explanation which states that there is a divergence between today's environment and "energy-thrifty genes" that multiplied over centuries under different environmental conditions when food was not always readily available. There was an advantage to those who could store energy more easily. In other words, the same genes that would have helped families survive times of food scarcity are now being challenged by environments in which food is abundant and calorie-rich and hence may now predispose to obesity.[21] While the thrifty genotype theory is difficult to prove in a real world setting, animal models support this hypothesis.[22] We are also beginning to discover a great deal about the way our genes shape how we store fat, where we store it and our susceptibility to food seeking behavior and overeating.

Human twin studies have suggested that about 40 to 70 percent of body mass index (BMI) variation in a population can be explained by genetic factors.[8,18] The reason for this variation has been studied using genome wide association studies (GWAS). In these types of studies, numerous individual genomes are scanned in an attempt to find genetic variations that appear to be associated with a particular disease. GWAS are particularly useful in common diseases like cancer, mental illness and obesity. Recently, one such study looked at severely obese children not believed to have any sort of genetic syndrome. These children tended to have normal intelligence, a voracious appetite and severe insulin resistance. In this study, researchers were looking for small variations, known as copy number variants, in the amount of genetic material between people. The most common copy number variant in the severely obese children was a small deletion on chromosome 16 containing the gene *SH2B1*. This gene (described in the monogenic obesity section above) is known to be involved in insulin signaling and appetite regulation.[8]

Although the association between obesity and chromosome 16p deletions happened to be discovered by GWAS, GWAS primarily tend to search for single nucleotide variations in the genome. Each variant by itself will have a relatively small effect, but in combination, may lead to a more measurable burden. To date, GWAS have identified 32 variants that are associated with obesity.[23] Typically, these are single-base pair changes called SNPs. Current estimates are that when added together, these variants may account for a 6 to 11 percent variation in BMI.[23] If an individual has a high number of predisposing variants, i.e. SNPs, there appears to be a significant increase in total weight and body fat percentage. As an example, since there are currently 32 known variations, every individual has 64





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It has been a long journey for me, but here I am 200 lbs. thinner and I have regained my life. I was extremely excited about my new body but yet I didn't feel my journey was over. I had so much loose skin. I felt I needed it tailored to fit the new me. I decided it was time to seek out a plastic surgeon for help. I found a wonderful place with a great group of surgeons and staff at Plastic Surgery Associates of S.D. in Sioux Falls. My surgeon suggested a thigh reduction and circumferential body lift. It has now been 5 weeks since my surgery. When I look in the mirror it still brings tears to my eyes, the body I now see. My stomach is now flat and my muscles have been tightened. I can jog and move freely without worry. I am happy to say that my self esteem is soaring.
K.M. 12-11-2010

I have lost 102 lbs and had an extreme amount of skin on my thighs. In fact, it looked like I had a "butt" in the front. Every pair of pants would show the saggy, extra skin and made it very uncomfortable. My legs rubbed together also. After my thigh reduction surgery, I look great. I feel great and I can't thank my surgeon from Plastic Surgery Associates enough. I also had a tummy tuck with the same surgeon. It was an awesome job. I would recommend everyone having it done if you have extra skin. My life has completely changed.
TB 12-3-2010

All the excess skin in my stomach and legs was always irritated and very uncomfortable. I decided to consult with one of the surgeons at Plastic Surgery Associates about the skin. My surgeon was very knowledgeable and provided some very good options for me. I elected to have a "full body lift" including a thigh reduction. My surgeon was very positive in all his communications with me. He didn't pull any punches about the pain and what was going to be done. I weighed in at 280 lbs pre-op and came out 28 lbs lighter. The pain I experienced was exactly what I was prepared for but what he did with my body was not. When they took the compression bandage off from my mid-section I was blown away. 100% of the excess skin and fat was gone. I would recommend this procedure to anyone. The doctor viewed everything about my procedure as if it was on himself and made very reasonable recommendations on what he should or might be able to do so the operation end results would be exceeded.
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total known areas of significance (32 from each parent). If an individual has greater than 38 predisposing variants, the relative extra weight gain for an adult who is 5'8" inches tall could be as much as 19 pounds.[23]

The most substantial of the variants discovered thus far have been in the "fat mass and obesity associated" gene (*FTO*). The effects of these variants start as early as childhood with measurable differences in obesity seen by age 7.[24] There are currently six SNPs in the *FTO* gene which show a propensity toward obesity and individuals with a particular SNP at rs9939609 are on average 6.5 pounds heavier than controls.[25] This specific SNP is associated with a reduced feedback response to insulin, so it is important in regulating feeding and fasting. Notably, 16 percent of individuals of European descent are homozygous for this specific variant.[26]

In addition to FTO, other important SNPs have been found in a number of genes including *TMEM18, GNPDA2, BDNF, MTCH2, INSIG2,* and *MC4R*. No single SNP will cause obesity; however, a combination of variants exposed to an obesogenic environment will increase the relative risk. Alternatively, some SNPs may have a beneficial role by providing a degree of protection against obesity. While the data coming from the relationship between SNPs and obesity is significant, the current predictive value of such testing is limited.

The combination of mutations, deletions and SNPs is helpful in discovering risk factors for obesity. The challenge, however, is that they account for only a small portion of human genetic variation. A major difficulty is that most studies have only been able to look at individual genes themselves and not necessarily at how those genes function in certain environments or how they work in combination. Most have not taken into account how genes can be turned on and off by external stimuli. One new area of research is the prenatal environment and what effects this environment might have on gene expression. It has long been noted that maternal health and diet play a critical role in the wellbeing of the baby. Studies now indicate that diet plays a significant role in the long term homeostasis of a child.[21] In fact, both malnutrition and high-energy diets can present challenges for a child. In times of malnutrition, women tend to have babies with low birth weights and smaller organs that store fat efficiently. Later on, if these children are then exposed to a higher-energy diet, it stresses their organs and increases the risk for obesity, diabetes and eventually heart disease. The opposite scenario is being seen in many Western cultures today; very high energy exposure via maternal diet, prior to birth, has also been associated with obesity.[21]

Another area of interest is how the prenatal environment could reprogram the genome. One hypothesis is that if a baby is exposed to a high- or low-energy diet *in utero*, there is "one hit" and this makes them more vulnerable to a "second hit."[21] In other words, it is not the child's genetic makeup that directly causes obesity, but it is one of the predisposing factors. An analogous area of research revolves around epigenetic reprogramming. Epigenetics refers to genetic patterning not directly evident by looking at the DNA sequence. One example is a genetic phenomenon known as imprinting, that is, certain genes are turned "on" or "off" depending on if they are inherited from the father or the mother. Epigenetic studies are much harder to conduct than studies focused on sequence variations, though mouse models are now providing measurable evidence about how the *in utero* environment is functionally reprogramming the genome.[21]

We are just beginning to understand polygenic obesity, how genes influence what we eat, and how what we eat contributes to both our own weight and our children's weight. There is still a great deal of work to be done to determine how genes interact and interface with the environment to contribute to obesity. The next steps will involve the discovery of more obesity susceptible loci, refining the phenotype, and testing for genetic interactions with environmental factors. What is evident from the studies done thus far is that genes do play a role in the population variance of weight gain. It is still important to remember, however, that those individuals with a genetic propensity toward obesity are not destined for obesity. One's genetic make-up, after all, is just one of the factors. These individuals can still implement lifestyle modifications to reduce their risk for excessive weight gain and decrease the risk for conditions such as diabetes and heart disease.

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Dysfunctional Hormonal Regulation of Metabolism in Obesity

By Kathleen M. Eyster, PhD

Abstract:
A complex network of hormones from the pancreas, adipose tissue, stomach, intestines and the central nervous system coordinates regulation of metabolism and energy balance. Obesity disrupts this regulatory network. This paper reviews the anorexigenic and orexigenic hormones and their dysfunctional regulation in obesity.

Introduction

The regulation of metabolism requires the integration of a variety of physiological functions, including the regulation of the storage and release of foodstuffs and the regulation of appetite and satiety. An array of hormones is involved in the coordination of these functions, ranging from the conventional metabolic hormones such as insulin and glucagon to the hormones of adipose tissue and the gastrointestinal tract. A prevailing concept is that hormones that regulate appetite, satiety and fat deposition, evolved to regulate these functions in times of normal and scarce food supply. The easy access to excess, highly palatable foodstuffs appears to overwhelm these hormones, leading to the current rising rates of obesity. This review will focus on the network of hormones that regulate metabolism and derangements of these hormones in obesity.

Conventional Metabolic Hormones

The hormones typically addressed in conventional discussions of the regulation of metabolism and energy homeostasis are insulin, glucagon, epinephrine, cortisol and growth hormone. These hormones regulate the minute-to-minute storage, release and utilization of foodstuffs in the body.

Insulin, secreted by beta cells of the pancreas in response to the absorption of foodstuffs, is the sole hormone responsible for the uptake and storage of foodstuffs in peripheral tissues. It stimulates the uptake of glucose into cells and its storage as glycogen. Insulin also stimulates the uptake of lipids into adipose cells and their storage as triacylglycerols, as well as the uptake and usage of amino acids. In addition to these effects in peripheral tissues, insulin crosses the blood brain barrier and affects metabolism centrally.[1,2] In the hypothalamus, insulin reduces appetite and stimulates energy expenditure. In the presence of obesity, insulin secretion is increased. However, excess insulin leads to insulin resistance both peripherally and centrally as has been well documented in type 2 diabetes mellitus.[1,2] Peripheral insulin resistance results in high blood glucose levels due to the inability to store glucose. Central insulin resistance results in the loss of appropriate appetite regulation. The replacement of insulin in type 1 diabetes mellitus results in weight gain due to its peripheral, rather than central, effects.

In contrast, glucagon is secreted by alpha cells of the pancreas in response to decreased levels of glucose in the blood. Glucagon stimulates the breakdown of glycogen in the liver, resulting in increased blood glucose levels. Epinephrine is secreted by the adrenal medulla in response to physiological stressors. Epinephrine also stimulates the breakdown of glycogen to release glucose into the blood. In addition, epinephrine stimulates lipolysis to release fats from storage to be used as an energy source. Cortisol and growth hormone also stimulate the release of foodstuffs from storage but in different circumstances. Cortisol stimulates the breakdown of adipose for energy, sparing blood glucose for usage by the brain. Cortisol also stimulates the breakdown of muscle to provide amino acids for gluconeogenesis. Prolonged cortisol excess results in the development of obesity with a unique distribution of fat consisting of truncal obesity, thin limbs and round face. Growth hormone also stimulates the breakdown of fats but spares muscle and glucose. Thus, these five hormones, insulin, glucagon, epinephrine, cortisol and growth hormone, regulate the conventional aspects of metabolism.

Prior to the discovery of leptin in 1994, adipose tissue was

considered to be a relatively inert storage depot for excess calories.[1,2] The discovery of leptin, a hormone secreted by adipose tissue, launched the search for more hormones from adipose tissue, as well as additional hormones involved in the regulation of metabolism. We now recognize many other hormones that are secreted by adipose tissue. Moreover, hormones secreted by tissues such as the stomach, gastrointestinal tract and pancreas form an interacting network with adipose hormones and the central nervous system to regulate functions such as appetite, satiety and fat deposition. Herein, we review the network of hormones engaged in the regulation of energy storage in adipose tissue and the derangements of these hormones in obesity. The hormones can be divided into orexigenic and anorexigenic hormones.

Anorexigenic Hormones

Leptin is produced by adipose tissue in direct correlation to the quantity of adipose tissue. Insulin and glucocorticoids also stimulate secretion of leptin. In the hypothalamus, leptin increases satiety, decreases appetite and food intake, increases energy expenditure and stimulates thermogenesis. Unfortunately, increases in leptin secretion by increased fat mass result in the development of resistance to leptin that is reminiscent of the resistance to insulin that occurs in obesity. The majority of obese individuals have excess levels of leptin as well as leptin resistance.[1,2]

Adiponectin is another anorexigenic peptide secreted by adipose tissue. Adiponectin is antiinflammatory, increases lipolysis and energy expenditure, and decreases appetite.[1,2] It has also been shown to counter insulin resistance. However, adiponectin secretion is reduced in obesity, thus neutralizing its ability to fight insulin resistance.

Adipocytes also secrete the peptide resistin.[1,2] Resistin secretion increases in obesity and has been shown to increase insulin resistance. However, early reports that resistin was the factor primarily responsible for the development of insulin resistance in type 2 diabetes[3] have not been fully substantiated.[1]

In addition to insulin and glucagon, the pancreas secretes the hormones pancreatic polypeptide and amylin, both of which are anorexigenic hormones. Pancreatic polypeptide reduces food intake and decreases gallbladder motility and exocrine pancreatic secretion.[1,2] In animals, pancreatic polypeptide reduces gastric emptying, but it is not clear whether this effect occurs in humans as well. Amylin and insulin are secreted together from the pancreas. Amylin increases satiety and decreases glucagon secretion. It also decreases gastric emptying and gastric acid secretion.[1,2] An amylin agonist, pramlintide, is used in the treatment of type 2 diabetes and has shown efficacy in stimulating weight loss. Pramlintide is in clinical trials for this application.[4]

Anorexigenic hormones are secreted from the stomach and the intestines as well. The stomach and duodenum secrete obestatin, which decreases hunger and gastrointestinal motility. Obestatin is derived from the same gene as ghrelin, but differential processing of the gene product yields a hormone with physiological properties that are the opposite to those of ghrelin.[1,2] The gastrointestinal tract also secretes peptide YY (PYY). PYY decreases gastric acid secretion and gastrointestinal motility, reduces food intake and increases fat oxidation. In the hypothalamus, PYY reduces the secretion of the orexigenic peptide, neuropeptide Y.[1,2]

Glucagon-like peptide 1 (GLP-1) is produced by the small and large intestine. GLP-1 increases insulin and decreases glucagon secretion from the pancreas. In the stomach, GLP-1 reduces gastric acid secretion and gastric emptying. It decreases energy intake and increases satiety.[1,2] Exenatide is a long-acting agonist of GLP-1 which is in use for the treatment of type 2 diabetes and is in clinical trials to test its efficacy in supporting weight loss. Oxyntomodulin is also secreted from the gastrointestinal tract; its effects include decreased food intake and gastric acid secretion, as well as increased energy expenditure.[1,2] Interestingly, both GLP-1 and oxyntomodulin are derived from the same gene product as glucagon. Differential processing results in production of the different hormones.

Cholecystokinin is a gastrointestinal hormone whose ability to stimulate reduced food has been known for many years.[1,2] The ability of cholecystokinin to affect weight has been tested; it was found that cholecystokinin reduced food intake at meals but subjects partook of more frequent meals to compensate for the reduced food intake at each meal. Overall caloric intake and weight did not change.

Anorexigenic neuropeptides in the hypothalamus include alpha melanocyte stimulating hormone (αMSH, also called melanocortin), melanin concentrating hormone (MCH) and cocaine and amphetamine-regulated transcript (CART). These peptide neurotransmitters mediate many of the anorexigenic effects within the network of interactions among hypothalamic nuclei and other brain centers involved in appetite, satiety, and energy homeostasis.[1,2]

Orexigenic Hormones

Ghrelin is the only peripheral circulating orexigenic hormone. It is secreted by the stomach and duodenum. Ghrelin

increases gastrointestinal motility; it also targets the hypothalamus where it stimulates hunger. Functionally, ghrelin antagonizes the actions of leptin.[1,2] The structure of ghrelin is interesting; it is a 28 amino acid peptide with an n-octanoic acid attached at the 3 position. The acylation is necessary for the orexigenic actions of ghrelin.

In the central nervous system, the hypothalamus and brainstem are the primary sites of coordination of signals involved in appetite and satiety. Of the neuropeptides involved in coordinating these signals, several are clearly orexigenic. Neuropeptide Y (NPY) and agouti homologous human protein (AgRP) are both orexigenic.[1,2] Their release stimulates appetite. Leptin inhibits the release of both NPY and AgRP.

The ability of D9-tetrahydrocannabinol, the active ingredient in marijuana, to stimulate appetite and food seeking behavior provided anecdotal evidence supporting the classification of cannabinoids as orexigenic factors long before the endogenous ligands, the endocannabinoids, were identified. Anandamide and 2-AG are the endogenous ligands for cannabinoid receptors.[1] Endocannabinoids are derived from arachidonic acid, synthesized in an analogous manner to the prostaglandins, and they share a similarly short half-life. Receptors for the endocannabinoids are found both centrally and peripherally. Their overall effect is the stimulation of appetite and of food seeking behavior, reduced satiety and energy expenditure, weight gain and decreased sensitivity to insulin.[1]

Other hormones have been implicated in the regulation of energy homeostasis, including retinol binding protein 4 (RBP4) and visfatin.[1,2] Both RBP4 and visfatin are secreted by adipose tissue, but their physiological actions are poorly understood. RBP4 has been shown to increase resistance to insulin and to increase hepatic gluconeogenesis. Visfatin, also known as nicotinamide 5-phosphoribosyl-1-pyrophosphate transferase and pre-B cell colony enhancing factor, is a proinflammatory cytokine, but studies of its effects on energy homeostasis have provided contradictory effects, so its function remains unclear. A variety of other hormones have been proposed to interact in the network of regulation of metabolism but with little functional information about each of them. These include omentin, vaspin, apelin, galanin, orexin and melanin-concentrating hormone.[1,2] It is likely that the roles of these factors will become clear with continuing studies.

Effect of Obesity on Hormonal Control of Energy Homeostasis

Considering the wealth of anorexigenic hormones available, one would expect that appetite and satiety could be easily controlled by endogenous factors, even in the face of ready access to excess calories. The rising tide of obesity in the world clearly demonstrates that this is not the case. Not only is it easy to gain weight, it is difficult to lose weight and even more difficult to maintain weight loss.

Serum levels of insulin, pancreatic polypeptide, amylin and leptin increase with increasing fat mass.[1,2] This leads to resistance to insulin, leptin and pancreatic polypeptide, so they are unable to carry out their anorexigenic effects. Inflammation, a common theme in the literature on diet induced obesity,[5,6] plays a leading role in the primary hypothesis proposed to explain the development of hormonal resistance in obesity. Inflammation occurs both in adipose tissue[6] and the hypothalamus with increased fat mass.[5] As the quantity of adipose tissue increases in obesity, monocytes invade and differentiate into macrophages and ultimately into foam cells.[6] Thus, in the presence of obesity, adipose tissue is considered an inflammatory tissue with the secretion of a variety of inflammatory cytokines and related factors. Two of the inflammatory cytokines most commonly described in regard to adipose tissue are tumor necrosis factor alpha (TNFα) and interleukin 6 (IL6). Interestingly, the individual effects of TNFα and IL6 support an anorexigenic effect in that they reduce food intake and increase satiety. However, both also increase insulin resistance and support further inflammatory actions in adipose tissue.6 In the hypothalamus, diet induced obesity causes inflammation which leads to hypothalamic resistance to insulin and leptin. Resistance to these hormones then contributes to further obesity.[5]

Several hypotheses have been proposed to explain the difficulty in maintaining weight loss. The concept has arisen that adipose tissue maintains its mass by "defending" itself, always attempting to return to the highest fat mass achieved.[7] One hypothesis that attempts to explain the difficulty in maintaining weight loss relates to the orexigenic hormone, ghrelin. Levels of ghrelin are decreased in obesity and rise again when weight loss occurs. The increase in ghrelin with weight loss stimulates hunger and increases food intake, thereby contributing to the difficulty in maintaining weight loss.[2] A second hypothesis relates to leptin. As weight is lost, leptin levels decline and its anorexigenic drive is lost from the hypothalamus.[7] The reduced leptin results in decreased satiety, increased appetite and food intake and decreased energy expenditure, all of which sabotage the ability of an individual to maintain weight loss.

Conclusion

Our concept of adipose tissue as an inert storage depot for excess calories has undergone significant changes. It is now clear that adipose tissue is a dynamic endocrine organ capable of secreting a variety of hormones that not only participate in a network of peripheral and central factors that regulate energy homeostasis but also maintain fat mass. The individual roles of each of the adipose hormones, and the contributions of other hormones involved in energy homeostasis, to weight gain, weight loss and maintenance of weight loss have been only partially defined. Much remains to be learned regarding the basic endocrinology of adipose tissue.

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Insulin Resistance, Obesity and the Metabolic Syndrome

By Richard J. Barth, MD

Abstract:
The metabolic syndrome is a clinically important but often misunderstood topic. A concept in evolution, controversy surrounds the metabolic syndrome. The medical literature documents disagreement in the criteria for diagnosis, a shift in emphasis as to the roles of obesity and insulin resistance as underlying causes, and questions about the fundamental clinical utility of the syndrome. The practical strengths and limitations of the metabolic syndrome in clinical practice are reviewed.

Introduction

The clinical association of obesity, glucose intolerance, hypertension, and atherogenic dyslipidemia with atherosclerotic heart disease is well recognized clinically, and in recent years referred to as the concept of the metabolic syndrome. The metabolic syndrome is a topic of great interest, as suggested by a Pub Med search of articles since 1988 in English with "metabolic syndrome" in the title showing more than 6600 published papers. The metabolic syndrome is also a topic of some confusion and controversy. What exactly is the metabolic syndrome? How is the metabolic syndrome recognized clinically? What is the underlying problem causing the metabolic syndrome? How should the diagnosis of the metabolic syndrome be used clinically? The purpose of this paper is to clarify these issues in a way that will be clinically useful to the practicing provider.

Definition of the Concept of the Metabolic Syndrome

The metabolic syndrome can be thought of as multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease and is strongly associated with type 2

diabetes.[1,2] Grundy offered the more precise but cumbersome term of metabolic-risk-factor-clustering.[3] It should be emphasized that the metabolic syndrome is a syndrome and not a disease. A syndrome is defined as a recognizable complex of symptoms and physical or biochemical findings for which a direct cause is not understood. With a syndrome, the components coexist more frequently than would be expected by chance alone. The syndrome becomes a disease when causal mechanisms are identified.[4] Implicit in the name is the fact that this is a concept in evolution and further refinement should be anticipated.

Unfortunately, terminology in this literature is confusing, with the phrase metabolic syndrome used interchangeably with the phrases insulin resistance and insulin resistance syndrome, and most recently, cardiometabolic risk. These are four separate concepts. Insulin resistance is defined as a subnormal biologic response to a given concentration of insulin.[5] This is not a disease state but rather a pathophysiologic condition that can be defined and measured.[1] The insulin resistance syndrome is a cluster of the abnormalities and related clinical outcomes that occur more commonly in insulin resistant/hyperinsulinemic individuals. These include type 2 diabetes, cardiovascular disease, essential hypertension, polycystic ovary syndrome, nonalcoholic fatty liver disease, certain forms of cancer and sleep apnea.[6] In contrast, the metabolic syndrome was developed to be a clinical tool to assess risk for vascular disease and diabetes. The most recent concept is that of cardiometabolic risk, which includes the metabolic syndrome plus other risk factors for cardiovascular disease, including race, sex, family history, inflammation, hypercoagulation, smoking status and physical inactivity.[7] In the literature, unfortunately, these concepts and names are sometimes used interchangeably.

Evolution of the Diagnosis of the Metabolic Syndrome

There has been an awareness of certain patient characteristics being associated with atherosclerotic disease for many years. A key point in the evolution of the metabolic syndrome occurred with Reaven's 1998 Banting lecture.[8] Reaven proposed Syndrome X as a series of related variables that occurred in the same individual and were important in the genesis of coronary artery disease. These included resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very low density lipoprotein cholesterol and hypertension. The common feature was insulin resistance, and all other changes were thought to be secondary to this basic abnormality.

Multiple groups have taken this concept and operationalized it into working definitions that are designed to be practical and useful to clinicians. The World Health Organization (WHO), as part of the 1999 report on the definition, diagnosis, and classification of diabetes, recognized the importance of insulin resistance as a major contributor to the metabolic syndrome.[9] Required was evidence of insulin resistance: either impaired glucose tolerance, impaired fasting glycemia, diabetes mellitus or insulin resistance based on insulin clamp studies, along with two or more of the following: raised arterial pressure >140/90 mmHg; raised triglycerides >150 mg/dl and or low high density lipoprotein cholesterol (HDL-C), defined as <35mg/dl in men, <39 mg/dl in women; central obesity, defined as waist-to-hip ratio greater than 0.90 in males and greater than 0.85 in females and /or body mass index (BMI) greater than 30 kg/m^2; and microalbuminuria, measured as urinary albumin excretion rate >20 ug/min or albumin to creatinine ratio >30mg/g.

The European Group for the Study of Insulin Resistance (EGIR) proposed a modified version of the WHO definitions to be used in non-diabetic subjects only.[10] Glycemic clamp studies were not required, but fasting insulin levels in the top 25 percent of fasting insulin levels were mandatory. In addition, two or more of the following were required: fasting glucose >110 mg/dl but not diabetic, hypertension >140/90 mmHg or treatment, triglycerides >178 mg/dl or treatment or HDL-C <39 mg/dl or treatment, and central obesity based on waist circumference of men >37 inches and women >31.5 inches.

