XII. ASSOCIATED DISORDERS

A. Autoimmune Disorders

Patients with type 1 diabetes have a greater incidence of autoimmune disorders including thyroid disorders, celiac disease, adrenal insufficiency, and polyglandular disorders. Thyroid disorders and celiac disease are the most common. It is recommended that close to the time patients are diagnosed with diabetes, thyroid function and thyroid antibody tests are performed as a baseline. Repeat screening annually of thyroid function tests is suggested.

1. Celiac Disease

Screening for the disease should be considered close to the time patients are diagnosed with diabetes, and repeated if clinically indicated. Celiac disease is usually asymptomatic.

- Symptoms:
  - recurring abdominal bloating and pain
  - chronic diarrhea and/or constipation
  - weight loss
  - steatorrhea
  - unexplained anemia
  - flatulence
  - osteopenia/osteoporosis
  - behavior changes/depression
  - muscle cramps
  - fatigue
  - delayed growth
  - failure to thrive in infants
  - bone or joint pain
  - seizures
  - tingling numbness in the legs (from nerve damage)
  - aphthous ulcers
  - dermatitis herpetiformis
  - tooth discoloration or loss of enamel
  - missed menstrual periods (often because of excessive weight loss)
- Laboratory screening:
  - IgA anti-tissue transglutaminase antibody, IgA endomysial antibody and a serum IgA should be obtained (patient must not be on a gluten free diet at the time of the blood draw).
  - Refer for small bowel biopsy if blood tests positive or if high degree of suspicion.
- Diagnosis:
  - Diagnosis must be confirmed by resolving symptoms on a gluten free diet.

2. Other Autoimmune/Endocrine Conditions

In addition to celiac disease, type 1 diabetes is also not infrequently encountered with other autoimmune mediated disorders. The possibility of these comorbidities should be considered in every patient with type 1 diabetes.

2a. Addison's Disease

- Adrenal insufficiency can occur alone or along with other autoimmune endocrinologic disorders including type 1 diabetes.
- Symptoms can include weight loss, fatigue, hyperpigmentation, hypotension, gastrointestinal symptoms (anorexia, nausea and vomiting, and abdominal pain), hypoglycemia and electrolyte abnormalities (hyponatremia and hyperkalemia); onset is often insidious and non-specific.

- Unrecognized adrenal insufficiency could be catastrophic; therefore, patients with type 1 diabetes who also exhibit some or all of the above symptoms should be considered for evaluation of adrenal function.
- Although a significantly abnormal serum cortisol level could be useful, the gold standard for assessment of adrenal function is a stimulation test with an adrenocorticotropic (ACTH) analogue (Cosyntropin) and measuring a serum ACTH level on a blood sample drawn before the Cosyntropin is given.
- Treatment is replacement of steroid deficiencies; those clinicians who are unfamiliar with this should refer to appropriate specialist.

2b. Thyroid Disorders

- Autoimmune thyroid dysfunction can result in either hypothyroidism or hyperthyroidism. It is commonly seen in diabetes, both because of shared underlying autoimmune pathophysiology, and also because there is a high prevalence in the general population.
- Depending on the thyroid abnormality and severity of disease, symptoms can range from vague and nonspecific to very significant and obvious.
- Measurement of serum T4 and TSH should be performed at the time of diagnosis of diabetes and subsequently as necessary in appropriate individuals; further evaluation and/or treatment depends on the underlying abnormality.

2c. Other Autoimmune Disorders

- There are other autoimmune mediated disorders occasionally found with type 1 diabetes either in specific autoimmune polyendocrine syndromes or sporadically.
- These can include not only thyroid disease, adrenal insufficiency, and celiac disease as described above, but also, hypogonadism, hypopituitarism, vitiligo, pernicious anemia, autoimmune hepatitis, hypoparathyroidism, alopecia, myasthenia gravis, and chronic mucocutaneous candidiasis.

B. Other Associated Disorders

Just as autoimmune disorders are found in greater frequency in type 1 diabetes, there are some disorders that are found with greater frequency in patients with type 2 diabetes. Three of these disorders (hemochromatosis, polycystic ovarian syndrome, and depression) are mentioned here.

