Endocrine problems in adolescence

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Abstract

Objective: to present and discuss clinical aspects concerning the most frequent endocrine diseases in adolescents and their effects on physical and psychoaffective fields in affected patients.

Methods: review of national and international literature combined with the authors’ own experience with the aim of proposing some guidelines for the management of endocrine diseases in adolescents.

Results: the physical and psychological impacts of these diseases on adolescents’ health may have different intensity. Diabetes mellitus as a chronic, self-limiting disease, with increased risk of late complications, is analyzed in more detail. Thyroid diseases and gynecomastia usually have a milder evolution, but may cause suffering and low self-esteem.

Conclusions: the repercussion of these diseases, especially diabetes mellitus and gynecomastia, on the sexuality of adolescents should be taken into consideration.

Introduction

Adolescence - a fabulous phase of hormonal effervescence, great changes and discoveries, some definitions and small fears - cannot be dissociated from the endocrine problems that surround it. Dealing with adolescents is neither easy nor difficult, it is just special. Just imagine how delicate this process becomes when dysfunctions responsible for making adolescents feel different and mismatched add up to the scenario.

The endocrine diseases discussed here are those most frequently observed in this age group, except for obesity, which is not going to be discussed in this chapter. All of these diseases, with distinct intensity, have an influence over the body and mind. The focus given here is essentially clinical, including a technical approach to physiopathology, diagnosis, and treatment, with no intention to discuss the psychological aspects that correlate with these diseases.

Although our aim is to offer health care providers theoretical and practical information, we find it is appropriate to make some considerations about our contact with adolescents.
Diabetes and its chronic nature ends up forcing patients and family members into learning how to deal with some stigmas: the fear of impotence, risk pregnancy, mutilations, and everyday life restrictions; thyroid dysfunctions and the fear of bulgy eyes, of thick neck, of ugly scars. Gynecomastia and the fear of being less of a man, of taking off one’s shirt in public. All these conditions may compromise adolescents’ self-esteem and influence their sexuality. This is certainly the most delicate and most difficult part of our job, which surely deserves a special chapter.

Diabetes mellitus in adolescents

Diabetes mellitus (DM) is a group of metabolic diseases that result from the total or relative deficiency of insulin. It is characterized by chronic hyperglycemia and alterations in the metabolism of carbohydrates, lipids, and proteins, associated with long-term failure of multiple organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

Classification

The current classification of diabetes mellitus is shown in Table 1. The most frequent forms of DM observed in adolescents are: DM type 1, DM type 2, atypical DM, and MODY.

<table>
<thead>
<tr>
<th>Type 1</th>
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<tbody>
<tr>
<td>– Autoimmune</td>
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<tr>
<td>– Idiopathic</td>
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<table>
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<tr>
<th>Type 2</th>
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<tr>
<td>Other specific types</td>
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<tr>
<td>– Genetic defects of beta-cell function</td>
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<tr>
<td>Chromosome 12 (MODY 3)</td>
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<tr>
<td>Chromosome 7 (MODY 2)</td>
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<td>Chromosome 20 (MODY 1)</td>
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<tr>
<td>Mitochondrial DNA (atypical DM)</td>
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<tr>
<td>Others</td>
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<tr>
<td>– Genetic defects in insulin action</td>
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<tr>
<td>– Diseases of the exocrine pancreas</td>
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<tr>
<td>– Endocrinopathies</td>
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<td>– Drug or chemical- induced</td>
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<td>– Infections</td>
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<tr>
<td>– Uncommon forms of immune-mediated diabetes</td>
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<tr>
<td>– Other genetic syndromes sometimes associated with diabetes</td>
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Table 1 - Classification of diabetes mellitus

DM type 1 (DM 1) results primarily from the destruction of pancreatic beta cells, causing total depletion of insulin and consequent tendency towards ketoacidosis. Autoimmune DM 1 is characterized by the presence of markers, such as auto-antibodies, islet cell antibodies (ICA), insulin autoantibodies (IAA), anti glutamic acid decarboxylase (anti-GAD), and antityrosine phosphatases IA-2 and IA-2b. Usually one or more antibodies are present in 85-90% of individuals when fasting hyperglycemia is initially detected. This type of diabetes is well-associated with the HLA system and is rarely found in Asians. In idiopathic DM 1, which more frequently affects individuals of African or Asian origin, the etiology is still unclear, and patients show no evidence of autoimmunity. This type of diabetes is strongly hereditary and is not associated with HLA.