The most commonly used definition for the metabolic syndrome is from the National Cholesterol Education Program-Third Adult Treatment Panel (ATP-III).[11] This definition was presented as part of an educational program for the prevention of coronary heart disease. The criteria were updated in 2005 to bring the cutoffs in line with the current diagnosis of diabetes and pre-diabetes.[2] To establish the diagnosis, three or more of the following five risk factors must be present: abdominal obesity, defined as waist circumference greater than 40 inches in men and greater than 35 inches in women, triglycerides ≥150 mg/dl or HDL-C <40 mg/dl in men and <50 mg/dl in women, blood pressure ≥130/85 mmHg or fasting glucose ≥100 mg/dl. The ATP-III panel did not find adequate evidence to recommend routine measurement of insulin resistance, such as plasma insulin, proinflammatory state, such as high-sensitivity C-reactive protein, or prothrombotic state, such as fibrinogen or plasminogen activator inhibitor-1, in the diagnosis of the metabolic syndrome.

The American College of Endocrinology (ACE) proposed that insulin resistance must be present in order to diagnose the metabolic syndrome.[12] Insulin resistance is suggested by a fasting glucose of 100 to 125 mg/dl, or an insulin glucose tolerance test twohour glucose value >140 mg/dl. Other

factors are noted as identifying abnormalities of the syndrome. These include: BMI >25 kg/m^2 or waist circumference greater than 40 inches in men and greater than 35 inches in women, triglycerides >150 mg/dl, HDL-C <40 mg/dl in men and <50 mg/dl in women, or blood pressure >135 systolic or >85 mm Hg diastolic. The ACE statement deliberately does not provide specific diagnostic criteria, recommending instead that the diagnosis should rely on clinical judgment.

The most recent definition of the metabolic syndrome was proposed in 2005 by the International Diabetes Federation (IDF).[13,14] Central obesity must be present, as defined by a waist circumference of >37 inches for Europid men and >31.5 inches for Europid women, with ethnicity specific values for other groups. In addition, two of the following must be present: raised triglyceride level of >150 mg/dl or treatment, reduced HDL-C of <40 mg/dl in men and <50 mg/dl in women or treatment, raised blood pressure of >130 systolic or >85 diastolic or treatment, raised fasting plasma glucose >110mg/dl or previously diagnosed type 2 diabetes, with an oral glucose tolerance test strongly recommended if fasting glucose >100 mg/dl.

There are subtle differences in the definitions offered by these groups. The WHO definition assumes insulin resistance to be the major contributor to the metabolic syndrome and requires insulin resistance or a surrogate marker to be present. The WHO definition is also the only that included microalbuminuria as a criteria. The EGIR modified the WHO definition by substituting the easier to measure fasting insulin level as a marker for insulin resistance, omitted the microalbuminuria criteria and modified the cut points for the other criteria. In contrast, the ATP-III is not glucose-centric and treats glucose abnormalities as equal with the other criteria in the diagnosis. The WHO, ATP-III and IDF do not exclude people with type 2 diabetes from having the metabolic syndrome; the ACE definition does exclude people with diabetes. The ACE proposal was designed not to be another competing definition but more of an explanation of the mechanism of the syndrome.[15] The ATP-III and IDF definitions are more lipid-centric, with high triglycerides and low HDL-C each being a separate criteria, in contrast to the WHO definition recognizing either as just one criterion. Lastly, while all of the definitions have obesity as one criterion, only the IDF definition recognizes obesity as both an etiologic factor and a good clinical surrogate of insulin resistance and is the only to require obesity for the diagnosis.[16] Also, the IDF definition was designed to be more practical in that it can be used in any country, allowing for better comparative long term studies. This is in contrast to the WHO and ATP-III definitions, that under estimate the prevalence of the metabolic syndrome in Asian populations by using obesity definitions not applicable to an Asian population.[17]

One of the problems with these various definitions is that they do not recognize the same individuals in a population as having the metabolic syndrome. Data from a national sample of 11,247 Australians was analyzed using the WHO, ATP-III and EGIR criteria.[18] Each identified 15 to 21 percent of the population as having the metabolic syndrome. However, only 9.2 percent of the population would have met the criteria for all three definitions, with the rest identified by one but not identified by another. A second study from Adelaide, South Australia, of predominantly European adults found the IDF definition recognized the metabolic syndrome in 22.8 percent while the ATP-III recognized the metabolic syndrome in 15 percent.[19] The DECODE Study Group, which looked at 11 prospective European cohort studies, found similar discordant results.[20] Ford looked at the NHANES 1999-2002 subset data and found the prevalence of the metabolic syndrome in the United States using the IDF definition to be 39 percent, in contrast to the ATP-III definition prevalence of 34.5 percent.[21] These two definitions agreed in classifying 93 percent of the population as having or not having the metabolic syndrome and disagreed in the classification of the other 7 percent.

In an attempt to harmonize the metabolic syndrome, in 2009, six international groups offered the following criteria for the metabolic syndrome: elevated waist circumference, with population and country-specific definitions; elevated triglycerides >150 mg/dl or treatment; reduced HDL-C, defined as <40 mg/dl males and <50 mg/dl females, or treatment; elevated blood pressure, defined as systolic >130 mmHg and/or diastolic >85 mmHg or treatment; elevated fasting glucose >100mg/dl or treatment.[22]

Causes of the Metabolic Syndrome

Implicit in the choices of the defining criteria is an attempt to understand the underlying causes of the metabolic syndrome. Three potential categories have been proposed: first, insulin resistance; second, obesity and disorders of adipose tissue; and third, independent factors, such as molecules of liver, vascular or immunologic origin that mediate specific elements of the syndrome.[23]

As indicated by the elements in the clinical definitions of the metabolic syndrome, insulin resistance is thought to be the prime underlying factor. Insulin itself may directly promote cardiovascular pathology through its actions on multiple compounds, such as mitogen-activated proteinkinase, plasminogen activator inhibitor-1, endothelin-1, tumor

necrosis factor and nitric oxide.[24] Insulin plays an important role in pathways of glucose homeostasis, lipid turnover, blood pressure control and vascular reactivity. Chronic hyperinsulinemia with insulin resistance, however, is not sufficient to alone cause the clinical problems.[25] Each of these systems is under redundant, multifactorial control. For example, an insulin-resistant person only becomes diabetic when there is a failure of the ability to continue to overproduce insulin.

The primacy of insulin resistance is questioned by the recognition of patients who meet the criteria for the metabolic syndrome but who do not have insulin resistance. In one study, only 78 percent of those with the metabolic syndrome had insulin resistance, and only 48 percent of those with insulin resistance had the metabolic syndrome.[26] In the Framingham Offspring Study, only 56 percent of individuals with an ATP-III definition of metabolic syndrome, and 52 percent with the IDF definition, were found to have insulin resistance.[27]

In addition, the cutoff point for insulin resistance is not clear. A frequently used assessment is the homeostasis model, using a definition of insulin resistance as being greater than the 75th percentile among non -diabetic subjects.[27] However, normal insulin-mediated glucose disposal can vary six- to eight-fold in healthy, non-diabetic men, absolute insulin levels in the population are variable, and there is no agreed upon absolute criteria for insulin resistance.[28]

Other arguments have suggested obesity to be the driving force behind the metabolic syndrome.[29] Clinically, as obesity increases, so does the prevalence of the metabolic syndrome.[30] Possible causative factors include the excess release of non-esterified fatty acids leading to ectopic fat accumulation in liver, muscle and visceral fat. In addition, adipose tissue is a dynamic endocrine organ, secreting multiple peptides and cytokines, referred to as adipokines, such as leptin, adiponectin, and tumor necrosis factor-alpha. Adipokines can have an influence on food intake, energy expenditure, body weight and multiple effects on organs such as the liver, muscle, pancreatic islets, heart and vascular endothelium.[31]

The distribution of excess fat in the body is important. Abdominal obesity, as opposed to peripheral obesity, is a marker of dysfunctional adipose tissue, and is associated with various atherogenic and diabetogenic properties.[32] For this reason, waist circumference or waist-to-hip ratio are favored over BMI or weight as a defining criterion.

Similar to insulin resistance, the role of obesity is not completely understood. Obesity is not necessary for insulin resistance. Insulin resistance occurs in 10-15 percent of people who are not overweight.[33] Meigs,[34] in a community based longitudinal study of 2,902 adults, mean age 53, using the ATP-III definition, found insulin resistance to be present in 7 percent of normal weight subjects with BMI less than 25 kg/m2 and 63 percent of obese subjects with BMI greater than 30 kg/m^2. Uncertainty about the causative role of obesity is reflected by the different attitudes towards central obesity as a requisite versus just one criterion in establishing a diagnosis of the metabolic syndrome.

Finally, other molecules appear to play a role in the metabolic syndrome. Clinically, evidence exists that there are proinflammatory and prothrombotic elements to the metabolic syndrome, although these are not recognized as part of the defining characteristics. Adipose tissue plays an important role, releasing many bioactive mediators that influence insulin resistance as well as obesity.[35] Associated with visceral obesity are elevated levels of interleuken-6, tumor necrosis factor alpha, and C-reactive protein, which increase inflammation and further insulin resistance. Increased plasminogen activator inhibitor-1 increases thrombosis. Increased leptin leads to elevated blood pressure and loss of feedback on appetite centers. Adiponectin, which has anti-inflammatory effects and is insulin sensitizing, is decreased with visceral obesity.[36] The immune response of low-grade inflammation and metabolic regulation are closely integrated, and dysfunction can lead to a cluster of chronic metabolic disorders.[37] Overall, there has been a shift in emphasis towards obesity as the underlying factor in the metabolic syndrome.

Clinical Usefulness of the Metabolic Syndrome

The purpose of identifying the metabolic syndrome, as originally visualized, is to recognize those at increased risk for vascular disease. Vascular disease is an important health issue. The prevalence of cardiovascular disease in the United States in 2003 is 34.2 percent.[38] In the United States, using the ATP-III criteria and data from the Third National Health and Nutrition Examination Study (NHANES) from 1988 to 1994, the metabolic syndrome was present in 22 percent of the adult population.[30,39] Overweight and obesity now affects 60 percent of adult Americans. Overweight, as defined by a BMI >25 kg/m^2, was found in 65.7 percent of adults, and obesity, a BMI >30 kg/m^2, was present in 27.6 percent of men and 33.2 percent of women.28 Women with a BMI >29 kg/m2, as compared to women with a BMI <21 kg/m^2, have a 3.3-fold increase in the development of coronary artery disease.[40] The diagnosis of the metabolic syndrome increases the likelihood of cardiovascular disease, ranging from 30 to 400 percent, with the variation probably due to differing definitions,

populations studied, and length of follow-up in various studies.[41] Wilson, using the Framingham Offspring Study data, and the ATP-III criteria, found a doubling of risk for vascular outcomes in men with metabolic syndrome. Interestingly, having three of the criteria for definition did not increase risk for outcomes over the risk associated with having just two of the criteria.[42]

However, there are limitations. Making a diagnosis of the metabolic syndrome offers a long term, global assessment of vascular risk, but not a short-term specific risk assessment. This is because the metabolic syndrome does not encompass some of the traditional risk factors, such as age, sex or smoking. Other risk assessment tools, such as the Framingham score, offers a better short term risk assessment for CVD.[43,44] A diagnosis of the metabolic syndrome adds to the risk assessment, but does not replace other assessments.

Similarly, a diagnosis of the metabolic syndrome increases the risk of developing type 2 diabetes. This is not surprising, considering the fact that some criteria for the metabolic syndrome are diagnostic for pre-diabetes, which carries a high likelihood of progressing to diabetes.[45] However, other risk-assessment tools, such as the Diabetes Predicting Model, are better at predicting the development of diabetes.[46] In a study of 1,709 initially non-diabetic persons, followed for 7.5 years, the presence of ATP-III defined metabolic syndrome predicted the development of diabetes with a sensitivity of 66.2 percent and a false positive rate of 27.8 percent. The Diabetes Predicting Model, at the same false positive level, had a higher sensitivity of 75.9 percent, and at the same sensitivity, a lower false positive rate of 19.2 percent.[44]

The metabolic syndrome appears better at predicting type 2 diabetes than vascular disease. Data from the West of Scotland Coronary Prevention Study of 6,447 men was studied using a modified version of the ATP-III, in which body mass index was substituted for waist circumference. As the number of metabolic abnormalities increased, so did the occurrence of disease: if four or five of the criteria were met, there was a 3.7 fold increase in coronary artery disease and a 24.5 fold increase in diabetes.[47] In the Strong Heart Study of Native Americans, risk of diabetes increased with the presence of the metabolic syndrome, 12.8 percent versus 24.5 percent, but the risk of coronary artery disease did not increase independent of individual cardiovascular risk factors.[48]

Treatment Recommendations

No matter how the metabolic syndrome is defined, the mainstay of intervention is lifestyle changes. Diet, physical activity and weight loss are consistently noted to be the cornerstone of physician interventions. Beyond this, drug therapy can be offered for the various elements of the metabolic syndrome, based on the criteria set for each element; for example, hypertension is treated per hypertension standard of care guidelines.

Blaha, after a comprehensive review of the literature, offered a practical "ABCDE" approach to the treatment of the metabolic syndrome,[36] with a recent update.[49]

"A" is assessment, make the metabolic syndrome diagnosis, calculate the Framingham risk, and consider aspirin in all people with greater that 6 percent 10-year Framingham risk with individualized decision-making in low-intermediate risk of 6 to 10 percent.

"B" is blood pressure control, with consideration of angiotensin converting enzyme inhibitors or angiotensin receptor blockers as first line choices and dihydropyridine calcium channel blockers as second line. Third -line antihypertensives are the beta-blockers and thiazide diuretics, if the benefit of reaching blood pressure goals when first- and second-line therapies are not sufficient, outweighs the risk of deterioration of glucose tolerance.

"C" is cholesterol management, with low density lipoprotein cholesterol (LDL-C) the first target, non-HDL-C the second target, HDL-C the third target, and high sensitivity C-reactive protein the fourth target. If the LDL-C is above goal after intensive lifestyle interventions, statin therapy should be considered in all high risk patients and those with an intermediate 10-year risk of > 6 percent.

"D" is diabetes prevention, with intensive lifestyle modification for all people, and diet, with weight loss and consideration of the Mediterranean diet: increased omega-3 fatty acids, fruits, vegetable, fiber, nuts and low glycemic index carbohydrates.

"E" is exercise, with daily vigorous activity and use of a pedometer with goal of more than 10,000 steps daily recommended.

Clinical Utility of the Metabolic Syndrome

There are many concerns associated with the metabolic syndrome. There is not agreement in the literature in the criteria to establish the diagnosis. The relative importance of insulin resistance versus obesity is in question. The metabolic syndrome does not appear to be the best predictor of the development of cardiovascular disease or diabetes. Apart from lifestyle changes, there is no specific treatment above and beyond the treatments for the various components. Finally, the question has been raised repeatedly in the literature about whether the whole of the risk assessment of

developing cardiovascular disease or diabetes when the metabolic syndrome is diagnosed is more than the sum of the risk assessments of the various individual components. In a joint statement, the American Diabetes Association and the European Association for the Study of Diabetes offered the opinion that the diagnosis of the metabolic syndrome itself, or the lack of the diagnosis, added nothing to the treatment of one or more cardiovascular risk factors in a given patient.[28]

In spite of these concerns, the metabolic syndrome is clinically useful. From a practical point of view, the metabolic syndrome could be thought of as an alert for the practicing provider. Recognition of any one element of the metabolic syndrome should prompt consideration of whether any other elements are present. Clinically, the provider should consider not only the defining characteristics, but also all of the conditions associated with the insulin resistance syndrome. Once recognized, a clinical decision can be made as to the proper course of action regarding each element to minimize the possibility of atherosclerotic heart disease and diabetes. Each abnormal component should be treated to usual standard of care. Common to all therapies is emphasis on lifestyle changes and weight loss when appropriate.

In summary, the metabolic syndrome is not a disease to be diagnosed, but rather a clinical tool to be used for cardiovascular and diabetes risk assessment and then risk intervention, and a tool to be used as a clinical prompt to search for other conditions associated with insulin resistance and obesity.

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Sleep Apnea and Obesity

By John C. Yu, MD; Paul Berger, III, DO

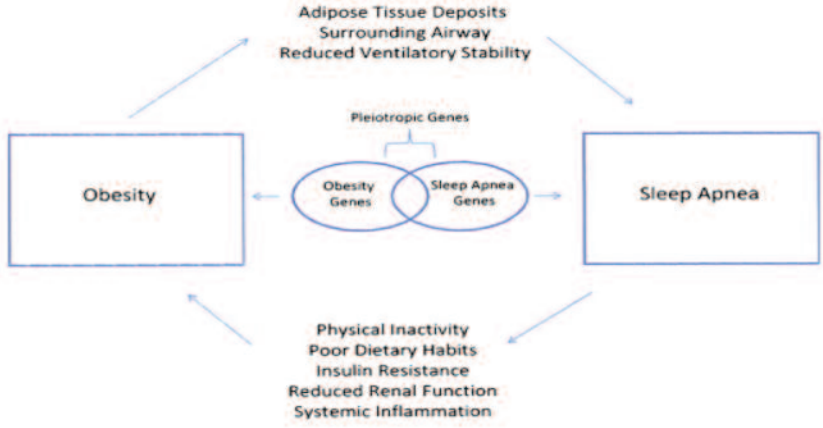
Abstract:
The dramatic increase in the worldwide prevalence of obesity has paralleled the increase in the prevalence of obstructive sleep apnea (OSA). Even with heightened awareness by the lay and medical communities, OSA is still markedly under-diagnosed, as evidenced by the persistent presentation of late-stage cardiovascular complications in obese individuals newly diagnosed with sleep apnea. The clinical sequela of untreated and poorly-treated sleep apnea include conditions that are considered components of the metabolic syndrome for which central obesity is one of the major case-defining features. Hence, in this review of obesity and sleep apnea, it is unavoidable to include discussion of sleep apnea and other components of the metabolic syndrome. Proponents of this clinical perspective suggest that there are mutual genetic determinants that give rise to common phenotypic features and allow clustering of sleep apnea with the other components of the metabolic syndrome.[1] Perhaps, the strongest observational evidence to support a link between sleep apnea and obesity is the similarity in age distribution of symptomatic sleep apnea and metabolic syndrome. The putative causal links between sleep apnea and each individual component of the metabolic syndrome have been extensively evaluated and have implicated bidirectional causality in certain metabolic conditions, such as obesity and sleep apnea, sleep apnea and diabetes mellitus, and obesity and diabetes mellitus. These studies collectively suggest that even modest weight loss improves OSA, and positively affects both metabolic and cardiovascular risk profiles.

Introduction

According to the criteria established by the second edition of the International Classification of Sleep Disorders (ICSD-2), a diagnosis of obstructive sleep apnea (OSA) is made when an Apnea-Hypopnea Index (AHI) of 5 or greater per hour is documented in a standard-in-lab polysomnography (PSG). The AHI is the sum of apnea and hypopnea per hour of sleep. Apnea is the cessation of airflow for at least 10 seconds in the presence of respiratory efforts. Hypopnea is the reduction of airflow of at least 30 percent accompanied by 3 percent or more desaturation from baseline for at least 10 seconds in the presence of respiratory efforts.[2]

The prevalence of obesity in the United States is approximately 30 percent of adults, translating to about 60 million adults.[3,4] Increasing weight has been associated with increasing prevalence of OSA (Figure 1).[5] The Sleep Heart Health Study showed a relationship between rising BMI to increasing OSA severity.[6] Peppard showed that weight gain directly correlates with AHI, while weight loss ameliorates OSA, further bolstering the causal relationship between obesity and OSA.[7] However, the incidence of newly diagnosed OSA has not paralleled the rising prevalence of obesity in

Fig. 1. Vicious cycle of obesity and OSA. (From Carter R, Watenpaugh DE. Obesity and obstructive sleep apnea: Or is it OSA and obesity? Pathophysiology 2008; 15:72; pending permission).



all age groups and ethnicity, suggesting a significant under-recognition of the public health impact of this disease.

Suspicion of an undiagnosed, sleep-disordered, breathing condition should be very high in obese patients. Multiple risk factors, including age, race, male gender, craniofacial abnormalities in congenital disorders, nasal obstruction, genetic factors, endocrine abnormalities and postmenopausal status have been associated with OSA. By far, central or visceral obesity is considered the most important risk factor for the development of OSA, secondary to its association with the major components of the metabolic syndrome. In fact, two very important objective metrics of central obesity, body mass index (BMI) and neck size or circumference, have correlated with the probability of diagnosing OSA during the initial clinical evaluation. It is intuitively obvious to primary practitioners that when obese patients present with symptoms of excessive daytime sleepiness (EDS), sleep-maintenance insomnia from sleep fragmentation, gasping arousals or startled awakenings, a formal sleep study (PSG) should be ordered. On the other hand, the presence of hypertension, dyslipidemia and glucose intolerance are less evident reasons to obtain an urgent evaluation for an underlying OSA, unless there are associated cardiovascular complications. These cardiovascular complications usually manifest with exertional dyspnea, leg edema, palpitations from paroxysmal atrial arrthymias and pulmonary hypertension. Not infrequently, cardiac evaluation of such patients reveal non-obstructive coronary disease, left ventricular diastolic dysfunction (LVDD), and secondary pulmonary hypertension that is out of proportion to any primary respiratory disorder. A morbidly obese patient (BMI greater than 40) with stigmata of chronic hypercarbic respiratory insufficiency, such as facial plethora, secondary polycythemia, pulmonary hypertension and cor pulmonale, should prompt an urgent evaluation for obesity hypoventilation syndrome (OHS). OHS is a subset of OSA differentiated by a marked reduction of respiratory drive.

The cardiovascular consequences of severe untreated OSA have recently been confirmed and elucidated by a large, multicenter population study, Sleep Heart Health Study, using standardized polysomnographic criteria.[8] Other population-based observational studies based in Spain,[9] Wisconsin[10] and Busselton (Australia)[11] have clearly implicated a strong association with future cardiovascular mortality. The severity of OSA (based on AHI greater than 40) directly correlates with the risk of developing cardiac disease and its composite endpoints of death, stroke and myocardial infarction.[8,12-13] The link between OSA and the development of hypertension is perhaps the strongest and the most studied as shown in a prospective study by Peppard and colleagues. Even in patients with mild OSA, there is a 42 percent greater risk of developing hypertension in four years.[14] A recent meta-analysis of 18 RCTs, involving 818 patients, clearly demonstrated blood pressure reduction with Continuous Positive Airway Pressure (CPAP) therapy.[15] Other investigators have found strong associations of OSA with coronary heart disease and MI, heart failure, stroke, sudden cardiac death during sleep and cardiac arrthymia.[13,16-18]

Albeit less obvious, other psychosocial and safety issues are also prominently affected by OSA. Examples include depression and chronic pain aggravated by chronic partial sleep deprivation, spousal sleep disorder causing a poor marital relationship, and impaired cognitive performance contributing to occupational and motor vehicle accidents, all of which increase health care utilization and contribute to poor life experiences.[19-20]

Pathophysiology

Repetitive upper airway narrowing or collapse during sleep, worsened by the supine position of sleep, is the main pathophysiologic mechanism of OSA. Obesity can significantly affect the structure and function of the upper airway by disrupting the equilibrium of counteracting forces that keep the airway open or collapsed. During inspiration, both, diaphragmatic contractions that generate negative intraluminal pressure and extraluminal tissue pressure of the pharyngeal wall, act to collapse the airway. These collapsing forces are counterbalanced by the pharyngeal dilator muscles. Obesity, with increased mucosal adiposity and redundancy, contributes to upper airway collapse by increasing pharyngeal wall stress and altering the compliance of the pharyngeal wall, thereby reducing airway patency. It should then be of no surprise to expect significant worsening of OSA during REM-associated atonia in obese patients with inherent pharyngeal airway compromise.