1. Hemochromatosis

- Hereditary hemochromatosis is the most common autosomal recessive disorder affecting individuals of northern European descent.
- In the general U.S. population its prevalence approaches 1 in 400. Patients with type 2 diabetes have been shown to have higher risk of having hemochromatosis than the general population.
- Hemochromatosis results from inappropriate absorption and deposition of dietary iron that can result in the development of hepatic and nonhepatic end-organ injury, leading to liver cirrhosis, hepatocellular carcinoma, diabetes, pituitary dysfunction, arthritis, skin pigmentation, and cardiac diseases.

Clinical Presentation

- In patients who are symptomatic, the most common presenting features of hemochromatosis are weakness, lethargy, arthralgias, abdominal pain, and impotence; these patients may also have a mild increase in their serum aminotransferase.
- Most patients with hemochromatosis are asymptomatic for many years.
- The frequency of diabetes as an initial presenting symptom has become less common because of more extensive population screening.

Screening

- Consider screening for positive family history or unexplained liver transaminase levels.
- Measure fasting serum transferrin and serum ferritin.
- If saturation is >45%, refer to gastroenterologist for consideration of genetic testing and/or liver biopsy.
- Other family members should be screened if diagnosis of hemochromatosis is established.

Treatment

- Consult a specialist trained in hemochromatosis.

2. Polycystic Ovarian Syndrome (PCOS)

- Polycystic ovarian syndrome is a syndrome of chronic anovulation and hyperandrogenism that affects 5% to 10% of pre-menopausal women; its association with insulin resistance has led to increased recognition of its importance.
- PCOS is the leading hormonally related cause of infertility.
- PCOS is a major risk factor for type 2 diabetes and is one of the factors in the AACE criteria for diagnosis of metabolic syndrome.
- Overall prevalence rates of glucose intolerance and type 2 diabetes have been reported to be as high as 40% in several studies of women with PCOS.

Clinical Presentation

- Women with PCOS often first present with complaints of menstrual irregularities.
- Oligomenorrhea and hirustism are often common early symptoms, but other complaints can also include: infertility, amenorrhea, dysfunctional uterine bleeding, acne, alopecia, and seborrhea.
- Central abdominal obesity is common in women with PCOS, but it does not occur in all patients. Thus, a lack of central abdominal obesity does not rule out PCOS.
- Acanthosis nigricans from insulin resistance is also a common finding, especially in obese PCOS women.
- Family history may also include infertility, menstrual irregularities, early type 2 diabetes, hypertension, and dyslipidemia.

Diagnosis

- The diagnostic criteria for PCOS are hyperandrogenism and chronic anovulation in pre-menopausal women in the absence of other endocrinologic etiologies.
- Although most women with PCOS will have polycystic ovaries on ultrasound, this finding is neither specific nor required to make the diagnosis; ultrasound is not recommended in a diagnostic work up unless there are other specific reasons to do so.
- The initial screening recommended in women with chronic anovulation and hyperandrogenism includes: b-HCG to rule out pregnancy, and then a 0700-0900 hr serum prolactin, TSH, total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone (17-OHP).
- Abnormal prolactin or TSH requires disease-specific evaluation.
- Moderately elevated total and free testosterone and/or dehydroepiandrosterone sulfate (DHEAS) suggests PCOS.
- Very significantly elevated testosterone (>150 ng/dl) and/or DHEAS (>700 ug/dl) means that ovarian or adrenal neoplasms must be ruled out.
- Elevated 17-OHP (>300 ng/dl) suggests possibility of congenital adrenal hyperplasia-non-classic adrenal 21-hydroxylase deficiency and in this case a referral to an endocrinologic specialist should be considered.
- An elevated leutenizing hormone/follicle stimulating hormone ratio can suggest PCOS, but because of the pulsate secretion of leutenizing hormone, single measurements are insensitive.
- Approximately half of the siblings of women with PCOS also have the condition, even without clinical symptoms; therefore, diagnostic testing of these at risk individuals should be considered.