DM 2 results from different levels of resistance to insulin and from the relative deficiency of insulin secretion. Most patients are overweight, and ketoacidosis occurs only in special situations. There is no autoimmune destruction of pancreatic beta cells. Recent studies have shown that the incidence and prevalence of DM 2 in children and adolescents are rising worldwide. Obesity, family history, female sex, and puberty seem to be additional factors to the development of DM in adolescents.

Atypical DM and MODY diabetes are rare and affect specific ethnic and racial subgroups.

Etiopathogenesis

Diabetes mellitus Type 1

DM 1 is a genetically-based disease with characteristic HLA, and susceptibility marker, which depends on a trigger (environmental), still undisclosed, to occur. There is evidence that cell damage mechanisms are related to an autoimmune pathogeny.

Genetic susceptibility: the risk of DM 1 is partially determined genetically, since the concordance rate for monozygous twins is approximately 35-50%. Genetic predisposition to diabetes is mainly determined by histocompatibility complex class II alleles. Susceptibility alleles are DQB1*0201 and DQB1*0302. The DQB1*0602 allele has a dominant protective effect. The role of alleles (DR3 and DR4) in the DR regions is questionable; they probably contribute independently to susceptibility. The presence of these alleles is necessary, but not enough for the development of the disease.

Triggering factors: several environmental factors have been investigated in terms of DM 1 pathogenesis; however, their role is not yet very clear. Viruses are believed to trigger the disease in susceptible individuals. The rubella virus is the only one that has a close association with DM 1 in humans. In congenital rubella, more than 30% of HLA DR3 and/or DR4 individuals develop DM 1. The role of early exposure to cow’s milk as a triggering factor for DM 1 is not totally clarified yet.
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Auto-antibodies: whatever the triggering factors, the evolution of DM 1 is always the same: autoimmune destruction of pancreatic cells, characterized by the presence of several immunological abnormalities, among which we have the development of autoantibodies against different pancreatic cell components. The most widely studied autoantibodies include islet cell antibodies (ICA), insulin autoantibodies (IAA) anti glutamic acid decarboxylase (anti-GAD), and IA2 antibodies, recently identified as tyrosine phosphatase.

Diabetes mellitus Type 2

The etiopathogenesis of DM 2 in adolescents and adults is related to the resistance to insulin, relative insulinopenia, and subsequent hyperglycemia. Most risk factors for DM in adolescents, including race, puberty, female sex, and obesity, predispose the condition since they are associated with insulin resistance. The increased incidence of DM 2 seems to be specially related to the higher frequency of obesity among children and adolescents, combined with reduced physical activity and increased calorie intake. Other obesity-related comorbidities such as acanthosis nigricans, polycystic ovary syndrome, hyperlipidemia, and high blood pressure are observed in adolescents with DM 2.2,3

Special attention has been paid to the fact that low weight during intrauterine life and during the first years of life is more frequent among adolescents with DM 2, which may enhance the risk of this condition in adulthood.6

Diagnosis

Diagnostic tests include serum glycemia after 8-12 hour fasting and glucose tolerance test (GTT). The GTT is performed after oral administration of 75g glucose (in children, 1.75 g/kg up to a maximum of 75g), with serum glucose measurements at 0 and 120 minutes after intake. The diagnosis of DM is made in the following situations, detected more than once1:

- fasting glycemia greater than or equal to 126mg/dl;
- glycemia on GTT two hours after glucose overload greater than or equal to 200mg/dl; or
- occasional glycemia greater than or equal to 200mg/dl, associated with classic DM symptoms, such as polyuria, polydipsia, and unexplained weight loss.

There are intermediate stages between normal glycemia and diabetes mellitus, which are denoted as altered fasting glycemia, and reduced glucose tolerance, defined as1:

- altered fasting glycemia: fasting glycemia greater than or equal to 110mg/dl and < 126mg/dl;
- reduced glucose tolerance: glycemia on GTT, two hours after glucose overload greater than or equal to 140mg/dl and < 200mg/dl.