When sleep is restricted by OSA, the risk of developing diabetes intensifies secondary to impairment in glucose metabolism from altered insulin sensitivity imposed by increased sympathetic activity, counter-regulatory hormones and abnormal appetite regulation.[21] In fact, these so-called intermediate pathways have been discussed by Punjabi and colleagues.[22] Glucose intolerance and insulin resistance are enhanced when sleep loss leads to increased sympathetic nervous system activity. This increased sympathetic activity results in increased lipolysis, gluconeogenesis and glycogenolysis. Increased counter-regulatory hormones, such as GH, glucagon and cortisol, result from recurrent hypoxia and arousals, and also from the disrupted circadian control of the hypothalamic-pituitary-adrenal axis.[23] Increased levels of these counter-regulatory hormones are associated with insulin resistance. Sleep loss has been

demonstrated in multiple studies to elevate these hormones (GH and cortisol).[24-25] Lastly, data from animal and human studies suggest that certain adipocyte-derived inflammatory mediators, such as IL-6, TNF-α, and leptin, may impart insulin signaling abnormalities on the feedback loop between adipose tissue and the pancreas.[26] Sleep deprivation also affects appetite regulation as shown in the altered circadian secretions of appetite-inhibiting hormone (leptin) and appetite-stimulating peptide (ghrelin).[27] Orexin, the absence of which is pathologically related to narcolepsy, also increases feeding during arousal and is associated with increased sympathetic activity, but the link to weight gain from sleep loss is not clear yet. Laboratory studies have been done on total and partial sleep deprivation's affect on abnormal glucose metabolism, leading to impaired glucose tolerance and eventual development of type 2 diabetes.[28]

From a behavioral perspective, symptomatic OSA promotes maladaptive coping mechanisms that perpetuate the risk factors for developing and worsening obesity. These coping mechanisms include decreased physical activity, reduced energy expenditure, lower motivation secondary to depression and chronic fatigue as well as increased appetite through a putative pathway related to leptin resistance. Hence, OSA may contribute to obesity by causing a state of increased energy balance (Figure 2). Obese patients often admit to being deconditioned, and the presence of easy fatigability and dyspnea with exertion which further limits their physical exercise. Intuitively, we also know that sleep-deprived individuals tend to make unhealthy food choices with a preference for high-carbohydrate, salty food, irregular meals and frequent snacking.[27] These pathological interrelated vicious cycles have feedback and feed-forward pathways that further increase weight and the development of OSA.

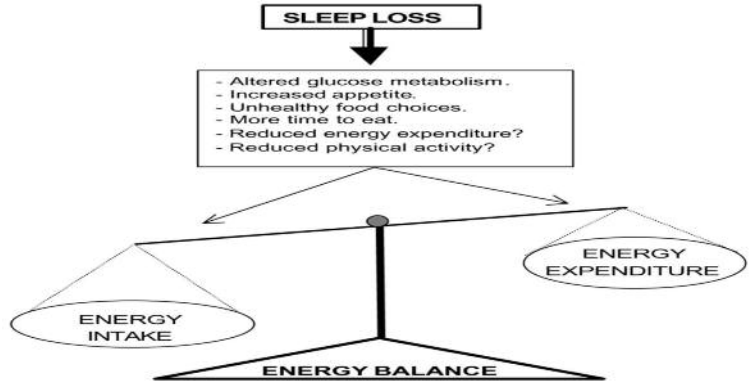
Obesity Hypoventilation Syndrome

When obese patients are diagnosed with severe OSA (AHI greater than 50) and manifest features of pulmonary hypertension and cor pulmonale with facial plethora, cyanosis and secondary polycythemia, Obesity Hypoventilation Syndrome (OHS) should be suspected. This condition is synonymous with Pickwickian Syndrome, an offshoot of the description first used by Charles Dickens to label a very sleepy, red-faced, overweight boy named Joe in *The Pickwick Papers*.[29] The diagnosis is based on a combination of obesity (BMI greater than 30), unexplained daytime hypercapnia (pCO_2>45mm Hg), and sleep-disordered breathing. The sleep disturbance may be OSA, central sleep apnea, sleep-related hypoventilation or a combination of the above. Other causes of sleep hypoventilation syndrome must be ruled out like the use of CNS depressants, severe COPD, severe restrictive lung diseases from chest wall deformities, neuromuscular diseases or interstitial lung diseases, hypothyroidism and congenital central hypoventilation syndrome. A recent review of nine studies pegged the prevalence of OHS in obese OSA patients at 10 to 20 percent, but OHS is significantly underdiagnosed because these patients often escape detection until late in the natural course of the illness.[30]

Patients with OHS often have comorbid conditions that complement their metabolic dysfunctions, such as angina, hypertension, diabetes, congestive heart failure, cor pulmonale, degenerative arthritis, hypothyroidism and behavioral disorders. Because these comorbid conditions frequently require urgent treatment the unifying diagnosis of OHS is frequently overlooked. This delay in diagnosing OHS has led to significant health deterioration presaging poor quality of life, emergence of associated psychological impairments and increased health care utilization.[31]

Hypoventilation in OHS is best understood from the perspective of increased work of breathing (WOB). The most obvious mechanical effect is decreased respiratory system compliance caused by abdominal mass loading, leading to a decrease in expiratory reserve volume (ERV) and functional residual capacity (FRC).[32-33] Moreover, the mechanical load from the chest increases airway resistance.[34] In a susceptible obese patient, OSA alone can also contribute to significant distortion of the chest wall mechanics and ventilator pattern, thereby enhancing the WOB and risk for hypercapnia. Lastly, the increased metabolic demands from obesity increases ventilatory drive and minute ventilation (MV) to maintain eucapnia. In OHS, with hypercarbia and hypoxemia, the hypoxic and hypercapnic ventilatory drives are blunted to prevent excessive

Fig. 2. Sleep loss leads to positive energy balance. (From Knutson K. Impact of sleep and sleep loss on glucose homeostasis and appetite regulation. Sleep Medicine Clinic 2007; 2:188; pending permission).



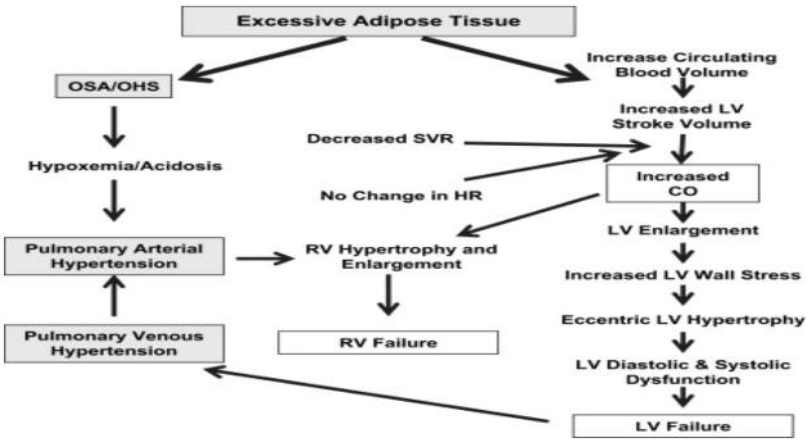
workload of breathing from contributing to respiratory fatigue. The patient's pH is maintained in the normal range by metabolically compensation for the higher pCO2 by the kidneys.

Leptin resistance has been proposed as a possible mechanism of hypercapnia in OHS because elevated leptin levels, typically seen in obese patients, correlate with reduced respiratory drive and ventilatory response to hypercapnia. Also leptin levels improve when these patients are treated with non-invasive positive pressure ventilation (NIPPV) or tracheostomy.[35-36]

Cardiovascular Health Consequences

The severity of OSA correlates directly with the degree of obesity and the risk of cardiovascular disease. Several inter-related pathophysiologic pathways from which untreated OSA can lead to cardiovascular disease have been described extensively by Selim, et al.[37](Figure 3)

Fig. 3. Pathophysiology of obesity and heart disease. (From Alpert M. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci 2001; 321(4):225-36; pending permission)



The repetitive cycles of apnea, arousal and O2 desaturation cause physiologic stresses to the general systemic and pulmonary circulations from recurrent sympathetic "jolt". These "jolts" are manifested by periodic tachyarrhythmia during arousal and loss of the normal nocturnal "dipping" in blood pressure. Over time, these "nondippers" have spillover effect of nighttime hypertensive responses into daytime, thereby contributing to hypertensive cardiovascular and cerebrovascular complications.[38-39] Because of the shared pathophysiological mechanisms in hypertension and diastolic dysfunction, it should come as no surprise that the prevalence of diastolic heart failure in OSA is high, about 40 to 60 percent.[40] Additionally, both systolic heart failure and OSA are characterized by increased sympathetic tone. The exponential effects of this adrenergic overdrive are deleterious to an already stressed cardiovascular system, and further increases mortality rate. Pulmonary hypertension may result from the same adrenergic overdrive, from repeated hypoxic pulmonary vasoconstriction, and by pulmonary vascular remodeling through local humoral factors, such as nitric oxide inhibition, oxygen radicals, endothelin and the peptide apelin.[41]

Intermittent hypoxia with reoxygenation in sleep-disordered breathing has been implicated in the generation of systemic inflammation and atherosclerosis by the formation of reactive oxygen species (ROS). ROS injure the vascular endothelium which results in the overexpression of proinflammatory cytokines, adhesion molecules and promotes apoptosis. These steps are the putative pathway that leads to vascular remodeling, atherosclerosis, and eventual heart failure.[42]

Another less apparent but equally important mechanism wherein OSA contributes to cardiovascular disease is the recurrent high negative intrathoracic pressures generated when breathing against a collapsed upper airway. The increased transmural pressure is transmitted to the heart and great vessels and may increase left ventricular (LV) afterload and diastolic dysfunction. This effect on the LV is further enhanced by an increase in right ventricular (RV) preload when the intraventricular septum shifts paradoxically from RV distention. Moreover, the high negative intrathoracic pressure impedes pulmonary arterial blood flow as demonstrated by high systemic venous pressure and lower body edema.[43] The increase in left and right cardiac loads increases myocardial oxygen utilization and decreases cardiac output. These affects especially when compounded with increased adrenergic tone may subtly progress to pulmonary hypertension, diastolic heart failure and frank cor pulmonale. This is basically, a "wear and tear" effect on the cardiovascular system. Special attention should be given to OSA occurring with any concomitant chronic lung disease or even moderate COPD (Overlap Syndrome), because of the risk of accelerated development of secondary pulmonary hypertension and cor pulmonale.

Sudden cardiac death from OSA-related arrthymia is not frequently reported. Recurrent hypoxia, acidosis, and arousals with increased adrenergic drive as well as sudden increased atrial stretching produced by periodic high intrathoracic pressure swings may be proarrthymogenic. Lastly, but less well-studied, is the potential for increased platelet activation from the above described mechanisms,

which could impact the management of cardiovascular diseases when OSA is also aggressively treated.[44]

Sleep in a patient with OSA is fraught with a period of intense cardiac instability. This is especially more poignant during REM sleep, when normal sleep is exemplified by increased sympathetic activity which is bolstered by concurrent OSA. Fortunately, treatment of OSA with CPAP or weight loss is quite successful in ameliorating sleep loss, and rapidly reverses cardiovascular instability.

Treatment of OSA and Obesity

Obesity is probably the only reversible risk factor of OSA that a patient can aggressively manage by various medical and surgical modalities. Weight loss, albeit difficult to attain and sustain in most patients, has been shown to reduce the severity of OSA with improved upper airway function and metabolic profile, even with very modest reductions in weight.[23] Weight-loss and weight-control programs should be implemented with whatever treatment is proposed for obese patients with OSA. Dietary weight reduction is only effective if it can be maintained long-term. The majority of studies evaluating the effects of weight loss on OSA had limitations due to lack of randomization, inability to control for study confounders and limited ability to follow-up.[45] Kajaste used a cognitive-behavioral program with a very-low-calorie diet with and without CPAP. Their results indicate weight loss in obese patients with OSA is achievable and may be a valuable tool in treating OSA, but the addition of CPAP was not significant. However, as in most weight loss programs, patients regained the weight after two years, accompanied by a worsening of OSA severity.[46] Over the years, many medications have emerged to treat obesity with varying efficacies, but have less than desirable safety profiles, as exemplified by the recent Meridia™ recall. Hence, treatment efforts have focused on controlling OSA with CPAP therapy, with about 60 to 70 percent acceptance rates, and sometimes combined with bariatric surgery as a last resort.[45]

The treatment of choice for patients with OSA is nasal continuous positive airway pressure (CPAP) therapy.[47] CPAP, first introduced as a treatment modality in 1981, is the most effective non-invasive treatment for OSA. CPAP decreases the number of apneic and hypoxic episodes during sleep, thereby reducing daytime sleepiness and improving the overall functionality of patients with OSA. CPAP provides a "pneumatic splint" in the form of continuous fixed pressure set at the lowest level necessary to maintain upper airway patency, while preventing upper airway collapse during sleep when muscle tone is reduced. For CPAP therapy to be fully effective, patients must be compliant to the recommended nightly treatment duration, generally defined as CPAP use for 4 hours each night for 70 percent of observed nights.[48] CPAP use is not known to be associated with serious complications, but does generate treatment related patient concerns that affect compliance such as sleep disturbance of the patient and their partner, nasal passage irritation/dryness, rhinitis, mask leaks, facial skin irritation, claustrophobia and discomfort from aerophagia. Multiple studies have shown optimal use of CPAP to be four to five hours per night with a 60 percent compliance rate. A recent Cochrane Review has indicated an improved compliance rate with patient education, appropriate mask sizing, partner education and close primary care follow-up.[48-49] Many equipment manufacturers are constantly devising more advanced proprietary features to improve patients' acceptance and adherence to CPAP therapy. These advancements include better mask designs, smaller machine for easier portability, improved humidification delivery system, and improved delivery of positive airway pressure that allow a transient drop in the stream of constant pressure to ease exhalation. The newest iteration in CPAP machine is the auto-titrating CPAP (APAP) that allows continuous adjustment of delivered pressure based on the changing severity of OSA during different stages of sleep and sleep positions. This is particularly useful in morbidly obese patients, who are motivated to lose weight or planning to undergo bariatric surgery. Despite these improvements in CPAP delivery systems, compliance continues to be a problem; even APAP has not been found to be clinically superior to conventional CPAP in the overall treatment of OSA.[50] More importantly, the potential of newer CPAP devices to record daily and cumulative usage patterns, estimate mask leak and document treatment-related residual AHI has increased our ability to monitor CPAP treatment compliance in commercial motor vehicle drivers diagnosed with OSA.

CPAP attenuates some of the cardiometabolic alterations present in OSA, obesity and sleep deprivation. Several studies have suggested that CPAP therapy is beneficial in hypertension control, with a greater effect seen in patients with higher baseline untreated BP, nocturnal hypertension and refractory hypertension requiring two or more antihypertensive medications.[15,51-52] Based on several prospective observational studies, CPAP therapy has been shown to improve long-term outcomes in CAD and its composite cardiovascular endpoints.[9,53-54] Cardiac arrhythmias are much more common in severe untreated OSA (AHI>30). As early as 1977, tracheostomy for OSA reduced or eliminated cardiac rhythm disturbances.[55-56] One observational study reported a marked reduction of atrial fibrillation recurrence after cardioversion in CPAP-treated OSA patients.[57] After only one or two nights of CPAP therapy

studies demonstrate improvements in inappropriate platelet activation and aggregation induced by increased sympathetic nervous system activity during repeated nocturnal hypoxia, sleep fragmentation and hemodynamic alterations.[44] Multiple studies have shown direct correlation between sleep loss, sleep fragmentation and recurrent hypoxemia and increased inflammatory biomarkers such as CRP and IL-6, suggesting that endothelial injury and its risk for future cardiovascular events may be alleviated by CPAP.[58-59] However, there is little evidence to support the use of CRP as a biomarker of effective, compliant CPAP therapy, since CRP levels can be confounded by the effects of obesity on systemic inflammation.[60] CPAP therapy has been associated with increased HDL, and decreased total cholesterol and visceral fat. Perhaps, the most intriguing finding is that weight loss was facilitated by CPAP therapy in obese adherent patients with OSA, with accompanying decrease in serum leptin. These findings are disputed by other investigators because of small sample size and self-reported CPAP adherence.[61-63]

Treatment of obese OSA patients with OHS is slightly different than that for eucapnic OSA patients. Bi-level PAP (BiPAP) as a form of NIPPV for OHS has been very effective, as evidenced by improved pCO2, AHI, sleep consolidation with slow-wave sleep (SWS) and REM rebound, as well as daytime sleepiness. However, because of associated cardiopulmonary morbidity, supplemental O2 is usually needed. CPAP is usually initiated first, but often fails to correct, nocturnal desaturation from persistent hypopnea, despite significant improvement in AHI. Then BiPAP with or without added O2 is provided. An occasional OHS patient is resistant to BiPAP therapy with prolonged central apnea contributing to persistent desaturation or in the setting of acute respiratory failure. In the resistant patient, timed BiPAP or BiPAP with a preset backup rate is used to maintain adequate MV as assessed by following serial ABGs. After initial clinical stabilization, most patients will need to undergo a repeat sleep study to optimize BiPAP settings. Long-term follow-up may be accomplished by monitoring improvement in clinical symptoms and pCO2 levels.

For patients who are refractory to or unwilling to use CPAP or BiPAP, tracheostomy offers the most effective method to treat severe life-threatening OSA or OHS With rapid improvement in AHI and daytime hypercapnia. For a subset of morbidly obese patients (BMI greater than 50), cautious monitoring and follow-up of pCO2 , serum bicarbonate and O2 saturation is recommended following tracheostomy because of persistent hypoxia and uncorrectable hypoventilation. These persistent findings suggest chronic, irreversible respiratory failure that requires continuous NIPPV or mechanical ventilation. Because of the variable response and tolerance to either form of NIPPV, long-term weight management should be part of a comprehensive treatment plan.

Surgical therapy for OSA should be reserved for patients that fail medical therapy or have specific anatomic abnormalities. Between the years 2000 to 2006, over 35,000 surgical procedures for OSA were performed annually, representing treatment of less than 0.2 percent of the estimated 18 million American adults diagnosed with OSA.[64] Nasal surgery can be beneficial if there is a discrete nasal obstruction or a significant nasal septum deviation. Typically, children with OSA that have tonsillar and adenoidal hypertrophy may improve with excision of these tissues. Uvulopalatopharyngoplasty (UPPP), consisting of removal of the tonsils and adenoids, uvula, distal margin of the soft palate and redundant pharyngeal tissue, is the most common surgical procedure for adults with OSA. UPPP should be considered in the mild OSA patient with retropalatal obstruction who fails or refuses CPAP treatment. Many patients who undergo UPPP may still require CPAP since UPPP carries a failure rate of at least 50 percent and has several significant complications, including oropharyngeal pain, infection and hemorrhage.[65] UPPP is actually much more effective in the overall treatment of snoring than for OSA with 80 to 90 percent success rate in the reduction of snoring. For patients with retrolingual obstruction, surgery includes genioglossal advancement, hyoid myotomy and suspension, maxillomandibular advancement (MMA) or multi-level or step-wise (MLS); often these procedures are performed in conjunction with a UPPP. Because surgical treatments of OSA in obese patients have traditionally shown poor results and because there are less invasive and more effective options for lowering AHI to less than five, surgical modifications of the upper airway for OSA have been relegated to optional in the recent Practice Parameters for Surgery of OSA in Adults released by the American Association of Sleep Medicine (AASM). Among the various surgical techniques, tracheostomy is the single most effective intervention to treat OSA, but is usually not the primary therapy offered unless pressing clinical exigencies are already present, i.e. cardiopulmonary complications.

Due to limited weight loss achieved with conservative dietary treatment, more studies are assessing bariatric surgery with the potential for dramatic weight reduction and OSA resolution.[66] Bariatric surgery is the most aggressive and effective treatment modality available for long-term weight loss; most sleep symptoms and physiologic

parameters are improved within a month.[67] Bariatric surgery essentially entails reducing the surface area for the absorption of nutrients by modifying the stomach size. Bariatric surgery is very effective in reduction of metabolic co-morbidity and mortality as shown by the landmark Swedish Obesity Study.[68] Obese patients contemplating bariatric surgery generally have an OSA prevalence of greater than seventy percent and should be preoperatively evaluated for OSA. OSA is a commonly used comorbidity in applying for insurance coverage for bariatric surgery after failure of aggressive non-surgical weight loss therapies have been documented. Regaining weight that has been lost after bariatric surgery occurs in about 5 to 10 percent of patients.[69] Unfortunately, obese OSA patients, especially those with OHS, have multiple additional co-morbidities at the time of surgery that increase the risk of perioperative complications with longer hospitalization.[70] Pulmonary embolism-related mortality is as high as 27 percent in a recent prospective data analysis by Carmody.[71] Fortunately, the routine use of CPAP or BiPAP is currently advocated in the immediate postoperative period to minimize pulmonary complications.[72] However, despite favorable reductions in BMI and AHI, OSA is only completely resolved in 4 percent of patients, and most continued to have moderate OSA and remain overweight requiring continued CPAP therapy.

Oral appliance is another modality used for treatment of OSA. In patients with mild to moderate OSA, most studies have indicated that oral appliances are effective noninvasive alternatives to CPAP.[73] Oral appliances are intraoral devices that improve clearance of the retropalatal and retrolingual spaces and are efficacious in treating non-obese positional OSA usually with AHI greater than 30 especially in patients with retrognathia and micrognathia. Oral appliances are less effective when AHI is greater than 30 and BMI is greater than 35, traits commonly seen in obese OSA patients. Mandibular repositioning appliances that advance the mandible forward are the most popular types of oral appliance. Regardless of which appliance is chosen, the ultimate goal is to prevent the tongue from falling back into the oropharynx and to strengthen the pharyngeal dilator muscles, but these conditions are not easily achievable in obese patients. Side effects from this treatment modality include excessive salivation, dental misalignment, and temporomandibular joint dysfunction. Because of the unpredictability of treatment outcome and the increased severity of OSA in most obese patients, CPAP therapy should always be considered first.

Whatever treatment for both obesity and OSA is chosen, the effectiveness of OSA therapy should be verified with a repeat sleep study, because there is reasonable evidence that the cardiovascular system is the primary target of OSA.[74] Not doing so would only expose the patient to a longer duration of unintended endothelial injury. Should a diagnosis of severe OSA then serve as a physiologic biomarker of an underlying high grade cardiovascular risk profile? An alternate point of view is to consider OSA as another component of the metabolic syndrome. Most patients with OSA are not sleepy and are not aware of their disease; however, this should not deter a practitioner from suspecting OSA if an obese patient fits the metabolic profile. Focusing on the bidirectional association of obesity and OSA, or OSA and metabolic syndrome, and their shared risk factors certainly help us improve our ability to diagnose OSA earlier so as to mitigate the corresponding cardiovascular complications.

Conclusion

It is well established that obesity is the primary risk factor for the evolution of OSA. There is also emerging evidence that OSA promotes weight gain with resultant obesity and glucose intolerance through complex pathophysiologic interrelationships (vicious cycles). Data are robust to support the relationship of OSA and cardiovascular diseases. Despite its suboptimal long-term compliance, CPAP remains the mainstay of therapy in moderate to severe OSA. There is an impetus on every practitioner to diagnose OSA early in the context of a comprehensive preventive health care program, and to adopt early aggressive approaches to treatment of OSA and obesity, so as to preempt the initiation of the above discussed pathophysiologic vicious cycles. Individually, as well as through population-based treatment programs, weight loss should be considered a primary goal of any preventive health care initiative in order to positively affect the cardiovascular risk profile of obesity, its associated metabolic syndrome and reduce the likelihood of OSA.

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Obesity and Cardiovascular Disease

By Pavithra Pattabiraman, MD; Scott Pham, MD

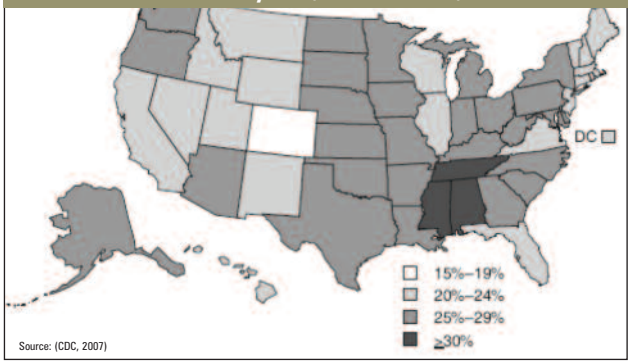
Obesity and Cardiovascular Disease

Over the past decade, obesity has become one of the major health problems in our country, and recent epidemiological data suggest that the problem is worsening. Today, the prevalence of obesity in the United States is 26.7 percent, with more than one third U.S. adults and 16 percent of U.S. children affected by the epidemic.[1] The most recent reports from the Behavioral Risk Factor Surveillance System (BRFSS) indicate a 1.1 percent increase in the prevalence of adult obesity from 2007.[2] As of 2007, no state had met the "Healthy People 2010" objective to reduce the prevalence of obesity among U.S. adults to 15 percent and in fact, the number of states with obesity prevalence of 30 percent or higher increased from none in 2000 to nine in 2009.[2] The prevalence of obesity is higher in the South (27.3 percent) and Midwest (26.5 percent), with South Dakota falling in the 25 percent to 29 percent category with 26 other states.[2]

Excess body weight increases the risk for many chronic diseases, reduces the quality of life and leads to early deaths.[2] Obesity-related health care costs have been a huge economic burden to the US health care system. Medical expenses for obese workers, depending on the sever¬ity of obesity are 29 percent to 117 percent greater than expenses for workers with normal weight.[1] In 2000, obesity-related health care costs alone were estimated to be around $117 billion.[1]

Obesity is associated with many health conditions, of which

Figure 1: Prevalence of obesity amongst adults aged ≥ 18 years – Behavioral Risk Factor Surveillance System, United States, 2007



* Persons with a body mass index (BMI) of ≥30.0; self-reported weight and height were used to calculate BMI (weight [kg] / height [m]^2)

cardiovascular disease (CVD) is the most important. Today, CVD is America's biggest health problem. According to current statistical reports, an estimated 81.1 million (36.9 percent) Americans have a cardiovascular condition.[3] It is the leading cause of mortality and accounts for 34.3 percent of all deaths or one of every 2.9 deaths in the United States.[3] Higher prevalence and control of traditional risk factors for CVD such as smoking, type 2 diabetes, metabolic syndrome, hypertension and hyperlipidemia still remains a major issue for most Americans.[4] Obesity is associated with all the major established risk factors for CVD. This article reviews how obesity is a risk factor for specific cardiovascular diseases and CVD mortality.