Therapy for PCOS

- Lifestyle modification including caloric restriction and increased physical activity should be considered the first-line therapy. As little as 7-10% weight loss has been associated with return of regular ovulatory cycles and improvement of insulin sensitivity.
- Because of the association with insulin resistance and metabolic syndrome, all women who have been diagnosed with PCOS should be screened for dyslipidemia, hypertension, and impaired glucose tolerance/type 2 diabetes.
- Because fasting BG* has been reported to fail to detect type 2 diabetes in up to 50% of PCOS patients who are later confirmed to have diabetes by OGTT, it is recommended that a 75 gm OGTT be considered in women with PCOS in which impaired glucose tolerance/type 2 diabetes is suspected.
- There are several pharmacologic options available, each directed at the different physiologic abnormalities that occur in PCOS.
  - **Metformin:** Metformin has been used with some success in women with PCOS. It has been found to reduce serum insulin levels and decrease androgen levels. There are more studies available regarding the use of metformin in PCOS than the currently available thiazolidinediones because this product has been available for a longer period of time.
  - **Thiazolidinediones (TZDs):** Most of the studies available for this group are with Troglitazone, a product no longer available. Some clinicians prefer TZDs over metformin because of their potent insulin sensitizing effects as well as successful clinical experience. However, the results of ongoing research with the two newer TZDs (Rosiglitazone and Pioglitazone) in PCOS are still pending.
  - **Oral contraceptives:** Menstrual problems include some of the symptoms that are often most concerning for women with PCOS. Appropriate use of oral contraceptives can be one tool to help restore cyclic menstrual bleeding.
  - **Spironalactone:** This drug has been used for its antiandrogenic properties that can lessen the symptoms of hyperandrogenism. It is not without side effects, however.
- Referral to a specialist with experience in PCOS may be considered for any PCOS patients in which the diagnosis or management is unclear or in those experiencing difficulty with infertility or other issues.

3. Depression

Definition

Depression has been shown to increase morbidity and mortality of many health conditions including diabetes. Multiple studies conclude that diabetes doubles the chance of depression. One study concluded that diabetes causes multiple psychosocial problems and that these issues are barriers to achieving adequate glycemic control and interfere with self-management behaviors. Many studies suggest our current health care systems are poorly equipped to handle and support chronic illness care. Effective treatment of depression can improve clinical outcomes and quality of life.

General Recommendations

Preliminary assessment of psychological and social status should be included as part of the medical management of diabetes. Psychosocial screening should include assessing attitudes about illness, expectations for medical management and outcomes, affect/mood, general and diabetes-related quality of life, resources (financial, social and emotional), and psychiatric history. Screening for psychosocial problems such as depression is needed especially when adherence to treatment regimen is poor.

Screening

Self-reported symptoms and/or scales such as the Beck Depression Inventory or the Center for Epidemiologic Studies-Depression Scale can be used to screen for depression.

** BG throughout these Recommendations means plasma or serum glucose. For a discussion on the ways of measuring glucose in the blood and their differences, see the Appendix, page 93.*

Symptoms of Depression:

- Persistent sad, anxious, or "empty" mood
- Feelings of hopelessness, pessimism
- Feelings of guilt, worthlessness, helplessness
- Loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex
- Decreased energy, fatigue, being "slowed down"
- Difficulty concentrating, remembering, making decisions
- Insomnia, early-morning awakening, or oversleeping
- Appetite and/or weight changes
- Thoughts of death or suicide, or suicide attempt
- Restlessness, irritability

If five or more of these symptoms are present every day for at least two weeks and interfere with routine daily activities such as work, self-care, and childcare or social life, seek evaluation and treatment for depression.

Treatments

Psychotherapy and/or pharmacotherapy may be required for patients diagnosed with depression. The following resources are listed to obtain further information on depression and treatments:
http://health.nih.gov/result.asp/183
http://www.psych.org/psych_pract/
http://www.fpnotebook.com/PSYCh5.htm

Metabolic Syndrome

Metabolic syndrome is a common associated disorder of diabetes. For information on the metabolic syndrome, refer to page 57.

REFERENCE SECTION XII

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