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Chapter XXVIII

Hyperandrogenism and Obesity: Ominous Co-Morbidities

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Abstract

This review has a two-fold objective. One, it addresses the association of hyperandrogenism and obesity and the complex metabolic derangements that are part of the problem. Clinical management of these co-morbidities is challenging and complex. Second, this article will aid health care providers with the key features to an early diagnosis and intervention to decrease the morbidities in the short as well as long term. Method: Systematic review of articles and information on the topic of interest that were published in the last 15 years. Conclusion: Obesity and hyperandrogenism are integral parts of Metabolic Syndrome/Polycystic Ovarian Syndrome (PCOS)/Hyperandrogenism, Insulin resistance, and Acanthosis Nigricans (HAIR-AN). With the childhood obesity epidemic, the metabolic syndrome and the associated abnormalities are routinely seen in clinical practice and these have a tremendous economic burden on the society and the quality of life.

Keywords: Adolescence, obesity, metabolic syndrome, hyperandrogenism, polycystic ovarian syndrome, hyperandrogensim, insulin resistance, acanthosis nigricans.

Introduction

Obesity in children and adolescents has increased at an alarming rate in the last two decades. Over the years, researchers have acquired a better understanding about the strong association of obesity in metabolic syndrome (MS, previously known as metabolic syndrome X) (1). Patients with MS have various metabolic abnormalities that can include abnormal glucose and insulin ratio, insulin resistance, high blood pressure, altered lipid profile, pro-thrombotic and pro-inflammatory state. Teenagers with MS are predisposed to long term morbidities, such as early coronary artery disease, hepatic steatosis, type 2 diabetes, and stroke (1). Evidence suggests that an overweight teenager has an 80 percent chance of continuing to be overweight in the adult life (2).

Approximately 17 percent of children aged 2-19 years are considered overweight based on a survey by National Health and Nutrition Examination Survey of 2003-2004 (3). As noted earlier, the rate of obesity has doubled in adolescents, who are in the 12-19 year age group (4). The prevalence of obese and overweight children may be different depending on the gender and ethnicity. For example, the obesity rates are higher in African Americans, Hispanic Americans, males, and those living in the southern states (2). The definition of obesity varies in adolescents when compared to adults due to different proportion of body fat in boys and girls at different ages (5). Body Mass Index (BMI) is a reliable tool to assess obesity, because it is easy to obtain and correlates well with the body fat (6). Any adolescent with a BMI of 30 kg/m^2 or 95th percentile for gender and age falls in the overweight category. They are considered at risk of being overweight if their BMI is between 85th and = 95th percentile. In the US, the economic burden of direct and indirect healthcare cost due to obesity and co-morbidities is estimated to be well over $ 117 billion annually. As the obesity rates have doubled and tripled respectively in children and adolescents, so have the health care costs (7). This impacts the healthcare burden directly.

Obesity and hyperandrogenism (HA) are strongly associated in patients who have been diagnosed to have polycystic ovarian syndrome (PCOS)/HA/MS. This article addresses their relationship with one another and specific management options. A subset of (PCOS) includes hyperandrogenism, insulin resistance and acanthosis nigricans, abbreviated as HAIR-AN (8,9). Historically PCOS was described based on findings of multiple cysts in the ovaries, irregular or no menstrual periods, and hirsuitism. However, absence of ovarian cysts does not rule out this syndrome (10). Women with high androgen levels have associated HAIR-AN features in about 5-10 percent of cases (11). The onset of PCOS/HAIR-AN may occurs in adolescent years and the diagnosis is likely to be delayed until early adulthood (8,9).

Pathophysiology

As PCOS/HAIR-AN is being studied more over the last two decades, different theories have been proposed to explain the features of the syndrome, including obesity. The primary problem in HA appears to be due to an altered hypothalamo-pituatary-ovarian axis. The anovulation and thus abnormal or absence of menstrual periods is from a persistent leutenizing hormone (LH) surge and its high concentration in the blood. There is also an

increased GnRH surge as the negative feedback from estrogen and progesterone is ineffective due to relative hypothalamic insensitivity. The LH surge results in increased production of androgens. The level of follicle stimulating hormone (FSH) is less when compared to the LH resulting in decreased enzymatic (aromatase) conversion of androgen to estrogen and thus anovulation.