Clinical status

Patients with DM 1 normally present with classic symptoms: polyuria, polydipsia, polyphagia, asthenia, and weight loss. In later diagnosed cases, there may be diabetic ketoacidosis (DKA), which is characterized by the exacerbation of previously described symptoms combined with dehydration, ketogenic breath, abdominal pain, vomiting, and acidosis, with Kussmaul’s sign. DKA is a serious condition that can evolve favorably when promptly recognized and properly treated; however, it usually requires hospitalization, if possible, at an ICU. Some patients present an apparent remission after the diagnosis of DM 1. During this period, known as “the honeymoon period” and which may last for weeks, insulin treatment is not necessary.

In general, adolescents with DM 2 are obese, have acanthosis nigricans, family history of DM 2, hyperglycemia, and glycosuria detected during routine procedures. Some adolescents present mild polyuria and polydipsia, while female adolescents may have vaginal candidiasis or lower urinary tract infection. About one third of adolescents with DM 2 have ketonuria at diagnosis. The disease may initially manifest itself as hyperosmolar nonketotic coma. In rare cases, DKA occurs as first manifestation and is usually associated with intercurrent diseases or infections. Although some patients may initially require insulin treatment due to ketoacidosis, most can be treated with a combination of diet, exercise, and oral hypoglycemic drugs.2,3

Chronic complications of DM may appear some years after diagnosis, leading to characteristic signs and symptoms. In DM 1, the major complications include retinopathy and diabetic nephropathy, followed by autonomic and peripheral neuropathies.

Treatment

The treatment of diabetes in adolescence aims at: a) offering individuals a normal life, trying to eliminate emotional disorders; b) maintaining growth and development, according to genetic potential and the environment; c) avoiding acute complications; d) preventing or delaying the development of chronic complications. To reach these objectives, it is essential to keep metabolic control as close to normal as possible, through a therapeutic scheme that preserves patients’ quality of life.4

Education and psychosocial support: this is one of the major aspects to be considered. Basic information on DM, insulin administration, self-monitoring, procedures in the event of risk situations (hypoglycemia, hyperglycemia) should be provided.

Education is not only information, but the adoption of new approaches. This requires the participation of a multidisciplinary team (physicians, nurses, nutritionists, psychologists), and should include patients, family, teachers, physical education teachers, friends, and partners.4
Accepting a chronic disease is a long process of maturation. Several kinds of psychological reactions have been reported, such as initial shock, denial, revolt, bargaining, sadness, and acceptance. It is important that health care providers recognize the phase patients are going through in order to adapt their attitudes and approaches in terms of treatment.7

The educational approach must alternate between individual and group modalities (classes, summer camps, etc). However, health care providers must be careful with the use of some specific technical words that are not mastered by patients and their families. The best educational approach consists in using problem-solving situations.

Dietary plan8: the main objective is to help adolescents change their eating habits, thus favoring metabolic control.

A dietary plan should: a) target on metabolic control (glucose and lipids) and on the prevention of complications; b) be nutritionally adequate, offering a total calorie value that is compatible with (TCV) the gain and/or maintenance of weight-height development (restrictive diets are nutritionally inadequate and have poor adherence); c) be personalized, meeting specific requirements such as age, sex, metabolic status, physical activity, intercurrent diseases, and economic status.

During nutritional assessment, the body mass index (BMI) should be interpreted, taking into consideration age and the stage of sexual maturity.

According to the National Research Council (1989), the TCV observed in the diet of most adolescents aged 11-14 years is 55 kcal/kg/day for males and 47 kcal/kg/day for females; for adolescents aged 15-18 years, it is 45 kcal/kg/day for males, and 40 kcal/kg/day for females. Carbohydrates should represent 50 to 60% of TCV, while fats should account for 30% (1/3 saturated, 1/3 monounsaturated, 1/3 polyunsaturated), and proteins should represent about 15%. The diet should be rich in fibers, vitamins, and minerals.8,9 It is important that adolescents have three basic meals, two snacks, and supper, according to the type and time of physical activity in order to prevent possible hypoglycemia. Supper protects adolescents from hypoglycemia during the night while they are asleep.