Body mass index (BMI) is the most commonly used measure of obesity, which is simply a person's weight adjusted for height. Persons with a BMI between 25 kg/m^2 and 29.9 kg/m^2 are classified as overweight and those with a BMI of ≥30 kg/m^2 as obese[5]. There are three classes of obesity: class I (BMI 30-34.9), class II (BMI 35-39.9), and class III (BMI ≥40)[5]. Waist circumference (WC) and waist hip ratio (WHR) are often used as measures of central adiposity, an independent risk factor for overall and cardiovascular mortality. In the United States, men with waist circumferences greater than 102 cm (>40 inches) and women with waist circumferences greater than 88 cm (>35 inches) are at increased risk of cardiovascular diseases.[5]

Obesity as An Independent Risk Factor for Cardiovascular Disease and Mortality

One of the first long-term studies to show an association between overweight, obesity and risk for CVD was the Framingham study. In a 44-year follow up study of Framingham participants, the age-adjusted relative risk for cardiovascular disease increased amongst overweight men (Relative Risk; RR 1.21, 95 percent CI: 1.05-1.40), women (RR 1.20, 95 percent CI: 1.03-1.41), obese men (RR 1.46, 95 percent CI: 1.20-1.77) and women (RR 1.64, 95 percent CI: 1.37-1.98) compared to people with normal weight.[6] A population-based study with 26-year mortality follow-up also showed an age adjusted RR of 1.62 (95 percent CI: 1.08-2.43) for obese patients compared to controls.[7] Recent studies have demonstrated that abdominal obesity is an independent risk factor for all-cause mortality. A PreCIS Database study showed a greater mortality risk for men with WC >102 cm and women with WC >88 cm (P <0.01) compared to controls, when actually; BMI was not significantly associated with mortality.[8]

Overweight and obesity are associated with several cardiac problems such as coronary artery disease, heart failure, vascular diseases and arrhythmias. The association between obesity and CVD is complex and still isn't well understood. Excess adipose tissue influences several metabolic pathways in the body, leading to the development of known CVD risk factors such as atherosclerosis, hypertension, dyslipidemia, insulin resistance and sleep apnea. It also causes hemodynamic changes in the body leading to direct alterations in cardiac structure and function. The following sections discuss the association between obesity and risk for specific cardiovascular diseases.

Obesity and Hypertension

Obese people have been found to have a much higher prevalence of hypertension. The pathogenesis of hypertension in obese people is very complex and is still an area of active research. Obesity leads to hemodynamic changes in the body such as increase in cardiac output, plasma, blood volume and total peripheral resistance.[12] Activation of the sympathetic nervous system also occurs with obesity due to increased synthesis of metanephrines, inflammatory cytokines such as IL-6 and CRP and leptin.[13] Plasma renin, angiotensinogen, angiotensin II and aldosterone levels are also significantly increased in obese individuals.[14] During the early phases of obesity, sodium is retained through increased tubular reabsorption.[14] This leads to extracellular volume expansion and the kidney-fluid apparatus is reset to a hypertensive level.[14]

NHANES III survey reported an increase in BP from 15 percent at a BMI of ≤25 to 42 percent at a BMI ≥30.9 Men had a higher prevalence of hypertension at all levels of BMI compared to women.[9] A 10 percent increase in BMI was associated with a 3.85 mm Hg (95 percent CI: 1.88 to 5.83 mm Hg) increase in systolic blood pressure and a 1.79 mm Hg (95 percent CI: 0.68 to 2.90 mm Hg) increase in diastolic blood pressure (P=0.002)10. This risk profile is not just limited to adults. The Bogalusa Heart study found that overweight children were 2.4 times more likely to have high diastolic blood pressure and 4.5 times more likely to have high systolic blood pressure, when compared with non-obese children.[11]

Obesity and Coronary Artery Disease

Atherosclerosis is a process that gradually occludes arteries through the deposition of fatty material on the inner vessel walls. It is the most important process underlying coronary artery disease and starts at a very young age. Studies that investigate atherosclerosis use CT scans of coronary arteries to assess calcification or examine autopsy specimens. The Bogalusa heart study involved autopsies conducted on 150 children and young adults aged 6 to 30.[15] The study revealed that obesity was associated with the early development of atherosclerotic lesions as evidenced by intimal fatty streaks and fibrous plaques.[15] Carotid intimal medial thickness (IMT) is a marker of generalized atherosclerosis and is measured by ultrasound. A Japanese study of 849 patients aged 20 to 78 found that general adiposity measured by BMI and central adiposity measured by WC and WHR positively correlated with IMT of the common carotid

artery, after adjusting for age and smoking habit.[16]

Several prospective studies have reported that obesity is an independent risk factor for coronary heart disease (CHD). The 26-year follow-up of 5,209 participants in the Framingham heart study showed that obesity was associated with CHD, independent of other CVD risk factors.[17] In the British Women's Heart and Health Study (BWHHS) (women only), there was statistical evidence that WC [hazard ratio (HR): 1.17 (CI 1.04, 1.31)] p=0.007 was more strongly associated with CHD than BMI [HR: 1.09 (0.98, 1.23)] p=0.12.18

Obesity and Heart Failure

In terms of incidence and prevalence, the magnitude of heart failure is enormous. According to the American Heart Association, heart failure affects nearly 5.7 million Americans.[19] Congestive heart failure (CHF) is the most common diagnosis in hospitalized patients aged 65 and older.[19] With an aging population and increased survival rates amongst patients with myocardial infarction, heart failure numbers will continue to increase in the future. Despite recent therapeutic advances, morbidity and mortality in heart failure patients continue to increase.[19] Prevention of heart failure (HF) through identification and management of risk factors during early stages of the disease is very important. Several studies have evaluated excess body weight as a risk factor for heart failure. Obesity leads to hemodynamic changes in the body such as increase in total blood volume, cardiac output, peripheral resistance and blood pressure.[20-21] The hyperdynamic circulation leads to increased cardiac workload resulting in eccentric left ventricular hypertrophy.[22] Over a period of time, this leads to poorer LV systolic function and even greater impairment of LV diastolic function.[23]

Kenchaiah, et al. examined obesity as a risk factor for heart failure. After adjustment for known risk factors such as age, smoking status and previous heart attack, they found a 5 percent increase in the risk of heart failure for men and 7 percent for women for a unit increase in BMI.[24] The risk of heart failure was greater for obese women (RR 2.1, 95 percent CI: 1.51–2.97) than obese men (RR 1.9, 95 percent CI: 1.30–2.79), compared to those with normal BMI.24 The Atherosclerosis Risk In Communities (ARIC) study based on an age 45 to 64 cohort showed an age-adjusted HF incident rate of 7.25 (6.10, 8.61) per 1000 person years among obese white women and 9.96 (CI 8.69, 11.41) among obese white men.[25]

Obesity and Thromboembolism

Obesity causes several hemostatic abnormalities in the body through increased platelet aggregation and decrease fibrinolysis. BMI correlates with plasma levels of plasminogen activator inhibitor-1 (PAI-1).[26] PAI-1 inhibits tissue and urokinase-derived plasminogen activators, thereby preventing the conversion of plasminogen to plasmin and inhibiting fibrinolysis. Inflammatory cytokines produced by adipose cells such as TNF-α and IL-6 has shown to increase the synthesis of PAI-1.[27] Obesity also increases platelet aggregation due to increased synthesis of von Willebrand factor, plasma fibrinogen, factors VII and VIII.[28] In a European Atherosclerosis Research Study (EARS) offspring study, fibrinogen, factor VII, and PAI-1 levels were positively correlated with BMI.[29] Bariatric surgery for morbid obesity in these patients led to significant decline in fibrinogen, factor VII, and PAI-1 levels.[29]

A prospective cohort study of 87,226 women in the Nurses' Health Study (1984–2002) showed a strong positive association between BMI and pulmonary embolism (PE).[30] The risk of idiopathic PE per 1 kg/m2 increase in BMI was 1.08 (95 percent CI: 1.06–1.10, P < 0.001) and non idiopathic PE was 1.08 (95 percent CI: 1.07–1.10, P < 0.001).30 The association was linear and was present even with modest increases in BMI (22.5–25 kg/m2).[30] There was a six-fold increase among subjects with BMI ≥35 kg/m2.[30]

Obesity and Arrhythmias

Concentric left ventricular hypertrophy that occurs in obese patients is often associated with diastolic dysfunction. Obesity is associated with atrial dilatation, neurohumeral activation and elevation of left ventricular diastolic filling pressure that triggers atrial arrhythmias, particularly atrial fibrillation (AF). Further, synthesis of proinflammatory cytokines by the adipocytes causes local inflammation and oxidative stress in the heart muscle. This leads to direct interactions between epicardial adipose tissue and the adjacent myocardium, resulting in myocardial remodeling and AF.[31] Several studies have demonstrated the association between obesity and atrial fibrillation.

The Danish Diet, Cancer, and Health Study investigated the association between body mass and atrial fibrillation. The study was based on a 5.7 years follow up of 47,589 participants without preexisting cardiovascular or endocrine disease.[32] The adjusted hazard ratio for atrial fibrillation or flutter per unit increase in the body mass index was 1.08 (95 percent CI: 1.05-1.11) in men and 1.06 (95 percent CI: 1.03-1.09) in women. While using normal weight as a reference, the adjusted hazard ratio for atrial fibrillation or flutter in overweight individuals was 1.75 (95 percent CI: 1.35-2.27) in men and 1.39 (95 percent CI: 0.99-1.94) in women. The adjusted hazard ratio for obesity was 2.35 (95 percent CI: 1.70-3.25) in men and 1.99 (95 percent CI: 1.31-3.02) in women.

Since the time of Hippocrates, the association between obesity and sudden cardiac death has been well described. Obesity results in increased myocardial thickness, which

leads to ventricular irritability and arrhythmias. The increased cardiac workload and oxygen requirement leads to subendocardial ischemia and ventricular ectopy. Messerli and colleagues documented short episodes of ventricular tachycardia, trigeminy and quadrigeminy in obese patients with eccentric left ventricular hypertrophy.[33] Bigger and colleagues demonstrated that ventricular ectopy, or runs of ventricular tachycardia, were independently associated with mortality in post myocardial infarction patients.[34]

Cardiovascular Effects and Benefits of Weight Loss

National Heart, Lung and Blood Institute have established clinical guidelines for the control and treatment of obesity. Their recommendations include prevention of further weight gain, reduction of body weight by approximately 10 percent from baseline initially and maintenance of lower body weight over a long term.[35] The key to a successful weight management program includes dietary therapy with consumption of low-calorie, low-fat diet, increased physical activity and behavioral modification.[35] Pharmacotherapy is indicated for those with a BMI of ≥30 with no concomitant risk factors or major systemic illnesses, and for those with a BMI of ≥27 with concomitant risk factors or diseases. Weight loss surgery is reserved for those with morbid obesity with BMI ≥40 or ≥35 with comorbid conditions.[35]

Intentional weight loss can improve or prevent many of the obesity-related risk factors for CHD, such as insulin resistance and type 2 diabetes mellitus, dyslipidemia, hypertension and inflammation.36 For obese individuals, modest weight reduction of even less than or equal to 10 percent appears to improve glycemic control and reduce blood pressure and cholesterol levels.[37] It also has positive health benefits and appears to increase longevity in obese individuals.[37] Some studies have demonstrated improvements in hemodynamics, cardiac structure and function with weight reduction.[38,39] The beneficial effects of weight loss on the cardiovascular system have been enumerated in Table 1.

In a study of 530 patients, marked improvements in CHD risk factors were noted among overweight and obese CHD patients who lost weight. This group also showed lower mortality rates.[40] A recent study of 377 patients showed the benefit of weight loss on a composite outcome of major cardiovascular events and mortality. Benefits were noted in those with a BMI less than 25 kg/m^2 as well as in overweight and obese CHD patients who lost weight.[41]

Some long-term studies have shown that weight loss in overweight and obese patients may be associated with increased mortality.[42] Some studies have demonstrated a better prognosis with a higher BMI, and it has been suggested that purposeful weight loss may not be beneficial and may even be detrimental in patients with existing CV diseases.[42] This is called the obesity paradox. So far, the available data is insufficient to conclude if intentional weight loss really reduces CVD mortality directly. Large-scale epidemiological studies are essential to address these issues.

Table 1: Benefits of weight reduction on the cardiovascular system

Cardiovascular effects	Effect of weight reduction
Blood volume	Decreases
Stroke volume & Cardiac output	Decreases
Pulmonary capillary wedge pressure	Decreases
Left ventricular thickness	Decreases
Resting oxygen consumption	Decreases
Systemic blood pressure	Decreases
Filling pressures of the heart	Decreases
Resting heart rate	Decreases
QTc interval	Decreases

Conclusion

Cardiovascular disease remains the leading cause of mortality, both in the U.S. and at a global level. Obesity and being overweight, as a part of metabolic syndrome and alone, are well-known risk factors for the development of various cardiovascular diseases. Obesity has been shown to be associated with increased mortality, but paradoxically, a positive correlation between BMI and survival in congestive heart failure and other CVDs has also been reported. Large-scale randomized controlled trials are essential to investigate these issues. The causes of obesity are multifactorial. Obesity is influenced by both genetic and lifestyle factors. As people in our country continue to consume high-calorie, high-fat diets and lead sedentary lifestyles, the prevalence of obesity will continue to rise. The importance of obesity control in the primary and secondary prevention of cardiovascular diseases is still under recognized. There is an urgent need to evaluate and implement strategies for obesity prevention and control to achieve reductions in CVD morbidity and mortality. Weight loss and prevention of weight gain through increased physical activity, dietary and lifestyle modifications have to become an integral part of health care strategies to reduce the incidence of cardiovascular diseases.

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The Effect of Obesity on Orthopaedic Conditions

By Keith M. Baumgarten, MD; Walter O. Carlson, MD; Eric S. Watson, MD

Abstract:
Obesity is a worldwide health problem leading to a range of health consequences.[1] This review summarizes the known effects of obesity on the musculoskeletal system. Specifically, the effects of obesity on the shoulders, spine, knees, feet and other areas related to sports medicine are examined.

Introduction

Obesity is a serious public health problem that is increasing in prevalence in adults and children. Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2. Obesity is one of the few disease risk factors that is potentially modifiable. Obesity has a significant effect on multiple orthopaedic conditions.

Shoulder

Obesity may be a factor in the incidence and treatments required for shoulder pathologies. The risk for shoulder pain was positively correlated with BMI when examining a cohort of forestry workers.[27] Wendelboe, et al. showed that individuals who are obese are at increased risk for rotator cuff tendonitis and surgery. This risk increased with the degree of obesity.[38] However, when examining the relationship between obesity and outcomes of rotator cuff repair surgery, obesity was not an independent risk factor for poor outcome.[30]

Obesity has been shown to affect the performance and outcome of shoulder arthroplasty, a treatment for end stage glenohumeral osteoarthritis. Although morbid obesity is not a contraindication to total shoulder arthroplasty, it has been shown to be technically more difficult in these patients.[23] There is increased complexity in achieving exposure and prolonged operative times. One study

demonstrated that the average operative time was 220 minutes (range, 152 to 337 minutes) in patients with elevated BMI compared to 179 minutes (range, 115 to 260 minutes) in patients with BMI less than 30.[23] There may be an increased rate of deep infections in patients with morbid obesity due to the larger wounds and longer operating times.[2,23,36] Patients with morbid obesity may have a higher rate of unsatisfactory results than those with more ideal body weights.[23]

Obesity and the Spine

Low Back Pain

Low Back Pain (LBP) remains a common health problem leading to time off work, disability and persistent pain. The relationship and potential mechanism of LBP and obesity remains controversial. Persistent obesity, especially abdominal obesity is associated with LBP in young women, but not men[1]. Patients with LBP do not demonstrate worse pain if obese, but have more disability due to their weight[3]. An elevated BMI has been demonstrated to predict an increased length of expected recovery from a LBP episode[7]. However, Aro and Leino found no relationship between weight and LBP in a 10-year follow-up study of Finnish adults[1]. Mirtz and Greene conducted a review of the relationship between obesity and LBP. They concluded that patients with a BMI less than 30 are at minimal risk; those with a BMI of 30 to 40 are at moderate risk, and those with a BMI greater than 40 are at high risk for developing LBP[28]. Interestingly, Melissas and others have studied the effect of surgical weight reduction on functional status in morbidly obese patients with low back pain. A review of 29 morbidly obese patients with associated LBP, undergoing bariatric surgery, showed statistically significant improvement of all measurable parameters of functional disability due to LBP[26].

Disc Herniation

Lumbar disc herniation is a common cause of sciatica, hospitalization and surgical treatment. Obese patients were more likely to have radicular pain and neurologic signs than the non-obese patients with lumbar disc herniation[19]. A high BMI was found to be a risk factor for hospitalization and subsequent surgical treatment for lumbar disc herniation[19]. Lee et al. studied a group of patients undergoing surgery for lumbar disc herniations. They concluded that patients operated for lumbar disc herniation are typically tall, with a high BMI and between the ages of 19 and 48 years[22]. They further noted that a significantly higher body weight and BMI were associated with severe lumbar disc herniation in women[22].

Spinal Stenosis

Gepstein and others studied the effect of obesity on lumbar decompressive surgery in the elderly. They noted that the prevalence of obesity among American adults aged 60 to 74 is around 35 to 40 percent.[12] Lumbar decompression has become increasingly common as elderly patients seek treatment for spinal stenosis.[12] The incidence of wound infections for this surgery is 4 percent in the non-obese and 9 percent in the obese.[12] Repeat surgical procedures occurred in 10 percent of this elderly obese group, similar to other studies.[12] Satisfaction rates did not vary dependent on BMI, although the percentage of very dissatisfied patients was higher in the obese.[12] Female gender, diabetes mellitus and peripheral vascular disease were associated with poor outcome.[12] This study suggests that functional outcomes were more limited in the obese. In spite of this, two-thirds of the patients remained very satisfied despite a high BMI. The authors suggest high BMI in the elderly is not a contraindication for lumbar surgery.[12]

Lumbar Fusions

Wound healing, surgical exposure and outcomes in lumbar fusion surgery remain concerns for physicians when considering this treatment option for obese patients. Often, surgical decision-making is affected by patient weight, limiting patient choices and thus outcomes. Djurasovic, et al. reviewed a cohort of patients to determine the effect of obesity on clinical outcomes after lumbar fusions. They determined that proper surgical indications are the predominant factors affecting results, and patient weight should not influence surgical decision making.[7] Obese patients did have a higher incidence of morbid-related complications at 5.5 percent. However, that has not been considered a contraindication to fuse the lumbar spine in the obese patient.[7] Patient directed quality-of-life measures in Djurasovic's study were equivalent in outcomes for the non-obese. Surgeons did document, however, that spinal exposure, managing the soft tissues and obtaining a safe trajectory for pedicle screw placement, is more problematic in the obese patient.[7] Currently, the anterior approach for exposure in lumbar fusion has gained in popularity. Peng, et al. showed that the obese patient had similar outcomes in terms of blood loss, analgesic use, length of time to ambulation and length of hospitalization when compared to the non-obese patients for anterior lumbar surgery.[33]

Knee

The incidence of knee injuries was elevated in athletes with greater mean heights and weights, compared with athletes of lesser height and weight.[13] In addition, the disability associated with knee injury has been shown to be increased in obese patients. Fear of joint pain with movement, a psychological response to pain and injury, was found to be prominent in morbidly obese adults with knee pain-related

diagnoses, compared with their non-obese counterparts.[37] Fear of joint pain has been shown to predict disability in orthopaedic conditions.[37] In addition, pain-related fear is also related to the degree of functional improvement made during rehabilitation of orthopaedic conditions.[37]

Obesity may be an independent risk factor for radial tears of the posterior horn of the medial meniscus. In a cohort of patients with radial tears of the medial meniscus, 81 percent of patients were obese or morbidly obese. The ratio of obese patients in the series studied was higher than the regional obesity rate.[31] Another study found a dose-response relationship between increasing BMI and the need for meniscal surgery in middle-aged to older adults.[10] This study also suggested that overweight adults, in addition to obese patients, may have an increased likelihood of needing meniscal surgery compared to patients with more ideal body weights.[10]

Knee arthroscopy procedures are technically more challenging when performed on patients with an elevated BMI. Difficulty in establishing arthroscopic portals in the morbidly obese patient is a known concern to arthroscopists.[25] In obese patients, it is difficult to palpate the bony landmarks required for anatomic positioning of the arthroscopic portals, due to the large amount of superficial adipose tissue.[25] Berg, et al. demonstrated that the number of arthroscopic portals required in obese patients was statistically higher compared to non-obese patients.[2] In addition, operative times are longer in obese patients. The mean operative time for morbidly obese patients was 65 minutes (range, 40 to 150 minutes), which was an average of 25 minutes or 62 percent longer when compared with the normal cohort group, which averaged 40 minutes of operative time (range, 25 to 110 minutes).[2] Recuperation has been shown to be longer in the obese patient after knee arthroscopy. Despite more sedentary vocational profiles, the time to work resumption was longer in the morbidly obese group, averaging 17 days (range, three to 33 days) compared with a mean of 10 days (range, one to 28 days) in the normal body habitus group.[2]

Obesity has been shown to adversely affect the outcomes of treatment of anterior cruciate ligament (ACL) tears. Obese (BMI of 30 to 39 kg/m^2) and morbidly obese (BMI greater than 40 kg/m^2) subjects had 0.35 times odds of success after ACL reconstruction compared to patients with normal BMI.[20] Another study demonstrated that an increased BMI was an independent risk factor for lower activity levels two years after ACL reconstruction.[8]

Elevated weight and BMI were significant risk factors for injuries to the articular cartilage surfaces and menisci identified at the time of ACL reconstruction.[5] In addition, obesity has been shown to be a risk factor for the development of osteoarthritis after both nonoperatively treated and operatively treated ACL tears.[21,35] These findings together suggest that the increased body weights may place excessive stress on the knee, accelerating the rate of degenerative changes.[20] Thus, by reducing weight and BMI to optimal levels, athletes potentially could minimize intraarticular chondral and meniscal injuries in the event of an ACL tear, which may decrease the incidence of osteoarthritis over the long term.[5]

Knee dislocations are complex injuries that involve rupture of multiple ligaments about the knee. They are typically due to high-energy trauma such as motor vehicle accidents and sports injuries. However, there have been multiple reports of low energy knee dislocations that occur in morbidly obese patients due to simple falls.[17,24,32] One case series reported on two patients with knee dislocations when the patients knee "gave out" while walking.[24] Another case series described seven patients with spontaneous knee dislocations. All patients were significantly overweight, with a mean BMI of 52.9.[16] Many of these dislocations were complicated by popliteal artery injuries,[16,24,29,34] and some even required above the knee amputations.[24,34]

Multiple studies have demonstrated the potential problems with rehabilitating these patients with prolonged hospitalizations and recovery times.[17] Some difficulties include prolonged operative times, increased blood loss and transfusion requirements. Incisions need to be longer and deeper, particularly in morbidly obese patients. Retraction can be difficult and specialized equipment is often needed.[16-17] Occasionally, two conventional operating tables need to be placed side-by-side to safely fit the morbidly obese patient.[16] In patients with more ideal BMI, ligamentous reconstruction has been shown to improve outcomes after knee dislocations. However, this complex procedure is relatively contraindicated in the morbidly obese patient, and temporary external fixation is often required instead.[29]

Foot and Ankle

Obesity presents all of the same increased risk factors in foot and ankle surgery as in any other orthopaedic surgery. Obesity increases the risk for wound infection and deep venous thrombosis. It also increases the risks of other comorbid conditions, not limited to, but notably, diabetes mellitus and peripheral vascular disease. These last two comorbidities can significantly impact surgeries of the foot and ankle.

Diabetes mellitus increases the risk of wound sepsis and slows bone and soft tissue healing. Diabetes also presents the risk of Charcot neuroarthropathy. Peripheral vascular

disease decreases the blood flow to the lower extremity, decreasing the ability to heal wounds and fractures.[15]

The foot and ankle have less subcutaneous tissue than many other areas of the body. There is also less mobility to the skin. Combined with the relatively decreased vascularity of the region, wound problems can arise. Obesity and the problems that sometimes accompany it further complicate the body's ability to heal these types of wounds.