Another key association of HA is hyperinsulinsm. This is due to peripheral insulin resistance, which can result in a hyperglycemic state. The level of sex hormone binding globulin (SHBG) is decreased due to the high insulin levels and consequently there is a rise in the free testosterone level (8). Insulin also increases the androgen production by directly stimulating the theca cells (12). Both hyperinsulinism and HA predispose an individual to have an athrogenic lipid profile. Total cholesterol, triglycerides (TG) levels are also elevated. Increased activity of the enzyme lipase affects the cholesterol metabolism and could result in a decreased level of the high density lipoprotein-cholesterol (HDL-C) (13). Another postulated mechanism for HAIR-AN is a genetic mutation of the insulin receptor (tyrosine kinase domain) (9).

Effects of HA can be multi-fold. Even though increased androgen production in women is associated with obesity, one study in 2002 by Gapstur et al (14) in obese men have found to have lower testosterone and dehydroepiandroterone sulfate (DHEAS) levels. High androgen levels in children and adolescents are linked to precocious puberty, accelerated bone growth, height, features of PCOS, and are more commonly seen in obese subjects compared to non-obese. In pre-pubertal obese children the level of DHEAS is often elevated (14).

Recently, researchers have looked at the effects of proteins like adiponectin, resistin, leptin, and TNF-a on the fat metabolism, peripheral insulin resistance, and energy expenditure (15). Resistin is produced by the mature visceral and subcutaneous adipocytes and influences insulin sensitivity. Adiponectin and leptin, also secreted from the adipocytes, have similar roles (16). A recently published study by Shin et al (17) suggested obesity as an inflammatory process due to findings of increased levels of C-reactive protein (CRP) and TNF found in obese children. The adiponectin level was found to be much lower concentration in these children. Retinol Biding Protein 4 (RBP4) is present in omental and subcutaneous fat and is expressed more in women with PCOS (18). The high levels of androgen and features of metabolic syndrome have shown to normalize in post-menarche obese adolescents after weight reduction (19).

Diagnostic Criteria

A standard list of the diagnostic criteria for MS in children and adolescents is still lacking. However, a modified diagnostic criteria for children using the NCEP criteria and data from the National Health and Nutrition Examination Survey (NHANES, 1988-94) is widely used. The National Cholesterol Education Program (NCEP) and the Adult Treatment Panel III (ATP III) include at least 3 of 5 of the following criteria for the diagnosis of MS in adults (1,2,20,21).

- Abnormal lipid panel: Hypertriglyceridemia (>150 mg/dl) and low HDL-C (<40mg/dl in males and <50 in females).
- High fasting glucose level. Hyperglycemic state is defined as fasting glucose level of 100 mg/dl or more.
- Elevated blood pressure, systolic, diastolic, or both using reference ranges. From example, blood pressure of >135/85 mmHg is considered abnormal.
- Increased waist circumference/abdominal girth. BMI is fairly reliable in assessing obesity in children.
- High insulin resistance (criterion in children).
- The World Health Organization (WHO) criteria required elevated insulin or glucose level (>110mg/dl) in addition to at least two of the following:[2]
- Abdominal obesity
- Waist size >94 cm or waist to hip ratio of >0.9
- Triglycerides > 150 mg/dl or HDL <35 mg/dl
- Blood pressure >140/90 mmHg.

HAIR-AN is a clinical diagnosis and includes the following, in addition to criteria mentioned above (9):

(a) Acne, hirsuitism, temporal balding, clitoromegaly, and deepening of voice (suggestive of high androgen level).
(b) Acrochordons (skin tags), acanthosis nigricans (usually found on the neck, axillae, and back). These are suggestive of insulin resistance and altered hormonal levels.

Suggested Workup

Anthropometric measurement, vital signs, with a complete history and physical exam (including genital) is recommended. A detailed family, past medical, and medication history should also be documented. Laboratory data that may be useful includes, fasting levels of insulin, glucose (complete metabolic panel to assess liver and renal function), lipid panel, glucose/insulin ratio, HgA1c, and AM cortisol level. Oral glucose tolerance test (2 hour) is also recommended to document hyperglycemic state. One test that has high sensitivity and specificity is the euglycemic hyperinsulinemic clamp. This may be impractical in a clinical setting due to the time consuming and complex nature of the test (9). A thorough endocrine evaluation should include thyroid function tests, serum prolactin, DHEA-S, am 17-hydroxyprogesterone (17-OHP), SHBG level, and free and total testosterone. IGF-1 level may be helpful in a suspected growth hormone producing tumor (22).

In order to establish the diagnosis of PCOS, the presence of multiple ovarian cysts is not necessary. Likewise, an abdominal/pelvic ultrasound detection of multiple ovarian cysts does not confirm that diagnosis either. Occasionally a computed tomography (CT) or an MRI of the abdomen/pelvis may be necessary in situations where there are progressive signs of hyperandrogenism (22).