Diet foods are indicated, but their calorie and nutrient contents should be considered. Soft drinks and diet Jell-O have a calorie value that is close to zero. Artificial sweeteners may be used, considering their calorie contents. Aspartame, cyclamate, saccharin, acesulfame potassium and sucralose are practically calorie-free. Fructose, however, has the same calorie contents of sugar. The World Health Organization recommends the use of artificial sweeteners within safe limits, either in terms of quantity or in terms of quality, alternating among different kinds, if possible.9

Physical activity: physical exercise offers diabetic patients several immediate and long-term benefits: a) increased glucose uptake by muscles; b) enhanced insulin action; c) reduction of glycemia; d) increased cellular sensitivity to insulin; e) improvement of cardiorespiratory function; f) reduction of body fat; g) well-being sensation.

Hypoglycemia may occur during physical activity, immediately after it or even hours later. It is recommendable that such activities be properly programmed in order to avoid the times of peak action of insulin or oral agents; if necessary, medication dosage have to be adjusted.4 To prevent hypoglycemia, diabetic patients should eat a carbohydrate-rich snack before the exercises.8

The frequency of physical activity should be at least three alternate days a week, but practicing exercises every day is desirable. In order to achieve the desired objectives, at least 20 minutes of aerobic exercises are required. Exercises lasting less than 15 minutes contribute very little to the reduction of glucose levels and to fat loss. Physical activity is contraindicated for patients with uncompensated DM and/or ketosis.

Insulin treatment: recommended for all patients with DM 1, in the presence of diabetic ketoacidosis and for patients with DM 2, with elevated glucose levels, despite the implementation of exercises, diet, and oral hypoglycemic drugs. In DM 2, insulin may be combined with oral hypoglycemic drugs. In cases of DM 1, insulin treatment should be implemented as early as possible in order to maintain the residual function of the pancreatic beta cell.

Insulin may be classified according to its origin or action time (Table 2). In origin, it may be animal (porcine or bovine) or human. Human insulin is preferred since it is less immunogenic. According to action time, insulin may be ultralente, intermediate (NPH and lente), rapid, and ultrarapid. The latter is an insulin analog developed by genetic engineering through the inversion of proline and lysine in positions 28 and 29 in the beta chain, and is associated with reduced incidence of severe hypoglycemia when compared to regular insulin.10 In addition, there is a mixed insulin regime that contains intermediate-acting and rapid-acting insulin in different proportion (90/10, 80/20 and 70/30). All available insulin are at the concentration of U-100 (100U/ml).

The initial insulin dose is 0.3 to 0.5U/kg/day, with a gradual increase until glucose levels are controlled. In adolescents, the required dose may reach 1.5 to 1.8U/kg/day. Infections, stressful situations, and surgeries may require larger doses and correction with regular insulin.4 Insulin treatment may start with the daily administration of intermediate-acting insulin; however, patients should be informed that the dose may be later divided.

Several treatment schemes may be used: a) only two daily doses of intermediate-acting insulin, with 2/3 of the total dose before breakfast and 1/3 before dinner or supper; b) two daily doses of mixed insulin; c) one or two daily doses of intermediate-acting insulin, associated with peaks
of rapid-acting or ultrarapid insulin before meals, according to the results of self-monitored capillary blood glucose. The last scheme is considered ideal, but requires (self-monitored capillary blood glucose 3 or 4 times a day), which is not attainable in our environment due to its high cost.

The Diabetes Control and Complications Trial (DCCT) revealed that the risk of development or progression of chronic complications of DM 1 was reduced by 50-70% with better metabolic control. This may be accomplished through intensive insulin treatment regimens (3 or more daily injections of insulin), when compared to conventional schemes. This objective is usually achieved by using long-acting or intermediate-acting insulin, combined with rapid or ultrarapid insulin. Nevertheless, glucose level control may be particularly difficult in adolescence, and attempts to intensify insulin therapy may increase the risk of hypoglycemia and cause some weight gain. Juul et al. suggest that the increase of GH secretion in adolescents with DM 1 is not followed by proportional increase in IGF-1. The feedback of IGF-1 on GH is compromised, causing hypersecretion of GH, with consequent increase of insulin resistance, thus hindering the control of DM 1.

Hypoglycemia is one of the complications presented by the treatment of diabetic patients, especially those who use insulin. If hypoglycemia occurs and the patient is conscious, he/she must take 10 to 20g of rapid absorption carbohydrate (e.g.: half a glass of regular soft drink or orange juice), and repeat the dose if necessary. If the patient is unconscious, he/she must receive an immediate glucagon injection (1mg, IM or SC) and be referred to emergency room for the IV administration of 20ml glucose at 50%.