A retrospective review of 176 pilon (intra-articular distal tibia) fractures was done with the hypothesis that a larger soft tissue envelope and dimensions of the ankle joint might be protective against wound complications. All patients had a body mass index (BMI) greater than 30. They were compared to a cohort with BMI less than 30 and similar injuries. They were treated with staged reconstruction and plating. The obese group had a 13 percent incidence of wound complications, compared with 5 percent in the non-obese group, thus refuting the hypothesis.[14]

This study mirrors what clinical experience shows. Obese patients often require larger incisions due to their body habitus. Larger wounds obviously require more healing. Increased subcutaneous fat also tends to more wound drainage, which can lead to wound infection. Obese patients have a higher rate of prosthetic and hardware failure, as well as fracture malunion. Some of these complications can be related to the increased complexity due to patient body habitus or positioning difficulties related to patient size. Difficulties with rehabilitation may also contribute.[1,4]

Rehabilitation is an important component of successful surgery. Lower extremity surgery often requires extended periods of protected or non-weight bearing. Obese patients are often deconditioned and tolerate less exertion. Supporting increased body weight on the upper extremities provides another hurdle to successful rehabilitation. Body habitus also makes the use of crutches or a walker more difficult. The need for a wheelchair is not uncommon. This can still be problematic as most homes are not equipped for a normal wheelchair, let alone an extra-wide chair. If patients are unable to use the appropriate assistive devices, this will often lead to noncompliance with weight bearing restrictions and potentially compromise surgical outcomes.

Obesity is a significant problem in America, with nearly one-third of all adults affected. Knowledge of potential risks and pitfalls related to care of the obese patient is more important now than ever before. Detailed discussions regarding these issues need to be carried out with patients and family members prior to surgery and in the perioperative period.

Heat Illness

Obesity is a significant risk factor for heat illness in athletes and members of the military.[6,9,11,18] Sixty percent of patients in one cohort affected by heat stroke were overweight.[9] The risk for developing exertional heat illness has been shown to increase with elevated body mass index.[11] In a study of military recruits affected by heat illness, the overweight, less fit subjects were about eight times more prone to exertional heat illness than lean, fit subjects. Recruits in the highest quartile for BMI had an approximately three-fold increase in risk compared with those in the lowest quartile, regardless of physical fitness level.[11] Maintenance of healthy body weights and monitoring of the obese athlete or soldier in at risk environments may help prevent heat illness.[18]

Conclusion

It is well known that obesity increases the likelihood of cardiovascular, endocrine, respiratory, and oncologic disease. Likewise, obesity negatively influences many orthopaedic conditions. Obesity does increase the prevalence of many orthopaedic ailments and can negatively influence the outcomes of their treatment. As obesity is a modifiable risk factor, initiatives to lower the incidence of obesity could decrease the prevalence and improve the outcomes of orthopaedic diseases.

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Obesity in Pregnancy

By Peter Van Eerden, MD, MS

Abstract:
More than one-third of U.S. women are obese, and the prevalence of obesity in childhood has increased. Excessive gestational weight gain and obesity are independent risk factors for maternal and fetal complications of pregnancy and may very well be implicated in the epidemic of childhood obesity currently seen in the U.S. There are many pregnancy related complications associated with obesity, including miscarriage, infertility and congenital anomalies as well as a variety of late-pregnancy related complications. Additionally, obesity can predispose to the development of fetal macrosomia which can lead to childhood obesity. This article reviews the effects of obesity on pregnancy and potential methods of prevention.

Background

Overweight and obesity have become an epidemic in the United States and other developed and developing countries around the world. More than one-quarter of U.S. women are overweight, and more than one-third are obese.[1] The problem is greatest among non-Hispanic black women (49 percent) compared with Mexican-American women (38 percent) and non-Hispanic white women (31 percent).[2] Additionally, the prevalence of obesity in childhood has increased by 11 percent between 1994 and 2000.[3] Behavioral and environmental changes have contributed to the rise in obesity; these include cheap, processed, energy-rich foods, increased portion sizes, advertising and lifestyle changes such as increased sedentary lifestyle.[4]

The World Health Organization and the National Heart Lung and Blood Institute (NHLBI) defines overweight as a body mass index (BMI, kg/m^2) between 25 and 29.9. Obesity is defined as a BMI of 30 or greater. Obesity is further categorized as Class I (BMI=30-34.9), Class II (35-39.9) and Class III (BMI=40 or greater).[4,5] The term "morbid obesity" is still used by the International Classification of Diseases for a BMI greater than 40, but more sensitive alternatives such as "stage III," "extreme obesity," or "clinically severe obesity" are preferred by the NHLBI.

Obesity is a risk factor for diabetes, hypertension, high cholesterol, stroke, heart disease, arthritis and certain types of cancer.[8] Excessive gestational weight gain and obesity are independent risk factors for maternal and fetal complications of pregnancy and may very well be implicated in the epidemic of childhood obesity currently seen in the U.S.

Effect of Obesity on Early Gestation

The obese woman is at an increased risk for a number of pregnancy-related complications. In early pregnancy, there is an increased risk of miscarriage and recurrent miscarriage. Obesity decreases the chance of spontaneous pregnancy,[9] and obese women are more likely to miscarry following spontaneous and assisted conception.[10] Release of inflammatory and prothrombotic factors may be contributing factors.[11] Additionally, fertility is reduced due to oligo-ovulation and anovulation.[12] Obese women who undergo fertility treatment are also at an increased risk for miscarriage.[13]

Maternal obesity is also associated with an increased risk of congenital anomalies. These include neural tube defects such as spina bifida, congenital heart defects and omphalocele.[14] Many of these anomalies can be seen with pregestational diabetes, which suggests that many of these women may have undiagnosed type 2 diabetes mellitus (DM). Several mechanisms have been postulated, such as maternal hyperglycemia and poor nutritional status.[15] Folic acid supplementation is not beneficial in severe obesity and obese women in areas with flour fortification of folic acid remain at high risk for neural tube defects.[16] However, even after controlling for diabetes, there is still an increased risk

of anomalies related to the neural tube, cardiac systems and facial clefting.[17]

Obesity can also impair our ability to detect congenital anomalies during pregnancy. The increased plasma volume can affect interpretation of the alpha-fetoprotein (AFP) test, particularly with maternal weight over 200 pounds. In this situation, there may be an increased risk of false negative results. Additionally, ultrasound visualization of fetal anatomy may be significantly impaired. Even with more advanced ultrasonographic methods, assessment of the fetal anatomy, particularly cardiac anatomy and spine may very well be suboptimal.

Effect of Obesity on Late Gestation

Obese women are at risk for metabolic syndrome and insulin resistance. This condition includes hypertension, glucose intolerance and elevated cholesterol/triglycerides. Obese pregnant women are at an increased risk for pregnancy related complications which are analogous to metabolic syndrome.[18] These complications include gestational hypertension, preeclampsia and gestational diabetes mellitus (GDM). A prospective multicenter study has confirmed Class I and Class II obesity to be associated with an increased risk of gestational hypertension (OR=2.5 and 3.2), preeclampsia (OR=1.6 and 3.3), gestational diabetes (OR=2.6 and 4.0) and fetal macrosomia (OR=1.7 and 1.9).[19] The risk of gestational preeclampsia has been found to double as the BMI rises from 21 to 26 and nearly triples at 30.[20]

Gestational hypertension and preeclampsia are not well understood. However, endothelial cell dysfunction as part of an overall inflammatory response involves the placental and systemic circulations. Normal pregnancy is a state of systemic inflammation, and preeclampsia may represent an exaggerated response. Maternal obesity and diabetes might enhance this response since they are themselves associated with endothelial dysfunction.[21] This may explain why there is an increased risk of cardiovascular disease later in life in women with preeclampsia.[22] A systemic review including 1.4 million women demonstrated a doubling of risk of preeclampsia for every six-unit increase in prepregnancy weight.[23]

Obesity predisposes to type II diabetes. Gestational diabetes is the clinical manifestation of glucose intolerance in pregnancy, with both decreased insulin sensitivity and inadequate insulin response. Normal pregnancy is associated with changes in glucose metabolism to provide fuel substrate to the developing fetus. As pregnancy progresses, insulin-mediated glucose utilization decreases and insulin secretion increases. Obesity has effects on glucose metabolism and potentiates these normal changes in pregnancy. A meta-analysis of 57,000 subjects showed that there is an increased risk of developing gestational diabetes with increasing BMI (OR=3.65 in obese women, OR=8.56 in severely obese women).[24] Complications associated with maternal obesity are worsened by the presence of GDM and type 2 DM. Maternal obesity may also be associated with other medical complications. There is an increased risk of sleep apnea, nonalcoholic fatty liver disease and chronic renal and cardiac dysfunction.

Maternal obesity is also associated with preterm delivery, although there is some debate in the literature. Preterm delivery is usually associated with underlying medical or obstetric complications such as diabetes and hypertension, and it can be difficult to separate out the effects of obesity from these comorbidities.[25] There is a higher incidence of elective preterm birth for maternal or fetal indications[26] and obese women are less likely to have spontaneous preterm labor.[27] There is also data to suggest that the mortality of preterm infants is higher in women who are obese and increases with increasing BMI.[28]

Obesity is a strong risk factor for stillbirth. Increased pre-pregnancy weight was the factor most strongly associated with stillbirth even after controlling for maternal age, diabetes and hypertensive disorders.[29] The risk for stillbirth is 2.1- to 4.3-fold greater in obese versus normal weight women.[30] Birth weights of fetal deaths in obese women are often lower than the median birth weight, implicating intrauterine growth restriction as an underlying cause. This is consistent with the fact that obesity-related stillbirths are associated with placental dysfunction.

Peripartum Complications Related to Obesity

Obesity during pregnancy is associated with difficulty in estimating fetal weight. Additionally, obesity is associated with difficulty monitoring and interpreting external fetal heart rate and uterine contraction patterns. These findings can lead to difficulty in making management choices regarding induction and mode of delivery.

There is an increased likelihood of failure to progress in labor, induction of labor, instrumental delivery, emergent cesarean delivery and prolonged labor. Also, there is a lower chance of successful trial of labor after cesarean (TOLAC). Obesity is also associated with an increased risk of fetal compromise and postdates.[31] An increased risk of maternal death has been reported, with almost 50 percent of women

who die during late pregnancy or intrapartum being overweight or obese.[32]

There may be difficulty with regional and general anesthesia in obese women. This may include difficulty with placement of a spinal or epidural as well as the need for multiple attempts. There may be difficulty with intubation for those women requiring general anesthesia, as well as an increased risk of failed intubation. Recovery from general anesthesia may also be more difficult. There is suggestion of an increased risk of sleep apnea postpartum.

The number of cesarean deliveries increases with increasing BMI, with rates as high as 47.7 percent in severely obese women.[34] Obesity may clearly be associated with difficulty in performing both non-emergent and emergent cesarean delivery. A vertical skin incision may offer better exposure, but will be associated with increased post-operative pain and increased risk of evisceration. The Pfannnenstiel type incision may be associated with increased comfort post-operatively, but management of wound breakdown may be more difficult. There is some data to suggest that closure of subcutaneous layers may lead to a decrease in wound disruption.[35] There is also a suggestion of prolonged operating time in obese women.[36]

There is an increased risk of postoperative complications and associated morbidities in obese women. There is an increased risk of hemorrhage, both intrapartum and postpartum, as well as an increased risk of wound infection and dehiscence.[37] There is an increased risk of venous thromboembolism, including deep venous thrombosis and pulmonary embolism.[38] Obese women are more likely to retain weight postpartum.

Weight Gain Recommendations in Pregnancy

Recommending a single standard of weight gain for all classes of obesity is concerning, since women with a higher BMI are at an increased risk of severe comorbidities and have long-term adverse health implications. Excessive gestational weight gain has been associated with retention of weight after delivery.[39] This leads to a "vicious cycle" of obesity as overweight or obese women have daughters who are macrosomic and become obese themselves.[40] Obese women are more likely to exceed the weight gain recommendations in pregnancy and are predisposed to higher postpartum weight gain and retention.[41] The Institute of Medicine (IOM) in 2009 revised its recommendations on weight gain during pregnancy.[42] The recommendations were similar to those from 1990. The current recommendations for weight gain in pregnancy for overweight and obese women are as follows: 1) overweight (BMI=25-25.9), 15 to 25 pounds and 2) obese (BMI 30 or greater), 11 to 20 pounds. The recommendations do not address the three classes of obesity. For many reasons, these recommendations have recently been challenged.[43] Artal, et al. have suggested that the recommendations were driven by a theoretical association between poor gestational weight gain and low birth weight. Additionally, the recommendations do not consider the long-term effects of excess pregnancy-associated weight gain, and the authors suggest that gestational weight gain should reflect a balance between an optimal outcome for both the fetus and the mother. The authors suggest that weight gain recommendations should be individualized, as poor gestational weight gain is unlikely to affect birth weights in obese women.

Fetal and Neonatal Risks of Maternal Obesity

Fetal growth disorders are associated with maternal obesity. Fetal overgrowth is more likely to occur in obese women. Large for gestational age is defined as fetal weight greater than the 90th percentile for a given gestational age. Macrosomia is defined as a birthweight of 4,000 grams or greater. The combination of maternal obesity and gestational diabetes only exacerbates the risk of excessive fetal growth. Obese women are also at an increased risk of giving birth to a small-for-gestational-age (SGA) infant. This may be mainly related to obesity related co-morbidities such as chronic hypertension and vasculopathies associated with diabetes.

There is an increased odds ratio of meconium aspiration, fetal distress and low Apgar score in neonates of obese women.[44] Other short term risks include an increased risk of shoulder dystocia and neonatal intensive care admission.[45]

There is an increased risk of childhood obesity in children born to obese mothers. New evidence over the last 25 years supports an increase in adolescent and adult obesity in infants born large-for-gestational-age (LGA) or macrosomic. Epidemiologic studies strongly suggest that the intrauterine and early postnatal environments have a significant effect on body weight. There is very good evidence to suggest that infants born SGA are at an increased risk for metabolic syndrome (obesity, hypertension, insulin resistance and dyslipidemia). The Dutch Hunger studies during World War II suggested an increased risk of obesity, cardiovascular disease and diabetes in adult male offspring.[46] The current environment is more of nutritional excess. Exposure to high nutrition before birth is associated with obesity in postnatal life, especially when combined with maternal gestational diabetes.[47] The proposed mechanism is epigenetic

programming, which is post-translational modification of DNA (usually by DNA methylation) which results in differential levels of gene expression without altering the DNA sequence. The epidemic of obesity and risk of the metabolic syndrome begins *in utero* with fetal overgrowth.

Bariatric Surgery

The ideal method of treatment of obesity before pregnancy is preconception weight loss. Unfortunately, greater than 50 percent of pregnancies are unplanned. If nonsurgical methods have failed, bariatric surgery may be considered in women with Class III obesity or in Class II obesity with comorbid conditions. There are two types of bariatric procedures: 1) malabsorptive procedures (ie, Roux-en-Y gastric bypass) or 2) restrictive procedures (ie, laparoscopic adjusted gastric banding).

There may be a delay in the diagnosis of bariatric-related operative complications. Restrictive procedures may be associated with an increased risk of gastric ulcer perforation, intragastric band migration, balloon defect and GI hemorrhage. Malabsorptive procedures may be associated with anastomotic leaks, bowel obstruction, internal hernia and ventral hernia.[48] Volvulus and intussusception have been reported. Obstruction may occur in up to 6 percent of pregnancies after Roux-en-Y gastric bypass.[49] Abdominal complaints usually considered benign in pregnancy should lower the threshold for evaluation, especially nausea, vomiting and abdominal pain. Symptoms of abdominal cramping, bloating, nausea, vomiting and diarrhea may also indicate the dumping syndrome due to ingestion of high glycemic carbohydrates or refined sugars. For restrictive procedures, early pregnancy nausea and vomiting may require partial or complete band deflation until resolution of symptoms.

There are no randomized prospective trials or long-term follow-up to help guide recommendations during pregnancy after bariatric surgery. Following bariatric surgery there is data to suggest that there will be a decrease in the frequency of gestational diabetes, gestational hypertension and preeclampsia, macrosomia and gestational weight gain.[50] There is also data to suggest that bariatric surgery may be an independent risk factor for cesarean delivery, even after controlling for potential confounders.[51] There may also be an increased risk of preterm rupture of membranes and labor induction. Other risks may include nutritional deficiencies (i.e., iron, folate, B12, calcium), fetal anomalies and intrauterine growth restriction. Monitoring blood count, iron, ferritin, calcium and vitamin D levels each trimester has been suggested, in addition to nutrition consultation.[52] Recent studies suggest bariatric surgery is not associated with any adverse pregnancy outcomes.

After bariatric surgery, there is an increased risk of unexpected pregnancy after weight loss. Delay for 12-18 months post-operatively has been suggested to avoid pregnancy during the rapid weight loss phase. After Rou-en-Y gastric bypass, extended release medications are not recommended due to the decreased time for absorption. Also there should be avoidance of combinations of multivitamins which can lead to teratogenic doses of vitamin A. NSAIDs should be avoided to decrease risk of gastric ulceration. Monitoring of drug levels should be performed if a therapeutic drug level is critical.[53] There is an increased risk of hypoglycemia during pregnancy after bariatric surgery. Dietary modification may be necessary. Oral glucose tolerance testing may not be well tolerated. Alternative approaches include fasting and two-hour postprandial blood glucose monitoring for one to two weeks at 26 to 28 weeks.

Management During Pregnancy

Preconception assessment and counseling are strongly encouraged for all women who are obese. Information should be provided about possible complications during pregnancy, intrapartum and postpartum. Women should be encouraged to undertake a weight reduction program, including diet, exercise and behavior modification, before attempting pregnancy.[54]

Early glucose challenge screening is suggested on all obese women in pregnancy, due to the potential risk of associated preexisting diabetes. An exercise program should be encouraged. Baseline ECG and maternal echocardiogram should be considered to rule out underlying cardiac disease. Baseline 24-hour urine collection for total protein and creatinine clearance as well as liver function tests can also be considered.

Increased awareness of comorbid complications, such as gestational hypertension, preeclampsia and gestational diabetes, which are known to be associated with perinatal mortality, is warranted. Close fetal monitoring with fetal kick counts is suggested. Additional monitoring may depend on associated conditions. Detailed fetal anatomic survey should be performed due to the increased risk of congenital anomalies. Serial sonography to estimate fetal weight should be considered due to the unreliability of measuring uterine fundal height in the office. Nutrition counseling should be offered to all women.

Early anesthesia consultation should be considered due to the risk of spinal and epidural anesthesia as well as the potential complications associated with general anesthesia. Intra-operative antibiotic prophylaxis and graduated compression stockings should be used if cesarean delivery is indicated. Additional blood products, a larger operating table and extra personnel may also be required. Hydration and early mobilization is encouraged post-operatively.

Summary

Obesity has become epidemic in the United States. There are many pregnancy related complications associated with obesity, including an increased risk of miscarriage, infertility and congenital anomalies, as well as a variety of late pregnancy related complications. Additionally, obesity can predispose to the development of fetal macrosomia, which in itself can lead to childhood obesity, thus creating a vicious cycle of obesity and other comorbidities. Preconception weight loss is ideal. Bariatric surgery is an alternative in difficult cases. Close monitoring of obese women is essential. Prevention of obesity is the best option for disrupting this cycle of obesity.

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Behavioral and Medical Management of Obesity

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Abstract:
South Dakota physicians are confronted by an epidemic of obesity. Developing an effective management strategy for patients with this condition can be daunting. This article reviews the evidence behind dietary, exercise-based, and pharmacological approaches to the care of the overweight and obese patient, offering recommendations to the clinician based on this evidence.

Introduction

In 2009, the prevalence of obesity in the U.S. population was 26.7 percent.[1] This is substantially above the "Healthy People 2010" goal of 15 percent. South Dakota, at 29 percent, compares unfavorably to the national figure;[2] obesity is the most common form of disturbed nutrition in the state.

The costs of obesity are enormous. Obesity has been implicated in the incidence of a number of medical conditions reviewed elsewhere in this special issue of *South Dakota Medicine*. Public and private health care costs for overweight and obese persons accounts for 5.5 to 7 percent of national health expenditures in the United States[3] to the tune of $147 billion annually.[1] Sustained modest weight loss of as low as 5 percent has been shown to significantly improve many risk factors,[4] and most individuals who achieve weight loss report improvement in their physical and emotional health.[5]

Energy balance is the key to weight. Caloric expenditure must exceed caloric intake for weight loss to occur. Maintenance caloric intake may be estimated using the formula shown in Figure 1. Expenditure may be enhanced by increased physical activity or pharmacologically modifying the metabolic rate; intake may be decreased through

Figure 1. Approximate daily energy expenditure, in calories.

Men's needs (±200 calories) =
(864 – (9.7 x age [years])) + (AC* x (6.45 x weight [pounds]) + (12.8 x height [inches]))

Women's needs (±160 calories) =
(387 – (3.8 x age [years])) + (AC* x (4.95 x weight [pounds]) + (16.8 x height [inches]))

*AC = activity coefficient:

Sedentary	1.0
Low activity	1.1
Active (walking ~7 miles/day)	1.3
Very active	1.5

dietary restriction, pharmacologically altered appetite or absorption, or surgically altered capacity or absorption. This paper addresses dietary modification, exercise and pharmacological (including "supplement") interventions. Surgical strategies are presented in a separate article in this issue.

Diet

A number of different dietary approaches have been employed in efforts to lose weight. These strategies fall into two categories: (1) altering the specific quality – but not directly the quantity – of constituent dietary components and (2) limiting the total caloric intake.

Calorie-restricted diets

Historically, the most common dietary approach to weight loss is restriction of the quantity of food consumed. A change of 3,500 calories intake correlates to one pound of body weight; decreasing intake by 500 calories per day yields a loss of one pound per week for a constant level of physical activity.

Aggressive restriction of caloric intake is effective for losing weight.[6,7] Very low calorie diets (400 to 800 kcal per day total intake) are effective for short-term weight loss, but maintenance of the weight loss via these diets is difficult.[8,9] Safety is a concern with these aggressive diets. Although the consensus is that they may be safe to implement for up to 16 weeks,[10] there is a risk of micronutrient deficiencies below 1,000 calories per day.[11] Additionally, semi-starvation diets alter serum free fatty acid, amino acid and electrolyte levels, potentially inducing lethal arrhythmias.[12]

More modest calorie-restriction (reduced by 500 to 1,000 kcal per day from baseline) appears to have better long-term efficacy, with weight loss maintained for more than five years.[10] For long-term effectiveness, the goals must focus on lifelong dietary modifications, rather than immediate but short-term results. Dietary consistency is important,[13] and structured meal plans may be of help.[14] Consistently decreasing portion size and energy density may be a better strategy than periodic aggressive restriction of intake.

A subset of those who engage repeatedly in hypocaloric diets actually end up weighing more than they did at their baseline; weight-cycling is counterproductive and leads to more weight gain.[9,15] It appears that the repeated starvation-feeding cycles enhance energy absorption and retention during the times food is available, resulting in a higher set-point for the individual's weight once caloric restriction ends. This response to repeated starvation-feeding cycles is advantageous in times of famine.[16] Resting metabolic rate (RMR) drops and efficiency of absorption increases, often within 24 to 36 hours of initiation of starvation-level caloric intakes. RMR may drop to half its baseline rate with repeated cycles.[17-20]

Content-restricted (or enhanced) diets

Dietary modification is an effective means of weight control. As an alternative to simple portion-limited approaches, several different strategies have been developed to accomplish this in a way that is both effective and tolerable to the individual attempting to lose weight.

High-fiber diets have been proposed. The rationale is that higher fiber content increases the sense of satiety and decreases caloric intake. Merely increasing fiber intake doesn't help with weight loss.[21] However, it does appear to help control hunger while on a restricted energy intake diet.[22-24] The addition of high-fiber foods such as fruits and vegetables to the menu does not result in weight loss independent of caloric restriction.