Outcome

Metabolic syndrome (PCOS and HAIR-AN subset) in children can lead to potentially complicated short and long term medical problems. This exhaustive list includes but is not limited to the following (6):

- Distorted body image and perception
- Low self-esteem and depression
- Acne
- Obesity associated problems like snoring, obstructive sleep apnea, disordered sleep, gastro esophageal reflux disease (GERD), gall stones, joint pain, exercise intolerance, features of diabetes, coronary artery disease, and skin changes, etc.
- Amenorrhea (predisposing to subsequent inadequate bone mineralization) and possibly infertility.

Treatment Options

The timeframe for the diagnosis of metabolic syndrome/HAIR-AN to the outcome of the treatment varies from patient to patient and can be often protracted. A multidisciplinary approach is often required to address the metabolic as well as the psychological stressors associated with this syndrome. reatment should be geared toward specific metabolic abnormalities as well (6,9,23). It is important for the healthcare provider to be aware of the concerns that teenagers may have when it relates to cosmetic appearance. At a psychological developmental stage where bodily appearance plays an important role in a teenager's life, skin related problems such as acanthosis nigricans, acne, and hirsuitism may be quite troubling (22). This can affect their self-esteem directly. Health care providers should have a low threshold for referring these teenagers to counseling services.

Lifestyle Modification

Although compliance can play a big role with this approach, it is considered one of the most favored and successful mode of treatment in obese patients, who also have HA (22). Weight loss can dramatically improve the ovarian function and decrease the levels of androgens (24). Different dietary changes such as caloric restriction of carbohydrates or fat with increased protein intake have been previously studied. There is no sufficient data available if restriction of carbohydrates is better than that of fat intake. It is therefore prudent to use the expertise of a dietician or nutritionist who can work with obese/overweight individuals.

Medication Management

Typically, in addition to the lifestyle modification, medical treatment may include a combination of one or more of these therapies such as anti androgens, insulin-sensitizing agents, combined hormonal contraceptives, bariatric surgery, and complementary and alternative medicine treatment options. As part of a multidisciplinary approach, psychological counseling is very crucial.

Insulin-Sensitizing Agents

Biguanide: Metformin (trade names such as Glugophage®, Rhiomet®), a pregnancy category B drug, has traditionally been used in type 2 diabetes mellitus (DM). From a glycemic stand point, Metformin interferes with the hepatocyte mitochondrial respiratory oxidative process and decreases gluconeogenesis. This however, is not a complete blockade of gluconeogenesis. It also facilitates the glucose transport in tissues such as the skeletal muscles, by activating the enzyme tyrosine kinase (TK) on the insulin receptors and enhancing the glucose transporter system. Some of this action is also on the adipocytes. It also acts against the gluconeogenic effects of glucagon. Metformin is particularly useful in obesity associated with HA. Due to its insulin lowering effect, there is a consequent decrease in the free and total testosterone and an increase in the estradiol level (25). This has a beneficial effect on ovulation, hirsuitism and acne.

As obesity is strongly associated with cardiovascular morbidity and mortality, metformin has an added benefit of being cardioprotective. It has shown to decrease the free fatty oxidation, which helps improve the insulin sensitivity as well. It may also help lower the total cholesterol (TC), very low density lipopoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C), and increase the high density lipoprotein cholesterol (HDL-C). It also lowers the platelet aggregation and adhesion, and decreases the levels of tissue plasminogen inhibitor 1 and von Willebrand factor. This has a positive effect on homeostasis (26). It can induce vascular relaxation and reduce the oxidative stress (25,26). A combination of flutamide (an androgen receptor blocker) and metformin with an addition of drosperinone (a 4th generation progesterone) has shown to decrease abdominal fat (27).

Usual side effects from metformin may include gastrointestinal symptoms such as nausea, flatulence and diarrhea. These may be reduced by taking it with food. Treatment may be started with a single daily dose, preferably at a lowest possible dose. It may then be increased to a twice daily dose. It is not recommended to go over the maximum dosage of 2.25 grams/day (25). One must be aware of the potential toxicity from metfromin that includes lactic acidosis in rare situations. Metformin is fairly safe for the mother and baby during pregnancy and lactation (28).

Thiazolidinediones: Rosiglitazone is an insulin sensitizing agent, whose action on the peroxisome proliferator-activated receptor (PPAR) on the adipocytes improves glucose transport into the cell by increasing the adiponectin secretion (29). In studies done earlier on overweight women with PCOS, there was a decrease in the insulin resistance and return of ovulation as indicated by regular menses. The SHBG level also shows an increase that helps

with the ovulation. Some of the side effects include weight gain and cardiac failure in susceptible individuals (30).