New insulin preparations and transplants offer perspectives to diabetic patients:

- **Insulin pump**: continuous subcutaneous infusion of insulin is an alternative for patients who cannot control their glucose levels with two or three injections a day; this way, there is more flexibility in adapting insulin therapy to variations in diet and exercise regimens. Disadvantages include: elevated cost, risk of infection at infusion site and susceptibility to ketoacidosis, due to interrupted insulin flow.

- **Insulin glargine**: an insulin analog with prolonged and constant action (24 hours), without peaks of action. This type of insulin will be available in Brazil by the first half of 2002.

- **Inhaled insulin**: the administration is made through a device that releases powdered insulin orally, with later inhalation and pulmonary absorption. This type of insulin should be available in the market within two or three years.

- **Pancreas transplantation**: transplanted pancreas is able to secrete insulin right after its revascularization, producing total independence of exogenous insulin. However, the procedure may cause a series of clinical and surgical complications, requiring intensive and continuous immunosuppressive therapy in order to avoid rejection. The American Diabetes Association recommends pancreas transplantation for patients with DM 1 and imminent kidney disease, who have already undergone or are planning to undergo kidney transplantation, without excessive risk for the procedure. If kidney transplantation is not indicated, pancreas transplantation should be considered isolatedly for patients who have a history of frequent, acute or severe metabolic complications and clinical or emotional problems with insulin therapy, which are severe and at the same time incapacitating.

- **Islet transplantation**: although there are some advantages in relation to pancreas transplantation, islet transplantation has not been satisfactory. The latest data from the International Islet Transplant Registry (ITR) show that 629 transplants were carried out until 1998, of which 407 were allotransplants (355 diabetic patients) and 222 were autotransplants (patients with chronic pancreatitis submitted to total pancreatectomy). In diabetic patients, insulin independence was attained in only 12% and 8% of the cases, after seven days and one year, respectively. Several causes have been considered: a) transplant and/or survival of insufficient islet mass; b) toxic effect of immunosuppressants; c) islet rejection; d) allogeneic transplanted islets in diabetic patients may be the target of autoimmune response against pre-existing beta cells.

Recently, Shapiro et al. reported the results of seven transplanted diabetic patients type 1. After a one-year follow-up, all patients were insulin independent. The protocol used reveals the implant of a large number of islets.

### Table 2 - Average action profile of human and animal insulins

<table>
<thead>
<tr>
<th>Action profile (hours)</th>
<th>Onset action</th>
<th>Peak action</th>
<th>Effective duration</th>
<th>Maximum duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human insulins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultra-rapid (UR)</td>
<td>&lt;0.25</td>
<td>0.5-1.5</td>
<td>3-4</td>
<td>4-6</td>
</tr>
<tr>
<td>Rapid</td>
<td>0.5-1.0</td>
<td>2-3</td>
<td>3-6</td>
<td>6-8</td>
</tr>
<tr>
<td>NPH (N)</td>
<td>2-4</td>
<td>6-10</td>
<td>10-16</td>
<td>14-18</td>
</tr>
<tr>
<td>Lente (L)</td>
<td>2-4</td>
<td>6-12</td>
<td>12-18</td>
<td>16-20</td>
</tr>
<tr>
<td>Ultralente (U)</td>
<td>6-10</td>
<td>10-16</td>
<td>18-20</td>
<td>20-24</td>
</tr>
<tr>
<td><strong>Animal insulins</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rapid</td>
<td>0.5-2.0</td>
<td>3-4</td>
<td>4-6</td>
<td>6-10</td>
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<tr>
<td>NPH (N)</td>
<td>4-6</td>
<td>8-14</td>
<td>16-20</td>
<td>20-24</td>
</tr>
<tr>
<td>Lente (L)</td>
<td>4-6</td>
<td>8-14</td>
<td>16-20</td>
<td>20-24</td>
</tr>
<tr>
<td>Ultralente (U)</td>
<td>8-14</td>
<td>minimum</td>
<td>24-36</td>
<td>24-36</td>
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</table>
(12,000 islets/patient), obtained from two to three consecutive donators; also, glucocorticoid-free immunosuppressive treatment and percutaneous transhepatic portal vein embolization were used right after the isolation of islets.