Another approach is the low-fat diet. This strategy seeks to exploit the fact that lipids contain over twice the calorie-per-gram concentration of carbohydrates or protein (9 kcal/g vs. 4 kcal/g); limiting this component of the diet would theoretically result in satiety with fewer ingested calories. Some studies show it is superior to simple calorie-restricted diets,[25,26] but others show no advantage[27,28] or even inferiority in the short term.[29] A systematic review found that a 10 percent decrease in fat calories is required for successful weight loss,[30] indicating an aggressive reduction, rather than minimal modifications, is essential. The low-fat diet appears more effective when coupled with exercise in the weight loss program,[31] and appears to be important for long-term weight loss maintenance.[32]

An approach currently popular is the "low-carb" diet. The

mechanism proposed in support of this approach is that the fast-release energy of carbohydrates, compared to more slowly metabolized lipids or proteins, triggers an elevated insulin response, appetite stimulation and weight gain. Restricting carbohydrates decreases this and shifts the metabolism to lipolysis, consuming the body fat stores, leading to weight loss. The resultant ketosis is believed to suppress the appetite, an additional mode of action.[33] An alternative explanation is that the increase in the dietary fat to carbohydrate ratio perturbs fatty acid oxidation toward dissipative lypolysis and away from fat accumulation, resulting in greater weight loss than in a more macronutriently balanced but isocaloric diet.[34] Carbohydrate-restricted diets result in weight loss,[35,36] but only comparable to other diets.[28,37] This suggests that total caloric intake, rather than the lack of carbohydrates, is responsible for the weight loss. A component of many low-carb diets is a high-protein intake.[38] High-protein diets failed to lower markers for disease risk corresponding to weight loss, suggesting that factors beyond mere weight are important for health risk reduction.[39]

A variation on the carbohydrate-restricted diet is the low glycemic index diet. Proponents suggest that a diet with a high glycemic index – i.e., rich in simple carbohydrates – stimulates appetite, insulin over-secretion and weight gain. By restricting intake of simple carbohydrates, this weight gain will be reversed. Although some studies indicate that a diet with a low glycemic index (low simple carbohydrates) is more effective for weight loss than one with a low glycemic load (low total carbohydrates),[40] others do not.[41, 42] Conversely, the inclusion of sugar in the diet increases the likelihood of weight loss for those consuming a low-fat diet.[43]

Most content-restricted diets work in the short term. There is a paucity of evidence that restricting any one particular dietary component is more effective for weight loss than restricting another (Table 1).[44] It may be that the reason for the effectiveness of these strategies is that limiting choice results in decreased caloric intake simply as a function of boredom with the available options.[45] There is increasing consensus that the more healthful approach is to consume a balanced diet of real food rather than an intentional imbalance in dietary component intake.[46]

Exercise

In addition to decreasing caloric intake, weight loss strategies have included efforts at increasing caloric expenditure by way of increased physical exercise. Not surprisingly, early studies indicated an inverse relationship between daily physical activity and body weight.[47] Exercise is one of most potent physiological stimuli for lipolysis,[47] and in sufficient amounts can lead to substantial decrease in weight, following a dose-response curve.[48] In another study of non-dieting, overweight individuals, both the low-amount and the high-amount exercise groups lost weight in a dose-response manner.[49] However, most studies indicate that exercise *by itself* does not lead to weight lost in most people.[50] As an isolated strategy, eating less is more effective than exercise.[51]

Numerous factors associated with obesity – gender, body fat mass, adipose distribution, size/number of adipose cells – contribute to the response to exercise training.[47] Men decrease their body fat more efficiently with physical training than women.[47] Combined with slight caloric restriction in women, exercise promoted greater weight loss than diet alone, but only for first six months, after which there was no difference between groups.[52] Exercise aids weight maintenance following weight loss in normal weight, but not obese, women.[53,54] There is no corresponding decrease in those inflammatory markers associated with obesity-linked diseases by exercise in obese patients.[55]

Exercise by itself does not reduce obesity in children or adolescents. A study specifically investigating the effect of increased physical activity on metabolic rate and body weight in teenagers found that increased exercise does *not* change the 24-hour energy expenditures or result in weight loss by either lean or obese

Table 1. Content-restricted diet strategies.

Diet	Rationale	Effectiveness
High-fiber	Bulk results in earlier satiety	Addition of fiber not independently effective
Low-fat	Elimination of high-calorie-dense fats results in satiety with fewer calories ingested	Requires 10 percent reduction in fat calories to be effective. More effective when combined with exercise. Important in maintenance of weight loss.
Low-carb	Decreases insulin response; shifts the metabolism to lipolysis, the resultant ketosis suppresses appetite	Effectiveness comparable to other diets
High-protein	Similar to low-carb	Effectiveness similar to low-carb No corresponding decrease in disease risk markers with decrease in weight.
Low-glycemic index	Decreases insulin response	Mixed results reported in literature

adolescents without dietary intervention.[56] The recent EarlyBird 45 study uncovered the association in children that obesity leads to inactivity, not *vice versa*![57] The direction of this association explains why weight loss by a strategy of increasing activity is largely unsuccessful, in children at least.

The reason for the relative lack of efficacy of exercise for weight loss has not been completely elucidated. Exercise stimulates compensatory increase in energy intake that attenuates weight loss.[58] Thus, in the absence of dietary restriction, an energy homeostasis is maintained with increasing expenditure triggering increased intake. The mechanism for this may be related to ghrelin, the only known appetite-stimulating hormone in humans.[59] This internal eat-more signal increases in response to long-term – but not short-term – aerobic exercise, consistent with what would be predicted for an effective adaptive response. Resistance (anaerobic) exercise *decreases* ghrelin levels,[59] suggesting this type of exercise might be more useful in weight-control strategies, though no studies specifically addressing this strategy were identified in the literature. Other affecters of ghrelin levels are interesting to note in the context of obesity. Ghrelin is increased by emotional stress,[59] perhaps explaining eating-as-coping-mechanism phenomena. Its levels are decreased by sleep,[59] consistent with observations that obesity and short sleep duration are linked.[60]

Though the effect of exercise in successful weight loss appears negligible, evidence suggests that it may be crucial to prevent weight regain.[61] Its importance in maintaining lean body mass after energy restriction-induced weight loss was demonstrated in a study of patients over 50 years of age.[62] Somewhat perversely, increased exercise levels limit weight gain in normal weight – but not obese – women, as mentioned above.[53,54]

Medication

The allure of a pill that allows one to lose weight, without requiring behavioral changes at the dinner table or in the gym, is irresistible. A burgeoning market for both prescription and over-the-counter diet pills exists. Unfortunately, the dream largely fails to materialize due to unrealized efficacy, safety or both.

Pharmaceuticals

Among the first pharmacological approaches to weight loss was the use of sympathomimetic agents.[63] The mechanism by which these agents work is primarily via appetite suppression rather than increasing the RMR. Amphetamines, phenteramine and phenylpropanolamine were commonly used in the past, though their adverse cardiovascular and behavioral effects preclude their use currently;[63] however, sympathomimetic herbal supplements are still widely used as discussed below. One of the most recent sympathomymetic agents marketed is sibutramine (Meridia™). Originally developed as an antidepressant, it exhibits anorexic actions which are effective in promoting weight loss.[64] Unfortunately, it has also been associated with significant cardiac events, prompting removal from the market in Europe and more recently, the United States.[63,65,66]

As an alternative to sympathomimetics, other agents have been developed that employ different mechanisms. Orlistat (Xenical™ and Alli™) inhibits the production of gastric and pancreatic lipases and decreases fat absorption. It has been shown to help minimize weight regain after weight loss and is well tolerated overall.[67] Unpleasant digestive disturbances may occur if high fat diets are consumed, and patients need to be taught about fat intake to reduce the incidence of these potential side-effects. These effects can be used to the patient's advantage, however, by altering dietary choices through a classical conditioning stimulus-response cycle: bad choice yields bad effects! Fat-soluble vitamin absorption may be decreased and require the use of fat-soluble vitamin supplementation.[68]

Nutriceuticals

Over one-third of adults report using a weight-loss supplement at least once in their life,[69] with nearly one in 10 having done so in the past year.[70] The proposed mechanisms of supplements' actions include appetite suppression, metabolism boosting (e.g., "fat burners") and inhibition of nutrient absorption (e.g., "fat- or carb-blockers"). In spite of the plethora of formulations available, there is little quantifiable evidence of safety or efficacy for the top 10 most common ingredients.[71] The evidence behind nutritional weight supplements was the topic of a recent review published in *South Dakota Medicine*.[72] The bottom line was that while there is clearly potential, few have been adequately studied and none can be definitively recommended at this time.[73] There is critical need for quality studies of the potential role for supplements in weight loss.

Summary and Recommendations

Table 2 presents a summary of the effectiveness of behavioral and medical strategies for obesity management, along with our recommendations for each. The role that diet, nutrition and exercise in promoting health and reducing chronic disease has been well established. The Surgeon General's report states "for two out of three adult Americans who do not smoke and do not drink excessively, one personal choice seems to influence long-term health prospects more than any other: what we eat."[74] Substantial health care resources could be saved by expanding health promotion

and disease prevention programs that target dietary changes. The National Health Promotion and Disease Prevention Objectives indicate that up to 50 percent of disease mortality is related to changeable lifestyle factors.[75] Nutritional intervention and encouragement of physical activity are essential in slowing the progression of chronic disease.

Table 2. Recommended behavioral and medical strategies for obesity management.

Intervention	Recommendation	Strength of recommendation (SORT)[76]
Diets	Decreased caloric intake has consistently demonstrated efficacy.	A[6,7]
	Very low calorie diets are effective short-term.	B[77]
	Close monitoring and short-duration of use is important to assure safety.	C[12]
	Maintenance of the weight loss long-term appears to be better with moderate calorie restriction (a decrease of 500-1000 calories per day from baseline intake), especially in the context of a weight loss program that also incorporates exercise and other behavioral modifications.	B[78]
	Content-restricted/enhanced diets are effective short term.	A[26,28,35,40]
	There is no convincing evidence that restricting one particular dietary component is superior to restricting any of the others or that such diets are safe long-term. The authors cannot recommend for or against these diets for long-term weight management at this time.	C[25,45]
	Weight cycling should be avoided, as this may worsen the obesity in some patients.	B[9,15]
Exercise	In the absence of dietary modification, exercise does not appear effective in promoting weight loss.	B[50,56,57]
	However, it does seem to have an important role in maintenance of weight lost through dietary modification.	C[59]
	Resistance exercise may be preferable for weight-control purposes.	
Medications	Stimulant-based pharmacological approaches to weight loss are effective, yet there are demonstrated safety issues; none can be recommended at this time.	B[63-66]
	Orlistat is modestly effective, and generally (though not universally) tolerated. It may have role in a carefully selected and properly educated subset of obese patients.	B[67]
	There is a lack of evidence of efficacy or safety of nutraceuticals for weight loss. None can be recommended for weight loss at this time.	C[73]
	Incorporating a vitamin supplement as a part of a calorie-restriction based weight-loss plan, one utilizing orlistat, or following bariatric surgery may result in better nutritional status.	B[79]

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Metabolic and Bariatric Surgery for Obesity: A Review

By Dennis Glatt, MD; Tracy Sorenson, CNP

Abstract:
The obesity epidemic in the United States is plaguing both the adult and pediatric population. As BMI increases, life expectancy drops. Metabolic and bariatric surgery can be an effective option for morbidly obese patients to enable substantial, sustained weight loss and result in improvement or resolution of comorbidities. The National Institutes of Health's criteria for bariatric surgery includes patients with a BMI of 35 and associated comorbidities, or a BMI of 40 and have failed conservative management. Currently, the common surgeries done in the United States are the laparoscopic Roux-en-Y gastric bypass, the laparoscopic adjustable gastric band, the biliopancreatic diversion with duodenal switch and the sleeve gastrectomy. Complications of the surgery are related either to the stapling, origin of the surgery or the implantable device. Optimal outcomes for patients are achieved with a Center of Excellence designated surgeon and designated facility, demonstrated operative skill, quality outcomes, multidisciplinary support, minimal complications and number of procedures completed. Insurance companies have seen the benefit of covering metabolic and bariatric surgery with comorbidity reduction and reduced health care costs. A multidisciplinary approach to postoperative care includes a dietician, exercise physiologist, psychologist and bariatric nurse coordinator as part of the bariatric surgery team. Metabolic and bariatric surgery pared with healthy food choices and regular exercise is imperative to achieve the desired goal of long-term weight loss and comorbidity resolution.

Incidence of Obesity

Obesity is one of the most important health problems in the 21st century. Its impact has reached pandemic proportions, across the age spectrum. It is estimated that 68 percent of the United States' population is overweight or obese, with 34 percent being obese, and 5 percent morbidly obese. Approximately 30 percent of children are also overweight or obese, 15 percent are obese.[13] Childhood obesity rates have tripled in the past 30 years. Obesity is defined as a body mass index (BMI: kg/m^2) greater than or equal to 30. In the United States, obesity healthcare continues to rise as well as medical costs, which in 2008 totaled over $240 billion.[1] Metabolic and bariatric surgery can be an effective treatment for obesity that aids patients in achieving substantial, sustained weight loss, as well as results in improvement or resolution of metabolic diseases.

Morbid obesity is defined as a BMI of greater than 40, which has a prevalence among U.S. adults of nearly 5 percent of the population, equal to 10 to 15 million individuals.[1] The National Institutes of Health (NIH) has recognized that morbid obesity is associated with a notable increase in mortality as compared to nonobese patients.[1,7] A BMI greater than 45 is associated with an average decrease in life expectancy of 10 years for white subjects and nearly 20 years for some minority populations. Cardiovascular mortality is 50 percent greater in obese persons and 90 percent greater in severely obese persons.[1,7] Because of the dramatically increased morbidity and mortality risk associated with extreme obesity, such patients who do not achieve a significant weight reduction with therapeutic lifestyle changes or pharmacotherapy or both would benefit from surgical intervention. Of the morbidly obese population in the United States, only 1 percent of the clinically eligible population is currently being treated for morbid obesity through metabolic and bariatric surgery.

Surgery for severe obesity goes far beyond weight loss. Perhaps the most important benefit that results from this surgery is complete remission or significant improvement of type 2 diabetes and other comorbidities. Due to the use of surgery for treatment of metabolic diseases, weight loss surgery is now referred to as metabolic and bariatric surgery.

Who is a Candidate?

The National Institutes of Health has developed guidelines for appropriate candidate selection for weight loss surgery. A patient must have a BMI of 40, or have a BMI of 35 or greater with comorbidities related to obesity. In addition, these patients must have made reasonable attempts at weight management with diet, exercise and behavior modification. All candidates must demonstrate appropriate insight and have a social support system in place.

Metabolic and bariatric surgery is increasingly becoming an option for the adolescent population. Overweight adolescents have a 70 percent chance of becoming overweight or obese adults. This increases to 80 percent if a parent is overweight or obese.[13] Comorbidities previously owned by the adult population are beginning to plague the morbidly obese adolescent population, such as diabetes, hypertension and sleep apnea. Preventive measures are optimal for this population; however, with the rising number of obese children, surgery may be an effective option.[12,13] Early intervention may produce more effective resolution of comorbid conditions, a lower achievable weight, and earlier improvements in quality of life.[12] Adolescents are probably one of the groups of patients that suffer the most from the social and psychological problems related to obesity. Intervening surgically at an early age may be a viable option to improve health, quality of life and long-term survival of this group.

The best evaluation of a candidate for weight loss is with a multidisciplinary approach. The metabolic and bariatric surgery team may consist of mid-level providers to assist with education and initial clinic evaluation of the patient. After evaluation, dietary teaching by a licensed nutritionist is necessary to ensure patients are educated on healthy nutrition, eating habits, and appropriate dietary changes that will occur after weight-loss surgery.[2] A psychological evaluation is necessary to aid in preparing patients for the lifestyle changes and stress that may be associated with life after surgery. It is also necessary to ensure pre-existing mental health conditions are optimally managed prior to surgery.[4] All team members are integral in evaluation and preparation of the patient to ensure appropriate expectations for life after surgery. Involvement of exercise physiologists, pharmacists and trained bariatric nurses during the perioperative period ensures optimal care during hospitalization and after discharge. A bariatric nurse coordinator is vital to managing the patient's hospital care.

Contraindications

Currently a consensus does not exist on the possible contraindications to bariatric surgery. Suggested contraindications would include an extremely high operative risk, active substance abuse, or major psychopathological conditions. Patients that cannot comprehend the nature of the surgical intervention and compliance with the lifelong diet, exercise and behavior modification required for success should not be offered these procedures.[1]

Benefits of Metabolic and Bariatric Surgery

The purpose of metabolic and bariatric surgery is to improve health, quality of life and long-term survival by inducing substantial sustained weight loss that is sufficient to reduce obesity-related medical comorbidities. In the morbidly obese population, surgery may reduce the relative risk of death by 89 percent.[16] The loss of fat, particularly visceral fat, is associated with improved insulin sensitivity and glucose disposal. Loss of visceral fat also reduces intraabdominal pressure, resulting in improvements in urinary incontinence, gastroesophageal reflux, hypertension, venous stasis disease and obstructive sleep apnea.[1,7] Gastric bypass leads to improvement in the physiologic responses of gut hormones involved in glucose regulation and appetite control.[11] Mechanical improvements include less weight bearing on the joints, enhanced lung compliance, and decreased fat around the neck which relieves obstruction to breathing and sleep apnea.[5]

Fluid and hemodynamic changes that lower blood pressure after bariatric surgery include: diuresis, naturesis, and decreases in total body water, blood volume and indices of sympathetic activity. Other clinical benefits include improvements in type 2 diabetes, obesity-related cardiomyopathy, cardiac function, lipid profile, respiratory function, disordered sleep, degenerative joint disease, obesity-related infections, mobility, nonalcoholic fatty liver disease, asthma, polycystic ovarian syndrome, infertility and complications of pregnancy.[1,7,9,11] Most bariatric surgery patients also experience considerable postoperative improvements in psychosocial status and quality of life.[10]

The incidence of diabetes is directly associated with increased obesity rates. Currently, 60 percent of adults in the U.S. with type 2 diabetes are obese, and up to 20 to 30 percent are morbidly obese. Dramatic improvement and resolution of diabetes mellitus may be the greatest benefit of metabolic and bariatric surgery. A shorter duration of type 2 diabetes and greater weight loss are independent predictors of type 2 diabetes remission, with up to 90 percent resolution of diabetes in patients who undergo Roux-en-Y gastric bypass and up to 73 percent resolution of diabetes in patients who undergo laparoscopic adjusted gastric banding. Prevention of the development of type 2 diabetes is also recognized with bariatric surgery.[11]

Procedures

Bariatric surgery may be classified as restrictive, malabsorptive or a combination of the two. There has been a broad variety of weight-loss surgeries over the years, many of which have been modified, and some abandoned. Currently, the most common surgeries done in the United States are the Roux-en-Y gastric bypass, adjustable gastric banding, biliopancreatic diversion with duodenal switch and sleeve gastrectomy.[1] As techniques have evolved, most weight-loss surgeries now are being done with a laparoscopic approach. Laparoscopy has benefits of decreased hospital length of stay, reduced wound complications, less postoperative pain and a more rapid postoperative recovery.[1]

Restrictive Procedures

The purpose of a gastric restrictive procedure is to produce early satiety with small portions of healthy food, and thus induce weight loss. This is most commonly done with the laparoscopic adjustable gastric band, which was approved by the FDA in June 2001.These gastric banding procedures have been performed internationally since 1993.[1] The adjustable gastric band is a silicone device that is buckled around the proximal stomach. There is an inflatable inner component of the band that is connected by tubing to a subcutaneous port. This port is accessed percutaneously with a non-coring needle to adjust insufflation of the band. The patients typically lose 50 to 70 percent of their excess body weight over three to five years.[1] A weight loss of 2.5 pounds per week is anticipated.The key to success with the adjustable gastric band is making healthy food choices and returning to the bariatric program for adjustments of the band. Four to six adjustments are typically required in the first year; however, as weight loss,–is achieved, minor adjustments may be made once or twice per year as the patient approaches the optimal restriction. A small amount of fluid in the band slowly diffuses over time, so small adjustments need to be made in the band annually to maintain restriction.

Dietary adjustments are imperative for success with the adjustable gastric band. Calorie-containing liquids will sabotage weight loss as the patient may consume high-calorie dense liquids without feeling satiety. Occasionally, patients get too much restriction from the band and will subconsciously learn to obtain their calories from liquids, potentially resulting in weight gain. Healthy diet and eating habits are particularly important after the adjustable gastric band to avoid getting a food bolus stuck at the stoma of the band. Patients may experience dysphasia from foods such as breads, pastas, rice, and dry or reheated foods. Effective treatment for an obstructing food bolus is usually simply accessing the port and removing all of the band's fluid.

Complications associated with the adjustable gastric band include band slippage, band erosion, balloon failure, port malposition, band and port infections and esophageal dilatation. A band that is adjusted with too much restriction may exacerbate symptoms of heartburn, reflux and chronic cough. It is rare for a patient with an optimally adjusted band to experience heartburn symptoms. Most adjustable gastric band complications are rarely life-threatening nor emergent and usually can be managed laparoscopically as an outpatient. Life-threatening complications with the adjustable gastric band are less than 0.019 percent.[1]

Sleeve gastrectomy was initially utilized as a risk reduction staging strategy for the biliopancreatic diversion duodenal switch. Many metabolic and bariatric surgeons have now adopted sleeve gastrectomy as a stand-alone operation. The short gastric vessels on the greater curve of the stomach are divided all the way up to the gastroesophageal junction. A bougie is then placed along the lesser curve of the stomach and stapler cartridges are deployed adjacent to the bougie starting approximately 5 to 7cm proximal to the pyloric valve. This is carried all the way up to the gastroesophageal junction, creating a long, tubularized stomach. The lateral stomach that is disconnected is removed, creating a "sleeved" stomach. Short-term studies have demonstrated safety and efficacy of the sleeve gastrectomy; however, its long-term outcome and durability are unknown.[3] Its mechanism of action as well as technical nuances of the surgery such as bougie-size calibration and proximity to the pylorus remain controversial topics. With 85 percent of the stomach removed, the smaller stomach helps the patient to achieve satiety with small portions. In addition, there appears to be an endocrine component to the procedure with a decreased production of the hormone ghrelin, which decreases hunger.[3] Most patients will achieve over 60 percent excess weight loss; however, 25 to 30 percent may fail to maintain that weight loss long term. Risks of a leak at the staple line in some reports are 3 to 5 percent. Advantages of this procedure include no implantation of an artificial device and less frequent follow up as compared to the band. In addition, there is decreased potential for malnutrition and vitamin and mineral deficiencies.[1,3]

Malabsorptive Procedures

Malbsorptive procedures include the jejunal-ileal bypass and the biliopancreatic diversion duodenal switch (BPD-DS). The jejunal-ileal bypass has been abandoned due to development of liver abnormalities in one-third of patients and cirrhosis in as many as 10 percent.[1] In the BPD-DS, bile and pancreatic juices draining into duodenum are diverted to the terminal ileum by a long small bowel limb in addition to a sleeve gastrectomy. Excellent weight loss results;

however, the procedure is not used widely because of the greater nutritional deficiency and metabolic risks.[1]

Combination Procedure

Currently in the United States, laparoscopic Roux-en-Y gastric bypass is the most commonly performed metabolic and bariatric surgery. The Roux-en-Y gastric bypass is a combination malapsorptive and restrictive procedure that has been performed for more than 35 years.[1] The weight loss achieved with the Roux-en-Y gastric bypass is greater than that attained with pure restrictive procedures. In the laparoscopic Roux-en-Y gastric bypass, the upper part of the stomach is transected creating a small gastric pouch measuring 20 cc. The gastric pouch is anastomosed to a Roux-en-Y proximal jejunal segment bypassing the remaining stomach, duodenum, and a small portion of the proximal jejunum. The Roux limb length is 100-150 cm. As a result, the Roux-en-Y gastric bypass limits food intake and induces some nutrient and caloric malabsorption. Patients typically lose 60 to 80 percent of the excess weight over 12 to 18 months. Long-term studies have demonstrated that substantial sustained weight loss is maintained in greater than 90 percent of patients.[1] The Roux-en-Y gastric bypass is particularly effective for resolving gastroesophageal reflux in patients with morbid obesity and has also been shown to dramatically improve and often resolve type 2 diabetes. Operative mortality rates are less than 0.3 percent for Roux-en-Y gastric bypass.[1]

The malabsorptive component of the Roux-en-Y gastric bypass necessitates nutritional supplementation. Bypassing the antrum and duodenum results in decreased absorption of several nutrients including iron, folate, calcium and vitamin B-12. A complete multivitamin with iron is recommended, as well as calcium citrate, vitamin D-3 and vitamin B-12 supplementation. Commercial bariatric-specific nutritional supplementations are available. Yearly monitoring for nutritional deficiencies is recommended.[14] Nutritional parameters are monitored on a yearly basis with supplementation accordingly.[1,14]

The fastest rate of weight loss occurs during the first three months postoperatively, when dietary intake remains very restrictive. After malabsorptive procedures, patients can lose 0.5 to one pound per day or 40 to 90 pounds by three months postoperatively. This rapid weight loss decreases by six to nine months after bariatric surgery and the peak weight loss is achieved at 12 to 18 months after the procedure.

Hypometabolism is common during the first six months after bariatric surgery. Cold intolerance, hair loss and fatigue are common complaints, which tend to diminish as weight loss stabilizes.[1,9] Reassurance and support are often all that is necessary.

