Recognizing the Signs of Metabolic Syndrome and Polycystic Ovary Syndrome in a Caucasian Adolescent Girl: Differentiating Type 2 From Type 1 Diabetes

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Case Presentation

C.K., a 12-year-old Caucasian girl, came to our office for a school entry physical. Her medical history included being diagnosed with type 1 diabetes 18 months earlier when she presented to an emergency room with flu-like symptoms of lethargy and dehydration and was found to have a blood glucose level of 994 mg/dl. After a short hospitalization, she had been discharged on split doses of rapid- and long-acting insulin. Because of her poor glycemic control, her insulin dosages had been increased at each of two subsequent visits with her previous diabetes care provider.

At the time of her first visit to our office, her insulin regimen was 60 units of lente with 40 units of lispro (Humalog) in the morning, 45 units of lispro at lunch, and 70 units of lente with 30 units of lispro at dinner. Her blood glucose ranged from low to 437 mg/dl (mostly in the high 200s) before breakfast, 63–174 mg/dl before lunch, 97–370 mg/dl before dinner, and 151–441 mg/dl before bed. A hemoglobin A1c (A1C) measured 7 weeks before this visit was 9.0%. She had been instructed after the A1C test to increase both her lente and lispro dosages but had not done so; she refused to take two injections (more than 100 units) at breakfast and dinner. Instead, she had continued with the same insulin dosages, which allowed her to fill a single 1-cc syringe.

Her family history was positive for diabetes, hypertension, cardiovascular disease, hypothyroidism, and depression. Menarche had occurred about 1 year ago, and her menstrual frequency was sporadic. Menstruation had occurred less than nine times during the past year, and the date of her last menstrual period was unknown.

A review of her dietary habits revealed usual breakfasts of cereal, milk, juice, bagels, muffins, and waffles or pancakes with low-calorie syrup; lunches and dinners of "grinders" (submarine sandwiches), other sandwiches, chips, macaroni and cheese, nachos, and diet soda; and snacks of chips, cheese puffs, popcorn, juice, and diet or regular soda.

Abnormal findings upon physical examination included a body mass index of 33.5 (height 64 inches; weight 208 lb), blood pressure of 130/86 mmHg, severe acne on face and back, and waist-to-hip ratio (WHR) >1 (waist 45.5 inches; hip 43 inches).

C.K. was given a new diagnosis of pubertal-onset polycystic ovary syndrome (PCOS) and metabolic syndrome, and the possibility of rapid-onset type 2 diabetes was raised. The clinical team prepared a request to obtain her previous medical records and ordered laboratory testing including a complete blood count, chemistry panel, lipid profile, erythrocyte sedimentation rate, total testosterone, sex hormone-binding globulin (SHBG), islet cell antibody 512 (ICA512), glutamic acid decarboxylase (GAD) antibody, C-peptide, and urinalysis.

To obtain better coverage through the night and provide for a consistent basal coverage during the day, C.K.'s long-acting insulin was changed to glargine (Lantus), 100 units at bedtime. This dosage was based on a 20% reduction of her 130-unit total daily dose of lente. However, a starting dose of 100 units of glargine was chosen instead of the 104 units indicated so that she would only need to inject once to deliver the total amount of insulin.

Medical nutrition therapy goals for C.K. were to decrease her caloric intake and reduce the glycemic load at meals by substituting complex and low glycemic–index carbohydrate for the more refined or high glycemic–index carbohydrate that she was used to eating at each meal. Her lispro dosages were significantly reduced to prevent hypoglycemia given the lower calorie level of her new meal plan. In addition, C.K. was asked to keep a food/insulin diary to document what she had eaten and the amount of lispro she had taken at each meal, as well as her pre-meal and 2-hour postprandial blood glucose levels. This would help to determine an appropriate insulin-to-carbohydrate ratio.