- **Oral hypoglycemic drugs**[^3][^9]: recommended for adolescents who have diabetes mellitus type 2, which is not compensated for by exercise and diet. The safety and efficacy of oral hypoglycemic drug therapy have not been established yet. Oral hypoglycemic drugs are contraindicated during gestation and breast-feeding. Next, you find some of these drugs and their major characteristics:

  - **Metformin**: drug of choice that reduces the production of glucose by the liver and increases sensitivity to insulin in peripheral tissues. The most frequent adverse effects are abdominal discomfort and diarrhea. Metformin is contraindicated for patients with renal insufficiency, congestive heart failure and chronic liver disease. Since most adolescent patients with DM 2 are above their normal weight, the same dose used for adults is recommended (500-2,550mg/day).

  - **Sulfonylurea**: stimulates the secretion of insulin and consists of several compounds: chlorpropamide, glibenclamide, glipizide, gliclazide and glimepiride. Sulfonylurea may be used in combination with metformin when metformin does not control glucose levels. Whenever possible, glimepiride should be preferred, since it is a third-generation sulfonylurea and offers less risk of hypoglycemia than the others.

Other oral agents for the control of DM 2 in adults (acarbose, repaglinide, nateglinide, rosiglitazone and pioglitazone) have been used less frequently in adolescents.

**Treatment targets**[^9][^17]:

- preprandial serum glucose: ideal - 80 to 120mg/dl; acceptable - up to 150mg/dl;
- serum glucose 2 hrs postprandial: ideal - less than or equal to 140 to 160mg/dl; acceptable - up to 200mg/dl;
- glycosylated hemoglobin (HbA1c): up to 10% above the upper limit;
- **BMI**: normal for age group and pubertal stage;
- total cholesterol: ideal <170mg/dl; acceptable- 170 to 199mg/dl;
- LDL-cholesterol: ideal < 100mg/dl; acceptable - 101 to 129mg/dl;
- HDL-cholesterol: greater than or equal to 35mg/dl;
- triglycerides: less than or equal to 130mg/dl.

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**Follow-up guide for diabetic adolescents**

**First medical appointment**: anamnesis and physical examination must be comprehensive, focusing on the onset of diabetes, infectious diseases, and previous autoimmune conditions, psychomotor and weight-height development, and family history of diabetes.

**Additional exams required in the first medical appointment**: hemogram, glucose level (fasting and postprandial), HbA1c, lipid contents, creatinine, thyroid function (TSH, free T4 and anti-TPO), immunological markers of the disease (ICA, anti-GAD, antityrosine phosphatase), urinalysis.

**Frequency of medical appointments**: in the therapeutic adjustment phase, patients need to be assessed at shorter intervals (weekly or fortnightly). When treatment objectives are reached, assessments may be made every three months.

**Additional exams for follow-up**:

- quarterly: fasting and postprandial glycemia, HbA1c;
- yearly: same exams required in the first medical appointment, except immunological markers of diabetes. After the fifth year, microalbuminuria and fundoscopy should be required.

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**Thyroid diseases in adolescents**

The most frequent clinical manifestation of thyroid disease in adolescents is the enlargement of the thyroid gland (goiter).[^18] The size and weight of a normal thyroid gland depend on iodine intake and are positively correlated with the individual’s age, weight, and height. The World health organization (WHO) classifies goiters in: 0) no palpable or visible goiter; Ia) palpable goiter, not visible with head tilted back; Ib) palpable goiter, visible with neck in normal position; II) palpable goiter, visible with neck in normal position; III) goiter visible in the distance.

**Endemic goiter**

Endemic goiter is when the enlargement of the thyroid gland is detected in more than 10% of a given population; in this case, the most common cause is iodine deficiency. A priori, endemic goiter was eradicated in Brazil, although the quality of our iodized salt is questionable. The RDA for iodine in children is 50µg/day while in adolescents it is 150µg/day. Iodine deficiency may be detected by 24-hour iodinuria, since iodine excretion is equivalent to its intake. The thyroid gland has mechanisms for adapting itself to iodine deficiency: increased depuration, preferred T3 secretion, increased peripheral conversion of T4 into T3, TSH elevation, which leads to goiter formation if iodine deficiency is not corrected.
**Goiter induced by certain drugs or by varied agents**

Some substances may trigger goiter formation. Foods that produce thiocyanate (cassava), perchlorate, lithium, and vegetables such as kale inhibit iodine uptake. Salicylates, phenylbutazone, and turnip block intrathyroidal organization of iodine. Amiodarone mechanism of action is curious: in iodine-depleted zones, it may cause hyperthyroidism, while in regions with normal iodination, it causes hypothyroidism. Other goiter-forming substances currently used include expectorants and iodized contrasts.