Complications associated with bariatric surgery may present either as an early or late problem. Complications unique to stapling procedures include a staple line leak or bleed. Attempts to identify and correct leaks intraoperatively have been shown to reduce the postoperative incidence to almost zero. Bleeding at the gastrojejunostomy usually stops without intervention. Later complications may include gallstones, internal hernias, stricture at the gastrojejunostomy, ulcer development and nutritional deficiencies.[1] An internal hernia may form due to the intra-abdominal mesenteric defect created by the Roux-en-Y gastric bypass. Laparoscopy with repair of this hernia may be done with rapid postoperative recovery, usually electively as an outpatient.[6] A stricture may be dilated with a single or occasionally serial endoscopies. Ulcer development may occur in the jejenum just distal to the gastrojejunostomy and is managed with proton pump inhibitors and Carafate. Avoidance of nicotine and NSAIDS is crucial after the Roux-en-Y gastric bypass.[1,2]

Choosing a Procedure and Program

The choice of bariatric surgery depends ultimately on individual factors including BMI, perioperative risk, metabolic variables, comorbidities, local surgeon expertise, and other physician/patient preferences. Roux-en-Y gastric bypass has yielded a significantly greater loss of excess weight at five and ten years postoperatively than did laparoscopic adjustable gastric band (66.6 percent versus 47.5 percent respectively).[1] However, those who have made healthy lifestyle changes have had great success with any metabolic and bariatric procedure. Appropriate expectations preoperatively will ensure the patient is set up for success with the procedure chosen.

Choosing the optimal metabolic and bariatric surgery program for the bariatric surgery candidate plays a large part in the patient's success. Bariatric programs can obtain certification that demonstrates excellence in operative skill, number of procedures completed, long-term outcomes, minimal complication rates and a multidisciplinary approach to supporting patients.[1] In bariatric surgery, the complication rates associated with weight loss surgery procedures are linked to the experience of the surgeon; the critical threshold for minimizing the complications occurs at approximately 100 to 250 operations and ongoing annual experience of 50 cases.[1]

Metabolic and bariatric surgery is recognized by insurance companies as beneficial to the patient's long-term health, and therefore many offer health plan benefits for surgery. Research shows that insurers recover their costs for

metabolic and bariatric surgery in two to four years, depending on the type of procedure performed.[15] There are some carriers that specifically exclude bariatric surgery, however, these are rare. For most third-party payers, prior authorization is required. After evaluation by a bariatric surgeon, many insurance carriers necessitate that a standard set of requirements must be met prior to authorization. These requirements may include obtaining records of previous weight history and interventions tried with a primary care provider, a psychological evaluation, a dietician evaluation and participation in a medically supervised weight-loss program. Participation in a medically supervised weight loss program has not been shown to achieve great weight loss results, but allows a patient time to become educated on healthy nutrition and develop exercise habits before surgery. Supporting patients through the insurance approval process is vital to ensure completion of requirements, as many get discouraged with the time commitment prior to proceeding with surgery. It is important to encourage patients who are seeking bariatric surgery to become well-informed regarding the requirements of their individual insurance policy to avoid misunderstandings or unnecessary delays.[1]

Postoperative Management

Continuity of care after bariatric surgery is vital to ensure long-term success. This continuity serves to monitor weight loss, assess the status of preexisting medical conditions, monitor for surgical and nutritional complications and provide guidance and support as patients pursue lifestyle changes. Many patients have maladaptive eating behaviors, nutritional deficiencies or other nutritional inadequacies preoperatively, which may persist after a bariatric procedure. Patients with the laparoscopic adjustable gastric band are managed by adjusting the band along with continued nutritional counseling. In general, the bariatric surgery patient should adhere to recommendations for a healthful lifestyle, including increased consumption of fresh fruits and vegetables, limitations on foods high in saturated fats, reduction of stress, and participation in exercise 30 minutes a day or more to achieve optimal body weight. Increased physical activity improves body composition in bariatric surgery patients.[1]

Knowledge and experience are needed for appropriate laparoscopic adjustable gastric band adjustments. During the first postoperative years, regular consultations for advice and adjustments are critical in providing good weight loss. Patients with adjustable gastric bands need to have follow up every four to six weeks until optimal band adjustment is achieved. Patients with laparoscopic adjustable gastric bands should have follow up examinations every year indefinitely. Adjustments for special circumstances, including major surgical procedures, intercurrent illness, pregnancy and remote travel can be beneficial as well.[1]

The perioperative management of the bariatric surgery patient is multidisciplinary, and patients can be overwhelmed with the necessary follow up. The bariatric surgeon and the team's registered dietitian are critical to have available for support postoperatively. Mental health professionals should be available to help patients adjust to the myriad of psychosocial changes they experience postoperatively. Depression can diminish during the first year after surgically induced weight loss. Regardless of the bariatric procedure, psychiatric counseling can benefit all bariatric surgery patients.[1,4]

Women of childbearing age have special considerations for weight-loss surgery. Adequate absorption of oral contraceptives is not well known after Roux-en-Y gastric bypass. Alternative forms of contraceptive are recommended such as an IUD, barrier methods, Depo-Provera or NuvaRing. Pregnancy is not recommended during the first year following Roux-en-Y gastric bypass and sleeve gastrectomy due to the rapid weight loss that occurs and risk for fetal malnutrition. Achieving pregnancy after the majority of the surgical weight loss is complete is optimal 12 to 18 months postoperatively. With adjustable gastric banding, however, if pregnancy occurs, the band may be deflated during pregnancy as needed to maintain appropriate weight gain and growth for the fetus. After delivery, the patient may return for adjustments as necessary to proceed with weight loss.[1]

Adolescents with morbid obesity require a multidisciplinary approach to their care involving a primary care physician, dietician and psychologist. In general, adolescents with morbid obesity and comorbidities who are mentally and physical mature should be considered for metabolic and bariatric surgery. Challenges present with both types of procedures when done at an early age. Follow up care with adjustable gastric band adjustments may be challenging to maintain. Malapsorptive procedures would require lifelong nutritional supplementation. Ethical issues for an adolescent when considering a bariatric procedure are whether the patient's health is being compromised by severe obesity, whether the patient has failed more conservative options and whether the patient has decisional capacity. Education of the entire family unit on appropriate food choices and healthful lifestyle behaviors is imperative to have success with the adolescent morbidly obese patient.[12,13]

Conclusion

Metabolic and bariatric surgery pared with commitment to

a lifestyle change is imperative to achieve the desired goal of long-term weight loss and comorbidity resolution. Patients must commit to both healthy food choices and regular exercise to have long-term success. All patients who undergo metabolic and bariatric surgery must be monitored throughout their lives, to ensure optimal postoperative weight loss, eventual weight maintenance and overall health. Comorbidity resolution that results from metabolic and bariatric surgery gives patients improvement in quality of life and long-term survival.

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An Overview of the Medical Model for Prevention, Assessment and Treatment of Childhood Obesity

By Chris Tiongson, MD

Abstract:
South Dakota physicians are confronted by an epidemic of obesity. Developing an effective management strategy for patients with this condition can be daunting. This article reviews the evidence behind dietary, exercise-based, and pharmacological approaches to the care of the overweight and obese patient, offering recommendations to the clinician based on this evidence.

Introduction

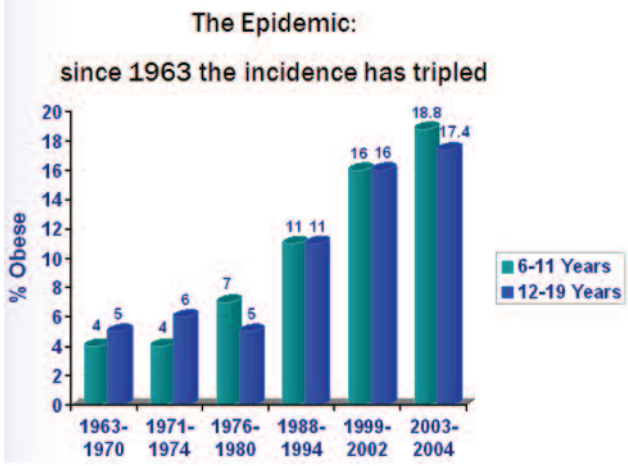
In 2007, the American Academy of Pediatrics published a supplement in the journal Pediatrics providing comprehensive guidelines for the prevention, assessment and treatment of childhood obesity.[1] These guidelines are a consensus statement based on an expert panel's review of evidence-based interventions in order to give the primary clinician a set of proven tools and interventions that can be used during office visits as well as outlining more intensive secondary and tertiary interventions. Development of the guidelines was sponsored by the Centers for Disease Control and Prevention (CDC) and the American Medical Association (AMA). The guidelines also have been endorsed by the American Academy of Pediatrics (AAP).

The Epidemic

Since 1960, the incidence of obesity among children in the United States has tripled. Starting at 4 to 5 percent in 1960, the rate has skyrocketed to 17 to 18 percent in 2004, as seen in Figure 1.[2]

America's children are not equally affected by the epidemic, as significant racial and ethnic disparities have been noted.

Figure 1.



from 11.7 to 17.7 percent (generally increasing with age), while the rate for African-American children ranges from 13 to 22 percent and for Hispanic children ranges from 16.3 to 22.5 percent.[2] Native Americans are at especially high risk. Data from the Aberdeen Area Indian Health Service show that from 38 to 43 percent of Native Americans are overweight or obese.[3] Statistics for overweight or obese children (all children regardless of ethnicity) show that South Dakota ranks 14th lowest for overall prevalence (28 percent). Our sister state of North Dakota ranks fifth (26 percent), while neighbor Minnesota boasts the lowest rate in the nation at 23 percent.[4] Although these numbers are good compared to other states, the health burden for our children is still three times higher than even 40 years ago.

To better understand the statistics, one should understand how a diagnosis of obesity is made. The key element is an accurate measurement of body mass index (BMI) starting at age 2 and determining the percentile using the U.S. Centers for Disease Control and Prevention (CDC) BMI growth chart or tables. Based on BMI percentiles, a child at less than the fifth percentile would be diagnosed as "underweight," children between the fifth and 84th percentiles are classified as "healthy weight," between the 85th and 94th percentile are considered "overweight" and children over the 95th percentile diagnosed as obese. Children at or greater than the 95th percentile are at especially high risk for weight-related health problems, but there is not a widely accepted term applied to this highest percentile group. More neutral terms can be used with children and families that focus on the health effects of obesity and not on appearance. The BMI is the key tool that correlates with weight-related health problems in children. Using phrases such as "excess weight", or "mismatch between height and weight"," risk of weight-related health problems" or even "BMI" can be helpful in communicating this to children and their parents.

Some electronic medical records will automatically calculate BMI when a height and weight are entered. The mathematical formula for English units is BMI=[weight (lb) / height (in) / height (in)] x 703. For metric units use BMI=[weight (kg) / height (cm) / height (cm)] x 10,000. Calculation tools are available online at http://apps.nccd.cdc.gov/dnpabmi and www.nhlbisupport.com/bmi/. Unlike an adult, a child's BMI changes over time with growth and maturity. Following the 85th percentile line through childhood shows an initial dip as children lose their "baby fat" from toddlerhood to kindergarten. If a child remains on the 85th percentile by age 8, the BMI climbs back up to 18. As a child matures into a teenager, body composition changes associated with puberty (i.e., increased muscle mass primarily for boys and development of secondary sexual characteristics for girls) cause the BMI to rise naturally to 24 for a 16-year-old.

As BMI percentiles increase from the 85th percentile and higher, the risk of weight-related health problems increases. The medical complications of obesity in children include nearly every organ system.[1] (Figure 2) Endocrine problems such as diabetes mellitus and polycystic ovarian syndrome are common. Cardiovascular complications include hypertension and atherosclerosis.

Psychosocial problems impact obese children greatly like sleep disturbances, mood problems, self-esteem and bullying. Gastrointestinal disorders include nonalcoholic fatty liver disease and gall stones. A common neurologic problem is headaches from pseudotumor cerebri. Orthopedic problems like Blount disease, slipped capital femoral epiphysis and osteoarthritis are important. Keep in mind that the health

Figure 2. Medical complications associated with obesity in children.

Short stature (Hypothyroidism, Cushing's, Prader-Willi syndrome)	Dysmorphic features (Genetic disorders, including Prader–Willi syndrome)
Acanthosis nigricans (NIDDM, insulin resistance)	Excessive Acne or hair (Polycystic ovary syndrome)
Violaceous striae (Cushing's syndrome)	Headaches (Pseudotumor cerebri)
Large tonsils (Sleep apnea)	Abdominal pain (Gall bladder disease, GERD, NAFLD)
Enlarged liver (Nonalcoholic fatty liver disease (NAFLD))	Undescended testicle (Prader-Willi syndrome)
Limited hip range of motion (Slipped capital femoral epiphysis)	Lower leg bowing (Blount's disease)

risk associated with childhood obesity is not just a future risk. Children can have complications as children. Particularly alarming is the rapid increase in the number of cases of type 2 diabetes mellitus. Thirty-two percent of new cases of type 2 diabetes are now children, a 10-fold increase from the 1980s and 1990s.[5] The lifetime risk of acquiring type 2 diabetes for a Hispanic female is 50 percent. This may be the first generation of children with a shorter life expectancy than their parents as a result of the consequences of obesity and type 2 diabetes.[6] Many obese children are diagnosed with hypertension and require pharmacologic treatment. Additionally, atherosclerosis can begin in childhood. Autopsy studies of obese children who died from trauma show that plaque formation can begin by elementary school with a higher incidence at higher BMI percentiles.[7] It is important to share the information with children and families that there is an immediate risk associated with obesity. This may be hard for a teenager to grasp.

Etiology of Childhood Obesity

There are many risk factors and influences that impact the health of our children. Genetics and family history, metabolic rate, behavior, environment, culture and poverty each play an important role. Some of these influences are clearly not modifiable, such as genetics and family history. Having one obese parent increases the child's risk of obesity by three times. Having two obese parents increases the risk 13 times.[8] Poverty is theoretically a modifiable risk factor, but it is, at least, daunting and perhaps impossible from a population standpoint, and very unlikely from an individual standpoint. Poverty decreases access to more healthful foods such as fruits and vegetables in part due to the dearth of grocery stores in urban centers or rural locations. These areas have recently been termed food deserts. Additionally, fresh fruits and vegetables are more expensive than high-calorie and low-nutrient-value convenience foods.

Environmental factors include weather and climate. Subzero temperatures in the Dakotas and Minnesota need to be considered when trying to increase physical activity. The human-made parts of the world cannot be neglected. Limited safe neighborhoods allowing children to walk to school and play outside, along with the lack of planning for shared roadways to provide safe passage for all (cars, pedestrians and cyclists), are impediments to regular exercise. The ways that cities have evolved over the years have led to a significant increase in the number of trips taken by car at the expense of biking and walking. For example, trips to work by car have increased from about 67 percent in 1960 to 87 percent in 2000.[9] Using public transportation, such as a bus or subway, is a good way to increase physical activity since one has to walk to and from the bus stop or subway stop on each end of the trip. Culture impacts both eating and exercise. Busy, overscheduled families tend to not eat meals prepared at home. Media advertising of fast food and snack foods to children can influence children's food preferences. Popular pastimes, like television, video games and computers keep kids indoors and sedentary. Behavior may be considered the most amenable factor to intervention, but making lifestyle changes is not easy. The guidelines for prevention and treatment focus on evidence-based interventions that have the best chance of impacting behavioral choices to increase healthy eating and physical activity. What can be done? The guidelines address prevention during well-child visits, assessment of risk and screening for complications, and four stages of treatment.[1]

Evidence-based Prevention Messages

Keeping in mind that there is limited time during a well-child visit, what are the behaviors and activities that a clinician can recommend that have the greatest likelihood of making a positive impact for that child and family? Dietary intake recommendations that are supported by the evidence include breastfeeding for the first 12 months or longer, limiting or eliminating sugar-sweetened beverages, and eating the recommended quantities of fruits and vegetables. Recommended eating behaviors include eating breakfast daily, limiting eating out (especially at fast-food restaurants), having regular family meals at home and limiting portion sizes.[1] Physical activity recommendations include limiting television and other screen time to no more than two hours per day, not allowing or removing a television from a child's bedroom, and moderate to vigorous physical activity for at least 60 minutes per day.

These recommendations have been further stratified by strength of evidence. There is clear evidence to support limiting sugar-sweetened beverages, limits on screen time, no TV in the bedroom, limiting fast food, appropriate portion sizes and daily breakfast. There is moderate evidence to support breastfeeding through 12 months, eating the recommended fruits and vegetable servings, eating meals together as a family, 60 minutes of exercise and a diet rich in calcium with limited energy-dense foods and balanced macronutrients.[1] One reason that breastfeeding is in the moderate evidence category is that the initial studies of breastfeeding only went up to six months of age, and given only limited evidence from 6 to 12 months of age, the strength of evidence for the 0 to 12 month recommendation as a whole is considered moderate.

The guidelines suggest narrowing the message even a bit more to be used with all children at well-child visits regardless of BMI percentile. Universally using the "5-2-1-0" message is a simple way to encourage healthy eating and

physical activity. Several states and institutions have adopted this mnemonic that can readily be used in the exam room. The "5" stands for eating five servings a day of fruits and vegetables. A typical serving size would be one half-cup. One of the five servings can come from 100 percent fruit or vegetable juice, but it is preferable to eat the fruit or vegetable itself. This would exclude starchy vegetables like potatoes and corn. The "2" stands for less than two hours a day of screen time, to include television, computers, texting and video games (but not including homework that requires a computer.) The "1" stands for at least one hour per day of moderate or more intense physical activity. This could include gym class and recess, and the 60 minutes does not need to be consecutive. The "0" stands for zero or almost zero servings of sugary drinks per day. This would include pop, sugary non-juice drinks, sports drinks and some coffee-based drinks with added sugar.

One way that I incorporate the 5-2-1-0 message into a well-child visit is to use the exam room chalkboard. (Figure 3) With younger children, the clinician can write the numbers and draw the pictures and have the child guess what they mean. For older children who like to draw, the child can draw his or her favorite options next to the corresponding number.

Figure 3.

In addition to universal obesity prevention guidance, all children over age 2 should have a BMI measured and a percentile plotted. Following the percentiles over time can help identify a trend before crossing the 85th or 95th percentiles, raising awareness and potentially allowing for earlier intervention.

Assessment of children who are already obese includes screening for comorbid conditions and medical complications. A full examination with special attention given to accurately measuring blood pressure – utilizing the norms for age, height percentile and gender from the National Heart, Lung and Blood Institute tables – is essential. A tailored review of systems and focused examination to detect known complications of obesity is needed (Figure 2). Acanthosis nigricans, thickening and cracking of the skin, particularly on the nape of the neck or axillae, is a major risk factor for type 2 diabetes mellitus and should be given special attention during the examination.

Screening laboratory tests are indicated for some children. The guidelines for children with BMIs between the 85 to 94th percentiles, and who are without risk factors (e.g., strong family history of hyperlipidemia or heart disease), should be considered for a fasting lipid profile. For children age 10 and older, a BMI percentile between 85-94th percentiles, and with a family history risk factors, a fasting glucose and lipid profile with AST and ALT is indicated to be done once every two years. Children older than age 10 with a BMI percentile at or above the 95th percentile should have a fasting glucose and lipid profile with AST and ALT, regardless of family history risk.[1]

Treatment

Prevention of childhood obesity is the goal, but there are recommended treatments that can help. The AAP-endorsed guidelines recommend a staged approach to treatment in order to achieve the goals of effecting behavioral change, improving parenting skills, and improving self-esteem and self-efficacy. Weight-related goals include slowing the rise of BMI percentiles and then decreasing BMI percentiles toward the 95th or 85th percentile (depending on the starting point for the child.) Keep in mind the overall goals of improving health and that adopting lifelong healthy behaviors will improve health outcomes, even without weight change.[10]

Treatment Stages

Stage 1: "Prevention Plus" is essentially the prevention

message, plus a little more. Taking the basic 5-2-1-0 message and then working on the other evidence-based recommendations that are most relevant for the particular family is a good strategy. This might mean tracking the frequency of fast-food dining and breakfast consumption, increasing exercise time or decreasing screen time beyond the standard prevention recommendations. The family could set a goal to prepare and eat meals at home five to six times per week. The whole family should be included in the lifestyle changes and make return visits to the office within a few weeks to months in order to track progress and troubleshoot barriers.[1]

Stage 2: "Structured Weight Management" adds to the Stage 1 recommendations. Other professionals are involved with the family in addition to the primary care clinician, typically a nutritionist and/or an exercise therapist or counselor. Individualized goal setting and self-monitoring of goals between monthly visits with the professionals is key.[1]

Stage 3: "Comprehensive, Multidisciplinary Intervention," is a big step up and requires significantly more resources than the first two stages. A multidisciplinary team with experience in treatment of childhood obesity approaches obesity through a chronic disease management model integrating mental health, nutrition, exercise therapy, medical expertise (including screening for and management of medical complications of obesity) with weekly and/or biweekly parent and child group sessions. Group sessions can include practice preparing healthy meals, exercise and encouragement of persistence. Some of the most successful programs across the country are Stage 3 programs.[1]

Stage 4: "Tertiary Care Intervention" programs are rare. Centers involved in clinical or research protocols may use medication, very-low-calorie diets or bariatric surgery in addition to a comprehensive Stage 3 approach.[1]

Summary

Childhood obesity is a major problem with detrimental health effects both during childhood and adulthood. Prevention messages at every well-child visit and Stage 1 and 2 treatment interventions based in the primary care clinician's office can make a difference. Referral to specialized Stage 3 and 4 interventions can be helpful for more difficult cases.

Review Quiz

1. What is the numerical mnemonic for preventive anticipatory guidance?
   a. 54321
   b. 58103
   c. 867-5309
   d. 5210
2. The "5" stands for
   a. Miles of walking per day
   b. Servings of fruits and veggies per day
   c. Minutes in the penalty box for fighting
   d. Golden rings
3. The "2" stands for
   a. Number it takes to tango
   b. At least two hours of exercise per day
   c. Less than two hours of screen time per day
   d. "to" or "too" in txt
4. The "1" stands for
   a. Weight per body surface area (kg/m2)
   b. At least one hour of exercise per day
   c. Partridge in a pear tree
   d. At least one hour of paperwork per day
5. The "0" stands for
   a. Oxygen
   b. Oprah
   c. No outcome, no income
   d. Zero (or almost zero) servings of sugary beverages per day
6. BMI
   a. An expensive German car
   b. Baltimore International Airport
   c. Weight/height
   d. Lowest risk zone of weight-related health problems is <85 percentile

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Obesity and Type 2 Diabetes Mellitus in South Dakota: Focused Insight Into Prevalence, Physiology and Treatment

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Abstract:
Type 2 diabetes mellitus is one of the significant comorbidities of obesity. This review addresses the prevalence of obesity and diabetes mellitus nationally and in South Dakota. It elaborates on some of the mechanisms of association of obesity with diabetes mellitus, including effects related to adipokines, lipotoxicity, vitamin D deficiency and apolipoprotein C1. This review addresses the prevention and treatment of diabetes mellitus in the obese population through life style changes, medications and/or surgery. Future directions in the management of diabetes are explored in the obese population.