At the 2-week follow-up visit, the diabetes team reviewed C.K.'s lab results, which included:

- Fasting blood glucose: 176 mg/dl
- Urinalysis: negative for glucose and ketones
- Creatinine: 0.6 mg/dl
- Blood urea nitrogen: 6 mg/dl
- Aspartate aminotransferase (AST): 32 IU/l
- Alanine aminotransferase (ALT): 54 IU/l
- Lipid panel:
  - √ Cholesterol: 175 mg/dl
  - √ HDL cholesterol: 43 mg/dl
  - √ Cholesterol-to-HDL ratio: 4.14
  - √ LDL cholesterol: 108 mg/dl
  - √ Triglycerides: 121 mg/dl
- Total testosterone: 64 ng/dl (normal range for Tanner IV female: 13–32 ng/dl; mean 22 ng/dl)

- SHBG: 14 nmol/l (normal range for pubertal females 15–123 nmol/l; mean 72 nmol/l)
- Calculated free androgen index 15.5 (formula is: total testosterone ng/dl × 3.467 ÷ SHBG nmol/l) (>5 associated with hyperandrogenism)
- ICA and GAD: negative for autoimmunity
- C-peptide: <0.3 ng/ml

A review of C.K.'s old medical records revealed that she had a history of disproportionate weight gain and that her blood pressure had been increasing at each visit, with the last recorded blood pressure of 140/90 mmHg before her emergency room visit when she was diagnosed with diabetes. The record from her emergency room visit revealed that her blood glucose on that day was 994 mg/dl with a normal bicarbonate level and mild to moderate ketones.

During this follow-up visit, C.K. was asked if there was anything in particular that she remembered as being out of the ordinary during the time period just before her visit to the emergency room 18 months previously. She remembered that someone had brought a lot of canned soft drinks to her home, which led to a soda-drinking contest, which she won. She revealed that she consumed 26 12-oz. cans of regular soda in 15 minutes (an intake of 4,000 calories of sugar). Over the course of the next 7 days, she said she became progressively ill with flu-like symptoms, and because she felt sick to her stomach and did not want to eat food, she continued to drink the extra sodas on a daily basis. When her symptoms, including feeling sick and achy, lacking an appetite, and experiencing increasing weakness, did not improve within 7 days, she was brought to the emergency room for further evaluation.

It was also ascertained from this follow-up visit that C.K. and her brother were known to eat snacks and drink soda continuously throughout the afternoon and evening hours, which had contributed to both of them gaining large amounts of weight over the course of a year. (C.K.'s younger brother also received a physical examination and laboratory workup that revealed morbid obesity, hypertension, dyslipidemia, visceral adiposity, and severe insulin resistance and hyperinsulinemia, determined from an insulin/glucose tolerance test.)

Based on her laboratory results, old medical records, and follow-up interview, C.K. was reassessed as having progressive metabolic syndrome/insulin resistance syndrome; an episode of exogenous-induced glucotoxicity leading to hyperglycemic hyperosmolar nonketotic syndrome (HHNS) 18 months earlier; non-autoimmune diabetes (most likely type 2); severe β-cell dysfunction due to the amount and intensity of insults to the β-cells; and pubertal-onset PCOS.

Because of her severe insulin resistance, an insulin sensitizer was warranted. Laboratory testing had confirmed normal kidney and liver functioning. Extended-release metformin (Glucophage XR), 500 mg with dinner, was initiated to reduce hyperglycemia, to reduce the nocturnal hepatic glucose output evidenced by blood glucose readings higher pre-breakfast than in the evenings, and to have a beneficial effect on the PCOS symptoms. The goal for this was to reduce C.K.'s insulin requirements while improving glycemic control.

Discussion

Much has been written about the epidemic of obesity in relationship to progressive insulin resistance, metabolic syndrome, and increasing risk of type 2 diabetes in children and adolescents.[1–14] Although much of the literature reflects a higher risk for obesity and type 2 diabetes in ethnic populations such as American Indians, African Americans, Hispanics, Asians, and South Pacific Islanders (all of whom are considered genetically predisposed for insulin resistance), the incidence is rising in all population groups.

Sinha et al.[12] recently completed a study investigating the prevalence of impaired glucose tolerance (IGT) in overweight but otherwise healthy multi-ethnic children and adolescents. Their findings were invaluable in helping us realizing the magnitude of the problem.