**Simple or idiopathic goiter**

This kind of goiter is more common in females (9:1) and together with chronic lymphocytic thyroiditis, it is the most frequent cause of goiter formation in young people, especially during puberty. Thyroid function is normal, and the antibodies are negative. The goiter is small, homogenous, symmetric, painless, and smooth. Ultrasonography shows diffuse goiter without inflammatory activity. Resolution is usually spontaneous. In some cases, thyroid hormone may be used for one or two years.

**Dyshormonogenesis**

Represents 10-15% of cases of congenital hypothyroidism, rarely occurring in adolescence. This type of condition results from a defect in thyroglobulin synthesis or iodination caused by an alteration in the thyroid peroxidase. The diagnosis is obtained by the perchlorate test, and competitive anion, which prevents iodine organification. Positive test results are highly suggestive of dyshormonogenesis, but are not pathognomonic, since similar results are observed in thyroiditis.

**Hormonal resistance**

Rare case of goiter that results from gene B mutations in T3 receptor. Hormonal resistance may be generalized or hypophyseal. In generalized hormonal resistance, the most common clinical finding is euthyroid goiter; in this case, the great phenotype variability depends on the intensity of the negative effect that the mutant receptor has on the normal receptor; therefore, the level of resistance varies from one tissue to another. Hormonal resistance normally occurs when T3, T4 and TSH levels are elevated. The major differential diagnosis is TSH-producing hypophyseal adenoma. Treatment with triiodothyroacetic acid (T3 analog) has been proposed, but it is usually inefficient. The form of hypophyseal resistance is selective, and occurs in the presence of elevated TSH levels, goiter, and clinical hyperthyroidism.

**Chronic lymphocytic thyroiditis (Hashimoto thyroiditis)**

This autoimmune type of thyroiditis is the most frequent cause of goiter among adolescents in nonendemic areas. The coexistence of chronic thyroiditis and Graves’ disease in a single patient suggests a common etiology. Chronic lymphocytic thyroiditis (CLT) or Hashimoto thyroiditis is associated with DR3, B8, DR5 and DQB1 alleles of the HLA system, and is characterized by the presence of thyroid autoantibodies. Anti-thyroid peroxidase (anti-TPO) antibodies, produced against iodine oxidation, are harmful to the gland. The detection of antithyroglobulin antibodies is also frequent, without alterations in the thyroid function and in anti-TSH receptor antibodies, especially in atrophic forms.

CLT has a family characteristic, predominates in females, and is associated with other autoimmune diseases (diabetes type 1 and vitiligo), also sharing an association with Down and Turner syndromes.

Goiter is the most frequent clinical finding (present in 85% of the cases), usually identified by a family member or by a physician during routine examination. Typical goiter is moderately sized, with irregular or micronodular surface, painless, although neck discomfort is not rare. Most times, patients have euthyroidism (80%), but hypothyroidism (5-15%) and hyperthyroidism (5%) may occur.

Initial investigation consists of TSH, T4, T3 analysis and assessment of anti-thyroid antibodies. When there is clinical suspicion of nodules, scintigraphy must be required. Ultrasonography may suggest but never confirm the diagnosis of CLT. The definitive diagnosis, revealing the presence of lymphocyte inflammatory infiltrate and follicular hyperplasia, is performed by fine-needle aspiration biopsy (FNAB), which is routinely indicated in cases of nodular pathology. 85% of the cases of lymphocytic thyroiditis, confirmed by FNAB, have positive anti-thyroid antibodies.

Autoimmune thyroiditis may be transient, and spontaneous resolution may occur. In general, the treatment consists in observing the clinical evolution, since most cases concur with euthyroidism. However, the use of thyroid hormone (1-5 μg/kg/day) for two years, followed by reassessment, may be proposed. Patients with hypothyroidism or hyperthyroidism require specific treatment.