Regulation of the Hormonal/Androgen Imbalance and Use of Oral Contraceptives

Combination birth control pills (BCP's) are the cornerstone in the treatment of HA. Their mechanism of action includes the following:

- Increase the SHBG production and level: This allows a reduction of free testosterone.
- Suppress LH: Decreases androgen production from the ovaries.
- Anti-minerelocorticoid activity: Certain progestins such as Drosperinone have low androgenic activity and are generally preferred in HA. The brand name contraceptives Yasmin® and Ortho-Tri-Cyclen® contain Drosperinone.

The effects of combination BCP's include normalization of menses and a decrease in acne and hirsuitism (22). In addition to the above, other pharmacologic agents have been tried in HA states are cyproterone acetate, finastreride, glucocorticoid, such as prednisone (patients with late onset congential adrenal hyperplasia (CAH) having PCOS features), and spironolactone.

Surgical Options

Bariatric Surgery: A decrease in obesity-related morbidity has been well documented in individuals that have undergone Roux-en-Y gastric bypass surgery. Although this is an optional procedure that has been evaluated mostly in morbidly obese adults, the guidelines are quite conservative for the adolescent population. Morbidly obese teenagers, who have failed the non-surgical approach may be considered for a gastric bypass surgery. Other justifications in addition to the above includes a BMI of 40 kg/m^2 or more, physical and psychosocial co morbidities from obesity (31). Bariatric surgery intended to result in weight loss can positively impact obesity, PCOS, and reverse anovulation. The risks from obesity during pregnancy in morbidly obese teens is also decreased by the procedure (31). A 1 to 2 year wait post operatively for becoming pregnant is usually recommended. As there can be potential complications from this surgical procedure, careful multidisciplinary evaluation for the need for surgery is needed.

Complementary and Alternative Medicine

Alternative approaches in the treatment of PCOS have been recently gaining popularity. In view of side effects from the traditional medical and surgical treatment, researchers have

looked at the benefits of acupuncture, a traditional form of Chinese medicine. Acupuncture has been shown to modulate neuro-endocrine systems that results in lowering of the increased sympathetic tone in individuals with PCOS. By releasing ß-endorphins the technique of acupuncture can directly influence the HPA axis and lower the cortisol and LH levels (32). As a result, its beneficial effects on metabolic, ovulation, and other neuro-endocrinal endogenous systems can positively influence the features of PCOS/HA. Other forms of alternative medicine such as homeopathy, Ayurveda, diet supplements, and hypnotherapy have been tried to treat obesity in adults with some encouraging results even though some are not very convincing (33).

Federal/State Program

The CDC (Center for Disease Control and Prevention), the Division of Nutrition and Physical Activity (DNPA) and the health departments of 28 states have established the Nutrition and Physical Activity Program to Prevent Obesity and Other Chronic Diseases (NPAO) since 1999 using the social ecological model (34). Healthcare providers are encouraged to contact their individual health departments to learn more about the program, where available.

Conclusions

Metabolic syndrome, hyperandrogenism, and PCOS are integral part of complex metabolic abnormalities that have a great impact on the health and general well-being of an individual. The diagnosis is often late and this adds to the economic burden from obesity related problems. The following key points will aid the healthcare provider with the timely diagnosis of HA/MS/PCOS and appropriate interventions.

- Healthcare provider awareness of obesity in childhood and adolescence.
- Utilizing diagnostic criteria and/or clinical diagnosis of PCOS/HA/MS. One may refer to the NCEP, NHANES, ATP III, WHO diagnostic criteria.
- A complete history, including that of the individual, family, past, and medications.
- Complete physical exam. As noted earlier, the diagnosis of HAIR-AN is clinical.
- Laboratory and radiological work up. The list includes fasting insulin, glucose (complete metabolic panel to assess liver and renal function), lipid panel, glucose/insulin ratio, HgA1c, and AM cortisol level. Oral glucose tolerance test (2 hour), thyroid function tests, serum prolactin, DHEA-S, am 17-hydroxyprogesterone (17-OHP), SHBG level, free and total testosterone, IGF-1 level are also recommended.
- Management that includes medical, surgical, lifestyle modification techniques, and appropriate referrals to other sub-specialty providers for addressing associated co morbidities. Keeping in mind that some patients may desire to utilize alternative and complimentary medicine options as well.

- Multidisciplinary approach that includes, the primary care provider, sub-specialist, social worker, nutritionist, and counselor/psychologist.

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