Discussion

As several contributors to this edition of South Dakota Medicine have documented, obesity is now a serious problem of epidemic proportion that challenges not only the health of our nation, but also the health of South Dakota citizens. It is a challenge not limited by gender, ethnicity or age. Between 2000-2009, the national, self-reported prevalence of obesity in adults and children increased 6.9 percent[1] (to 26.7 in 2009), with a higher prevalence among non-Hispanic black individuals (37 percent) and among Hispanic individuals (30 percent). In South Dakota, 28.4 percent of children ages 5-19 (2007 figure)[2] and 64.2 percent (2006 figure) of adults are overweight or obese.[3]

Increasing prevalence of type 2 diabetes mellitus in South Dakota

Type 2 diabetes mellitus is one of several comorbid conditions associated with obesity.[4] According to the International Diabetes Federation (IDF), the estimated global diabetes prevalence of 285 million (2010) represents 6.6 percent of the world's adult population and is expected to increase 54 percent by 2030 to 438 million.[5]

The Centers for Disease Control and Health Prevention predicts the number of Americans with diabetes (type 1 and type 2) will double or triple by 2050.[6] Currently, one in 10 adults have diabetes and this number could increase to as many as one in three by 2050, if current trends continue.[6] This significant increase is mostly multifactorial, with obesity considered one of the primary risk factors, in addition to older age, minority ethnicity, family history of diabetes and sedentary lifestyle.[6] Diabetes currently affects approximately 23.6 million individuals, with about 57 million adults having prediabetes.[7] In South Dakota, approximately 44,000 adults (7.2 percent) over age 17 have diabetes (type 1 or type 2) and approximately 25 percent of these adults are unaware they have the condition. More than 150,000 adults in South Dakota have pre-diabetes.[8] In the following seven counties, more than 10 percent of adults are diagnosed with diabetes: Buffalo, Corson, Dewey, Mellette, Shannon, Todd and Ziebach. In these counties, as well as in 13 additional counties, approximately 30 percent or more of adults are obese.[9]

The pathophysiology of type 2 diabetes in obese persons

The pathophysiology of type 2 diabetes involves both insulin resistance and beta cell defects, which ultimately lead to fasting and postprandial hyperglycemia.[10] Insulin resistance is now linked to truncal adiposity within a cluster of signs and symptoms known as insulin resistance syndrome (IRS), syndrome X, or metabolic syndrome.[11] Other symptoms of IRS include glucose intolerance, elevated blood pressure and triglycerides and decreased HDL cholesterol. Almost all adults with type 2 diabetes are overweight, and more than half of these adults are obese.[12]

Mechanisms associated with obesity that also might be associated with diabetes

White adipose tissue (WAT) was formerly viewed as a storage depot, but is now known to be a major endocrine and secretory organ,[7] secreting various peptide hormones and cytokines (adipokines).[13,14] Adipokines include leptin, adiponectin, resistin, TNF-α and interleukin-6, as well as steroids and prostaglandins, among others.[13] These are linked, directly or indirectly, to insulin resistance and to inflammation, two conditions known to be fundamentally associated with development of type 2 diabetes and with other closely related comorbidities, such as hypertension, dyslipidemia and atherosclerosis.[7,14,15] Insulin resistance is manifested physiologically by 1) decreased insulin-stimulated glucose transport; 2) decreased glucose metabolism in adipocytes and skeletal muscle; and 3) impaired suppression of normal hepatic glucose production which is reflected in fasting, especially morning, hyperglycemia.[14,15]

Adipocytes are the only cells that are specialized and perfectly adapted to store lipids without this compromising their functional integrity.[13] The dyslipidemia and hypertriglyceridemia associated with obesity in some individuals also can lead to increased free fatty acid flux to other tissues with increased triglyceride storage in these tissues. This consequently promotes insulin resistance and other adverse effects, referred to by some as lipotoxicity.[14] The hyperinsulinemia observed with insulin resistance in obese individuals can contribute to the obesity itself, because insulin is a critical regulator of adipose tissue by promoting lipogenesis.[14]

Some patients with a severe deficiency or absence of fat (lipoatrophy) are quite insulin resistant and can develop lipoatrophic diabetes.[14] Such insulin resistance and diabetes is associated mainly with deficiency of some adipocyte secretory products, such as leptin, that are associated with improved insulin sensitivity. In studies, both type 2 diabetes and insulin resistance were improved in mice by either leptin administration[16] or by fat transplantation.[17]

Additional associations

In 2007, researchers at the University of Minnesota identified a variant of apolipoprotein C1 (T45S ApoC1) occurring more frequently in people of American Indian and of Mexican ancestry. This variant also is linked to elevated body mass index (BMI), obesity and type 2 diabetes. Study subjects carrying the variant had a 9 percent higher BMI and a 50 percent higher incidence of diabetes.[18] Further studies are needed to explore whether the association of this variant with diabetes is consequent to increased obesity or whether it is related primarily to diabetes.[18]

Obesity is associated with deficiency of vitamin D-25, mostly due to increased sequestration of this vitamin in body fat.[19] Vitamin D deficiency has been reported to be associated with insulin resistance.[20,21] Treatment with vitamin D analogues have been shown to provide antiproteinuric effects in patients with stage III or IV chronic kidney disease.[22]

Prevention and Treatment of Diabetes in Obese Individuals

Since insulin resistance both precedes and predicts type 2 diabetes mellitus, a successful prevention and treatment

program should target insulin resistance via lifestyle changes and/or use of medications.[14,23] Seventy percent of insulin-mediated glucose transport occurs in skeletal muscle[24]; therefore, skeletal muscle insulin resistance contributes significantly to the metabolic derangement seen in type 2 diabetes.[24]

Lifestyle changes

A C-peptide level of >0.8 ng/ml or a two-fold increase in C-peptide levels after injecting 1 mg glucagon is a good indicator of preservation of beta cell function and is an important factor in predicting the efficacy of diet and exercise in decreasing blood glucose in obese patients.[7,25]

In study subjects with pre-diabetes who participated in the Diabetes Prevention Program (a multicenter clinical study ending in 2002), lifestyle changes reduced the incidence of diabetes by 58 percent (95 percent CI 48-66) compared with placebo and were found to be more effective than metformin treatment (30 percent reduction in incidence, 95 percent CI 24-51).[26] Lifestyle changes targeted a weight loss of 7 percent of initial body weight through a healthful, low-calorie, low-fat diet with approximately 150 minutes of moderately intense exercise weekly.

Independent effects of lifestyle changes

In people with diabetes, caloric restriction, weight loss and physical activity have independent beneficial effects in improving glycemic control[27,28] and can contribute to decreasing HbA1c as much as 2.4 percent.[28]

Weight Loss

Individuals newly diagnosed with diabetes who lost 10 percent of their weight have maintained better glycemic control than those who did not lose weight. This improvement was maintained up to three years after weight loss, even despite weight regain. Therefore, early weight loss is critical.[29]

Nearly 40 percent of obese, non-insulin dependent patients with diabetes greatly improve glycemic control (to 126 mg/dL), with a weight loss of 20 pounds or less. In one study, glycemic control improved early in the course of weight loss (within the first five pounds) and continued with further weight loss. Patients who remained hyperglycemic after losing five to 20 pounds were unlikely to improve with additional weight loss and, therefore, may be candidates for treatment with additional agents.[30] Moderate weight loss (17.6 pounds) may improve hepatic insulin sensitivity and, in studies, has been associated with reversal of nonalcoholic steatohepatitis (NASH).[31]

A short-term (two days) energy restriction (450 Kcal/day) reduces basal endogenous glucose production, but not glucose disposal in obese, insulin-treated type 2 diabetic patients. This is reflected by improved fasting glucose levels, but has less effect on postprandial glucose levels.[32,33] In contrast, long-term energy restriction via the Very Low Energy Diet (VLED, 450 Kcal/day) till substantial weight loss (more than 50 percent extra weight loss) reduced endogenous glucose production and improved insulin sensitivity in skeletal muscle, liver and adipose tissue in obese, insulin-treated type 2 diabetics.[25] This improvement occurred despite the fact that patients still were clinically obese at termination of the VLED.[25] This improvement in insulin sensitivity (100 percent) is similar to that achieved with restrictive bariatric surgery in obese, insulin-resistant non-diabetic patients.[25]

Medications to improve insulin resistance

Patients who cannot achieve adequate blood glucose control through lifestyle changes may require medication that targets insulin resistance.[34]

Metformin

Metformin use in the Diabetes Prevention Program reduced the incidence of diabetes by 31 percent (95 percent CI 17-43).[26] Metformin was more effective in patients with higher baseline BMI or higher basal fasting plasma glucose, compared with patients having lower values for these two variables.[26] Metformin improves hepatic insulin resistance, thereby suppressing hepatic glucose production and leading to improved fasting plasma glucose.[10,35] It is associated with minor weight loss in patients with type 2 diabetes[10] and has been associated with reduction in HbA1c by 1.5-2 percent when used as a monotherapy.[35,36] However, metformin also has been associated with vitamin B12 deficiency by inducing malabsorption of B12 in as many as 22 percent of patients with type 2 diabetes.[37] Dose and duration of treatment were significant risk factors for this problem: every 1g per day dosage increase nearly tripled the risk for developing B12 deficiency (OR 2.88).[38] Metformin also is associated with gastrointestinal discomfort and diarrhea.[10] It cannot be used in patients with decreased renal function, due to increased risk for developing lactic acidosis.[10,37]

Thiazoladinediones (TZD)

Thiazoladinediones (TZD) represent a significant therapeutic advance in type 2 diabetes management.[14] This class of drugs improves peripheral and hepatic insulin sensitivity and consequently improves hyperglycemia.[10,34] TZDs have been associated with a 0.7-1.6 percent reduction in HbA1c in some patients.[34] TZDs primarily target the action of peroxisome-proliferator–activated receptors (PPARs), a

subfamily of the nuclear-receptor superfamily that regulates gene expressions in response to ligand binding. Three PPARs (PPAR α, PPAR δ [also known as PPAR β], and PPAR γ), have been identified, to date. PPAR γ receptors are expressed mainly in adipose tissue and are the primary target for TZD action.[34]

Three thiazoladinediones have been introduced into the U.S. pharmaceutical market as glucose-lowering drugs.[34] In 1997, troglitazone was approved by the FDA for this purpose,, but was withdrawn from the market in 2000 due to hepatotoxicity. Rosiglitazone and pioglitazone were approved in 1999.[34] In 2010, the use of rosiglitazone for patients with type 2 diabetes uncontrolled by other medications was significantly restricted in the U.S., in response to data showing an increased risk of cardiovascular events, such as heart attack and stroke, in patients using this medication.[39] In September 2010, the FDA issued a Drug Safety Communication addressing a potential increased risk for bladder cancer in patients taking pioglitazone. An ongoing, 10-year, epidemiologic study designed to assess this risk is being reviewed by the FDA.[40]

TZD medications, in general, are associated with weight gain, fluid retention and plasma volume expansion, which lead to peripheral edema.[10,34] Therefore, they are contraindicated in patients with congestive heart failure class III or IV.[41] There also is recent concern that these drugs may be associated with more distal extremity bone fractures, especially in women.[10,42] Such fractures may be associated with TZD inhibition of osteoblasts without comparable inhibition of osteoclasts.[42]

Medications to enhance weight loss

Phentermine

Phentermine was approved by the FDA in 1997 for short-term use (12 weeks or less), with long-term use being off-label.[7,43] Use of this medication, with its adrenergic properties, is limited in patients with metabolic syndrome, because it may worsen pre-existing hypertension or tachycardia, or underlying cardiac comorbidities in these high-risk patients.[7] Phentermine is classified as a Schedule IV medication, due to its low-to-moderate potential for psychological or physiological addiction.[7] Combined use of fenfluramine (also an anorectic drug) with phentermine was associated with a 0.7 percent reduction in HbA1c after 12 months; however, fenfluramine was withdrawn from the U.S. market in 1997, due to its association with cardiac valvular disease.[44]

Orlistat

Orlistat is a potent selective gastric and pancreatic lipase inhibitor approved in 1999 as a prescription medication (Xenical® 120 mg) and in 2007 as an OTC medication (Alli® 60 mg) for weight loss in conjunction with a reduced-calorie diet. It is recommended that this medication be taken with daily supplements of fat-soluble vitamins (A, D, E and K).[45] In obese non-diabetic patients, a four-year study (XENDOS Study) of orlistat combined with lifestyle changes resulted in a 37 percent relative risk reduction in progression to diabetes (P=0.0032) with significant weight loss (P<0.001) when compared to placebo with lifestyle changes. A larger effect was seen in subjects with impaired glucose tolerance than in subjects with normal glucose tolerance.[46, 47] In a randomized double-blinded placebo-controlled study, use of orlistat with a mildly hypocaloric diet (500 kcal/day deficit), in obese type 2 diabetics, was associated with improved glycemic control and consequent dose reduction of other concomitantly used diabetes medications (P=0.0019).[48] In a metanalysis of the use of orlistat in adults with diabetes, orlistat was associated with an average weight loss of 2.6 kg [95 percent CI, 2.1-3.2 kg] [2.6 percent loss] at 52 weeks, with less than 0.5 percent reduction in HbA1c.[49]

There have been other weight loss medications that either were not approved by the FDA or were withdrawn from the market due to safety concerns.[7] Currently, there are few data regarding other drugs for weight loss or for weight control in overweight or obese persons with type 2 DM.[50]

Medications approved primarily for diabetes management, but also associated with weight loss

Some medications originally approved primarily for diabetes management also help patients achieve weight loss, an indirect effect which assists diabetes control.[7,10] Metformin, for example, is associated with modest weight loss of two to three kg (1 to 2 percent) in the first six months of treatment.[35]

Glucagon-like Peptide-1(GLP-1) Agonists

Glucagon-like peptide-1(GLP-1) agonists (exenatide and liraglutide) potentiate nutrient-induced insulin secretion to control hyperglycemia, but not in patients with pre-existing hypoglycemia.[51,52] In clinical trials, exenatide and liraglutide lowered HbA1c 1 percent or more over oral diabetes medications and were associated with modest but progressive weight loss (3 percent, two to five kg) for up to two years.[52-55]

Pramlintide

Pramlintide, an analogue of amylin, has been approved for diabetes management in conjunction with insulin in both type 1 and type 2 diabetes. It has been associated with reduction in HbA1c of 0.3 to 0.6 percent and weight loss of 0.5 to 1.4 kg. It works in concert with insulin to slow

gastric emptying and to suppress meal-related glucagon secretion.[52-56]

Surgery

Bariatric surgeries are characterized as being either 1) restrictive (Laparoscopic Adjustable Gastric Band (LAGB) or Vertical Banded Gastroplasty (VBG)); 2) restrictive with some malabsorption (Roux-en-Y Gastric Bypass (RYGBP)); or 3) restrictive with significant malabsorption (Biliopancreatic Diversion without or with Duodenal Switch (BPD/DS)).[7]

In a meta-analysis of results from different bariatric surgeries (LAGB, VBG, RYGB, BPD/DS), the average excess weight loss (EWL) after two years was 61.2 percent, with the greatest loss occurring with BPD/DS (70 percent EWL).[57] There was no significant difference in outcome when assessed for less than two years or assessed after two years.[57]

A 2004 meta-analysis of bariatric surgery showed the procedure resolved type 2 diabetes in approximately 77 percent of patients and either resolved or improved type 2 diabetes in 86 percent of patients.[57] These outcomes varied according to the bariatric procedure performed.[57] The best outcome was achieved with BPD/DS (98.9 percent resolution or improvement) with the lowest percentage resolution (50 percent to 60 percent) achieved with LAGB (either Swedish Adjustable Gastric Band (SAGB) or Lap-Band (LB)).[57,58] Reduction in fasting glucose was significantly greater for patients with diabetes (71 mg/dl) compared with the total population (13 mg/dl).[57] Operative mortality was 0.1 percent for purely restrictive surgeries, 0.5 percent for patients undergoing gastric bypass procedures and 1.1 percent for patients undergoing BPD/DS procedures.[57]

In a meta-analysis of the two most commonly used LAGB procedures, (SAGB and LB,)[58] significant excess weight loss occurred at one-, two-, and three-year follow-up for both procedures, compared with baseline. On average, more than 50 percent of excess weight loss occurred after the third year.[58]

Effect of adipose tissue on variable blood glucose control in people with diabetes treated with injectable insulin

One cause of significant glycemic excursions and variability is suboptimal insulin injection and the presence of lipohypertrophy.[59,62] In a study of 500 insulin dependent diabetics of variable weight range treated with an intensified insulin regimen, the prevalence of lipohypertrophy varied between 35 percent (self-reported) to 41 percent (verified by exam).[62] Lipohypertrophy was associated with duration of insulin use, outflow of insulin from sites of injection, multiple use of needles and use of relatively limited areas of injection in the abdomen.[62] The prevalence of lipohypertrophy in patients rotating the insulin injection site (arms, abdomen, legs, buttocks) weekly was one-third of those who rotated the insulin injection site with each injection.[62]

A study of non-diabetic adults showed that maximal total epidermal-dermal thickness is 2.4 (±0.4) mm, regardless of the subject's gender, BMI, adult age or ethnic origin, with the main variability factor being body site.[63] This data is being confirmed in other ongoing studies of patients with diabetes.[59] However, subcutaneous tissue thickness increases with BMI, female gender, and at the abdomen and buttocks versus other sites. Therefore, a needle of 3 mm length or more should deliver insulin into shallow subcutaneous tissue.[59] Shallow versus deep SC tissue insulin injection does not appear to affect the absorption or pharmacokinetics of insulin.[64]

Thickness of abdominal wall subcutaneous tissue varies in pregnant women by up to 8 mm.[59] Therefore, the risk for unintended intramuscular injection of insulin is increased among pregnant women with diabetes. A 5 mm injection needle with a two-finger pinch-up, rather than a perpendicular injection technique, is recommended for these patients. For thin patients, the lateral gluteal region is recommended for injections, rather than abdominal injection.[59]

A 5 mm needle can be used safely in obese diabetic patients without a significant increase in glycated hemoglobin and without local injection-related complaints.[62] However, there currently are no insulin syringes with needles less than 8 mm in length, due to incompatibilities with certain vial stoppers.[65]

Although the absorption rate of rapid-acting insulin analogues is similar in fat tissue and in muscle tissue at rest, absorption in active muscle tissue has not been studied.[66,67] Injection of long-acting insulin into muscles should be avoided due to significantly increased risk for hypoglycemia.[68]

Current Initiatives Targeting Type 2 Diabetes and Obesity

At least two recent initiatives specifically target people with type 2 DM and obesity. In conjunction with study results mentioned earlier in this paper, blood protein screening for apolipoprotein C1 variants may be used to determine individuals at higher risk for developing both obesity and type 2 diabetes, thus leading to additional possibilities for prevention. Other preventive efforts may include use of somatostatin, a counter-regulatory protein hormone, under investigation for treatment of obesity. In May, 2010, Sioux Falls firm, Braasch Biotech, LLC, was awarded a project grant to continue development of somatostatin. Preclinical

results suggest the drug may have therapeutic potential as a vaccine for treatment of type 2 diabetes and obesity.[69]

Resources for Providers and Patients:

- *AAP Recommendations for Prevention of Pediatric Overweight and Obesity* http://www.aap.org/obesity/index.html
- *BMI Toolkit for Providers, Centers for Disease Control and Prevention* www.cdphp.com/images/providers/Toolkit_BMI_Provider.pdf
- *Healthy South Dakota, a resource to support the State Plan for Nutrition and Physical Activity to Prevent Obesity and Other Chronic Disease (2006). The toolkit is designed to assist providers in developing their own management plans for patients.* http://www.healthysd.gov/StatePlan.html

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Quality Focus:

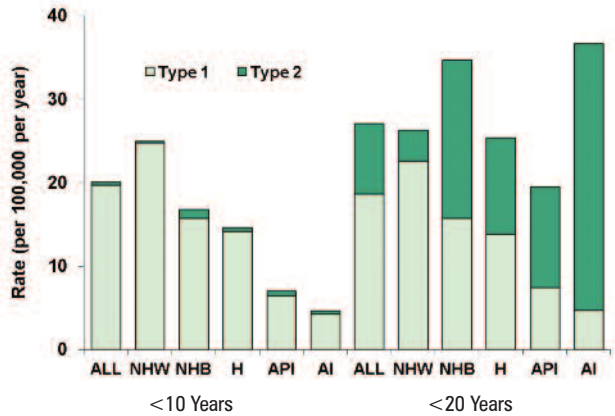
Childhood Obesity and the Emerging Epidemic of Type 2 Diabetes

By Stephan D. Schroeder, MD
Medical Director,
South Dakota Foundation for Medical Care

An epidemic of type 2 diabetes among American youth has emerged over the past 20 years, and this phenomenon parallels the increase in obesity in children and adolescents. According to the U.S. Centers for Disease Control and Prevention (CDC), the obesity prevalence among children and teens tripled in the 1980s and 1990s.[1] Concurrently, type 2 diabetes, which previously accounted for 1 percent of cases of childhood diabetes, now accounts for 8 percent to 45 percent of newly diagnosed cases in children according to recent clinical case data.[2] There are now about 215,000 Americans younger than age 20 years who have diabetes (type 1 or type 2).[3]

Among non-Hispanic white youth aged 10 to 19, the rate of new cases was higher for type 1 than for type 2 diabetes. For Asian and American Indian youth aged 10 to 19 years, the opposite was true; the rate of new cases was greater for type 2 than for type 1 diabetes.[4] Among Mexican-American children less than 17 years of age in a California study, 31 percent of those with diabetes had type 2 diabetes.[5]

Rate of new cases of type 1 and type 2 diabetes among youth aged <20 years, by race/ethnicity, 2002–2005[4]



NHW= non-Hispanic white; NHB= non-Hispanic blacks, H= Hispanics; API= Asians/Pacific Islanders; AI= American Indians

What can we do to curb the onset of type 2 diabetes in teens? We learned from the Diabetes Prevention Program (DPP) that it is possible to prevent or delay the onset of type 2 diabetes. The DPP showed that lifestyle intervention to lose weight and increase physical activity reduced the development of type 2 diabetes by 58 percent during a three-year period. The DPP also showed that monitoring and documentation of food intake was the single most effective strategy for successful weight loss.[6]

Some strategies to consider:

- Aim to identify more teens with pre-diabetes by increasing screening among populations at risk.
- Discuss the importance of lifestyle modification for reducing diabetes risk.
- Talk to your patients about initiating dietary and lifestyle changes.
- Set a realistic long-term goal, such as 5-10 percent weight loss and 150 minutes of exercise per week over the next 12 months.
- Set a realistic short-term objective, such as 30 minutes of exercise per week for the next 30 days and reduce total daily fat consumption by 10 percent.
- Encourage community-based exercise programs.
- Offer behavioral support and tools such as log books for documenting food intake and exercise.
- Express confidence in your patient's ability to make changes.
- Follow up, reinforce, and encourage.

The efforts already under way for obesity prevention and control are strengthened by "Let's Move," First Lady Michelle Obama's initiative to end childhood obesity in a generation, by empowering parents, encouraging healthier foods in schools, increasing physical activity, and increasing access to affordable healthy foods. Other policy and environmental interventions are showing early evidence of improving environments that will lead to lower rates of obesity. Working together, the rates of childhood obesity and type 2 diabetes can be levelled or reversed.

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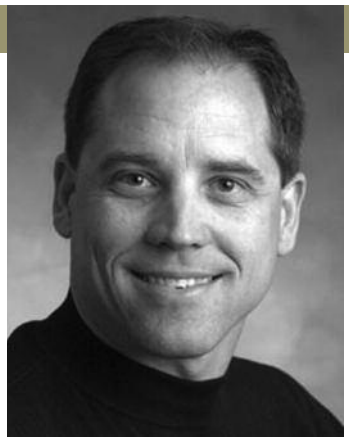

DAKOTACARE Update:

5-2-1-0

By E. Paul Amundson, MD
DAKOTACARE Chief Medical Officer

By the time you get to this article, combined with your personal clinical experiences, it will become obvious that obesity has become the No. 1 health issue that will impact our future health care utilization and associated direct/indirect costs. The medical care costs of obesity in the United States are staggering. In 2008 dollars, these costs totaled about $147 billion. Some important long-term sequelae of this health issue are increasing prevalence of fatal heart attacks, diabetes, certain cancers and osteoarthritis.

U.S. Centers for Disease Control and Prevention (CDC) data from 2009 reveal that 29.6 percent of South Dakota adults have a Body Mass Index (BMI) greater than or equal to 30. The overall prevalence in the US for non-Hispanic white (our most common racial category in South Dakota) is 23.7 percent. The Midwest region has a higher average prevalence than all other regions with the exception of Southeast states.

Our children are not immune to this extremely worrisome trend. Since 1980, obesity prevalence among children and adolescents has almost tripled. As of 2009, one in seven low-income, preschool-aged children in the U.S. was obese. This percentage is even higher (15 to 20 percent) in South Dakota, especially in the Native American population centers.

Our family members, patients, and communities look to us to be leaders in promoting healthy habits. So, what can we do to combat this expanding epidemic? The answers are not costly but do involve an effort of encouragement and investment of time to improve our own heath and assist others:

1. As individuals, let's look at our own personal and family health habits. The strength of your words are much more powerful if your patients know you and your family also embrace the healthy values you are recommending to them. Drink more water. Challenge yourself. Set reasonable goals, accomplish them and then set higher ones.

2. As a physician, regardless of your specialty, consider these recommendations to your adult and pediatric patients:
   - Increase physical activity;
   - Increase the consumption of fruits and vegetables;
   - Decrease the consumption of sugary and high fructose corn syrup-sweetened beverages;
   - Increase breastfeeding initiation and duration;
   - Reduce the consumption of high energy-dense foods; and
   - Decrease television and screen-time viewing.

3. As community leaders, we have the ability to facilitate partnerships with local organizations to have a significant impact on public health. A recent *Wall Street Journal* article described a community-wide initiative to combat obesity in Portland, Me. Like South Dakota, they have some long harsh winters that impair one's ability to get adequate exercise. A large part of this initiative was to encourage families to adopt a "5-2-1-0" philosophy each day:
   - At least five servings of fruits and vegetables;
   - Two hours fewer of screen time;
   - At least one hour of physical activity; and
   - Zero sugary beverages.

Inaction on our part should not be an option. I am a firm believer that cooperation and encouragement can significantly impact healthy outcomes. We have seen it firsthand here at DAKOTACARE among our employees and in our clients utilizing our wellness services. Recently, 49 of our employees participated in a 12-week wellness program based on "The Biggest Loser", resulting in a total combined weight loss of 638 pounds. If you would like further details please contact Trisha Dohn, DAKOTACARE Director of Health & Wellness.

We owe it to our patients and communities. You owe it to yourself and your family. See you outside. Plug in your iPod and move!

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