All 167 of the subjects recruited underwent a 2-hour glucose tolerance test, and blood samples drawn every 30 minutes were analyzed for glucose, insulin, and C-peptide levels. Of 55 children (ages 2–10 years), 25% were found to already have IGT (defined by the American Diabetes Association [ADA] as a fasting blood glucose [FBG] <126 mg/dl but a 2-hour blood glucose of 140–200 mg/dl). Of 122 adolescents (ages 11–18 years), 21% were found to have IGT, and 4% were identified as already having progressed to silent type 2 diabetes (defined by the ADA as a FBG ≥126 mg/dl and/or a 2-hour blood glucose ≥200 mg/dl).

It is especially interesting to note that FBG levels of the subjects with IGT were all within normal range, but their insulin and C-peptide levels were elevated after the glucose challenge. This reinforces the fact that FBG measurement does not always tell the whole story. Often, people can have IGT with completely normal FBG levels.

An FBG >110 mg/dl but <126 mg/dl is diagnostic of impaired fasting glucose, one of the criteria used in diagnosing the metabolic syndrome, which has an etiology of insulin resistance. According to the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,[14] there are five risk factors, of which three must be present to make a diagnosis of metabolic syndrome. These risk factors are:

- Abdominal obesity as measured by a waist circumference >40 inches in men and >35 inches in women
- Triglycerides >150 mg/dl
- HDL cholesterol <40 mg/dl in men and <50 mg/dl in women
- Systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg
- FBG >110 mg/dl

C.K. had all the risk factors except for elevated triglycerides. In addition, she was noted to have another sign of insulin resistance—that of severe acne, a significant symptom of PCOS, prior

to her diagnosis of diabetes. A review of the literature reveals many articles[15–35] that substantiate the role and clinical implications of insulin resistance and hyperinsulinemia in the pathogenesis of PCOS. However, PCOS in adolescents is just beginning to achieve recognition. Apter,[15] Ibanez et al.,[24] and Pasquali et al.[32] are a few of the researchers bringing attention to this often unrecognized problem that can begin in alolescence.

Although a full discussion of the pathophysiology of PCOS with all of its metabolic ramifications is beyond the scope of this article, a brief overview is needed in order to correlate some of C.K.'s laboratory values to the diagnosis of PCOS and its relationship to insulin resistance.

In PCOS, the two main diagnostic criteria are signs of anovulation and hyperandrogenism. Hyperinsulinemia, either from endogenous origin as a compensatory response from the β-cells or from exogenous origin by requiring the administration of large amounts of insulin to overcome the severe state of insulin resistance, affects hormonal balance and the production of binding globulins (proteins) from the liver.

Higher insulin levels can result in a chronically higher LH to FSH ratio, which can prevent the release of the ovum. Without the ovum (which turns into the corpus luteum), there is no production of progesterone during the second half of the menstrual cycle to inhibit the ongoing effects of estrogen. Estrogen's effect is proliferation of the endometrial lining. Intermittent or chronic anovulation will result in amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding, which can present with regular or irregular cycles but is associated with heavy, prolonged, or painful menstruation. Chronic anovulation associated with PCOS is the leading cause of infertility and of endometrial hyperplasia.

The diagnosis of hyperandrogenism can be made either by visual clinical symptoms (acne, hirsutism, visceral adiposity, or male-pattern alopecia or hair loss) or by laboratory testing to evaluate the level of free or active testosterone. Elevated insulin levels can stimulate the ovaries to secrete higher amounts of testosterone while at the same time inhibiting the liver from producing normal amounts of binding proteins (including SHBG).

In females, 95–99% of testosterone is inactive because it is bound to a binding protein that is, for the most part, SHBG. Either a higher level of testosterone or a lower level of SHBG will result in a higher level of free and active testosterone. In the literature, a free androgen index (FAI) of >5 is associated with hyperandrogenism. Many women who are hyperandrogenic have testosterone levels within normal limits but a lowered SHBG, which renders a high FAI. Nestler,[36] in his years of research on PCOS, identified the direct inverse relationship between insulin and SHBG. In our case study, C.K. had both elevated testosterone and low SHBG resulting in a very high FAI of 15.5. She also had the clinical manifestations of severe acne and visceral adiposity (WHR >1).

Apter[15] discussed the development of early-onset hyperandrogenism and PCOS in adolescent girls and explored whether it can be prevented if identified early. Arslanian and Suprasongsin[37] investigated the relationship among insulin sensitivity, lipids, and body composition in children, asking "Is Sydrome X [metabolic syndrome] present?" In our case, the answer is most definitely "yes."

Because PCOS can be considered a subset of the metabolic syndrome, the question we should be asking ourselves is, "How can we prevent or reduce the insulin resistance and compensatory hyperinsulinemia that can be a precursor to PCOS, IGT, and eventually the full spectrum of metabolic syndrome and type 2 diabetes?" The answer can be found in the recently published results of the Diabetes Prevention Program (DPP).[38] After an average follow-up of 2.8 years of the 3,234 participants identified as having IGT but not diabetes, the lifestyle intervention group, which exercised an average of 150 minutes/week and lost an average of 4% of body weight, had a 58% reduction in their risk of progressing to type 2 diabetes. Those in the group taking metformin (an insulin-sensitizing medication), 1,750 mg per day, had a 31% reduction in their risk of progressing to diabetes. Although this study was done in adults, the take-home message of the DPP is that early identification and appropriate interventions can make a difference in one's risk for type 2 diabetes despite the genetic components of the disease or the age of the person.

Case Study Follow-Up

Within 3 days of being started on extended-release metformin, 500 mg in the evening, with glargine, 100 units, C.K.'s FBG, which had been 200–300 mg/dl, was reduced to 88 mg/dl. Glargine doses were then immediately tapered down, whereas metformin was titrated upward in weekly 500-mg increments to a total dosage of 2,000 mg/day.

Within 4 months, through a combination of improved nutrition (including adequate lean protein, reduced saturated and trans fats, adequate polyunsaturated fats, and low glycemic–index carbohydrates), supplementation of vitamins and minerals, and a slight increase in exercise, C.K. only required 35 units of glargine at bedtime to maintain an FBG in the 90–120 mg/dl range. She needed only 2–10 units of lispro (and sometimes none at all) to keep her postprandial blood glucose readings in the 100–140 mg/dl range most of the time. She lost 40 lb in the 4-month period.

Repeat laboratory testing at 4 months revealed (with previous values in parentheses):

- Cholesterol: 152 mg/dl (175 mg/dl)
- HDL cholesterol: 41 mg/dl (43 mg/dl)
- Cholesterol to HDL ratio: 3.8 (4.14)
- Triglycerides: 124 mg/dl (121 mg/dl)
- AST: 12 IU/l (32 IU/l)
- ALT: 26 IU/l (54 IU/l)
- Total testosterone: 23.1 ng/dl (64 ng/dl)
- SHBG: 16.7 nmol/l (14 nmol/l)
- Calculated FAI: 5.0 (15.5)

Most of C.K.'s acne was resolved, and her WHR had decreased. Menstrual cycles had restarted, although she did not keep track of when her period occurred.

Conclusions

Looking back over C.K.'s history, one must conclude that she was what I

call "a metabolic syndrome/type 2 diabetic patient in the making." Her sedentary lifestyle and eating habits that included grazing on large amounts of food high in unhealthy fats and refined carbohydrates fueled her genetic predisposition for insulin resistance and led to disproportionate weight gain.

Her chronic hyperinsulinemia played a role in the hyperandrogenism (acne and visceral adiposity) and the development of dyslipidemia and hypertension and placed a great burden on her pancreatic β-cells. The episode of the 15-minute, 4,000-calorie sugar load was the proverbial straw that broke the camel's back, causing a huge insult to the β-cells and a state of glucose toxicity from which the β-cells could not recover. As a result, she deteriorated into HHNS (with mild ketosis) but not diabetic ketoacidosis. Her severe insulin resistance required large amounts of insulin, causing an exogenously induced hyperinsulinemia, which promoted the hormone imbalance of hyperandrogenism and oligomenorrhea.

The good news is that her problem has now been appropriately identified. Lifestyle changes and insulin-sensitizing medication have greatly reduced her daily requirements for insulin, and her health status has markedly improved.

It may be too late to prevent C.K. from developing diabetes, but it is never too late to institute healthy lifestyle interventions that can slow its progression. Hopefully, others will be able to reduce their risk of developing diabetes because health care professionals recognize the early signs of insulin resistance. We can now better help our patients make choices that will positively affect their health and reduce their risk of the comorbid medical problems associated with obesity, insulin resistance, and hyperinsulinemia.

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