**Subacute and acute thyroiditis**

Subacute thyroiditis is a rare, self-limited condition in adolescents, usually associated with viral infections. The typical clinical symptoms are: diffuse goiter, painful, initially occurring with clinical and laboratory signs of hyperthyroidism (caused by the rupture of thyroid follicles), followed by euthyroidism or mild and transient hypothyroidism. Iodine uptake is too low or absent, strongly suggesting the diagnosis. The treatment sometimes requires...
the use of corticosteroids. The thyroid gland totally retrieves its function within two to nine months. Acute thyroiditis, also rare in adolescents, is a bacterial infection that concurs with local pain, dysphagia, fever, and regional lymphadenopathy. There might be abscess formation. The use of antibiotics is unavoidable.

Graves’ disease and hyperthyroidism

Only 5% of the cases of hyperthyroidism occur before the age of sixteen. The autoimmune etiology is highly frequent (95%), either in terms of Graves disease or, very rarely, in terms of Hashimoto thyroiditis (hashitoxicosis). Both situations are more prevalent among females (10:1). Usually, there is family history of thyropathies or other autoimmune diseases. From a genetic standpoint, it is related to B8 and DR3 alleles of the HLA system, but the concordance rate between homozygous twins (30-60%) indicates that environmental factors are involved. In the humoral aspect, TSH receptor antibodies (TRAb) induce the thyroid gland into working autonomously and independently from hypophyseal control. Other causes of hyperthyroidism in adolescents that are not so common include autonomous nodular pathology and the use of weight loss medication.

The most common signs and symptoms are attention deficit, sleeplessness, weight loss, emotional lability and tachycardia. Tachycardia is often the revealing sign. Pretibial edema is uncommon in this age group in opposition to exophthalmia (50%), which usually reduces with treatment. The presence of goiter, although moderately sized, occurs in 99% of the cases. In adolescents, the clinical manifestations of thyrotoxicosis are usually less severe than in children.

Lab-based diagnosis is made by the analysis of reduced or blocked TSH, and elevated T4 and T3 levels. In pregnant adolescents or in those who use contraceptive pills, free T4 levels must be preferably required since there is an increase in carrier proteins in this situation. Positive antibodies (antiTPO, antithyroglobulin, TRAb) are present in 93% of the cases. Thyroid scintigraphy is only necessary in cases with associated nodular pathology or when radioactive iodine is used. Iodine uptake in Graves’ disease is usually elevated. Ultrasonography has limited importance.

The drugs of choice for the treatment are propylthiouracil (PTU) at 5-7mg/kg/day, three times a day, or methimazole (0.5 to 0.7mg/kg/day). Both drugs inhibit the hormone synthesis. PTU has an additional action, reducing the peripheral conversion of T4 into T3. The methimazole can be used twice a day, and during the maintenance phase of treatment, in a single daily dose, increasing adherence to treatment, which is normally long (1-3 years).

The major side effects of these drugs are leukopenia, skin rashes, and gastric symptoms. Drug-induced hepatitis and agranulocytosis are rare and require immediate discontinuation. The combination with a beta-blocker (2-10mg/kg/day) is usually beneficial to control cardiovascular symptoms, in addition to inhibiting the peripheral conversion of T4 into T3. The predictive values for treatment success are associated with goiter size, presence of elevated antibody titers, family history, and initial T3 level.

Treatment with 131I is a safe method, but it is not widely used in our country due an apparently unfounded fear of neoplasia in the neck region due to radioactivity. In patients with frequent relapses and/or very large goiter, this possibility must be considered, since the remission rate is 98%. Surgical resection of almost the entire thyroid gland is usually effective and has been preferred in cases in which drug treatment fails. Surgical risk includes recurrent laryngeal nerve injury and hypoparathyroidism.

Hypothyroidism in adolescence

Iodine deficiency is the most frequent cause of hypothyroidism in adolescents, followed by chronic thyroiditis, which predominates in zones that are not affected by iodine depletion. Classic clinical symptoms include growth deceleration or interruption, pubertal stage retardation, obstipation, dry skin, scarce and brittle hair, learning difficulty, adynia, myxedema. The later the diagnosis, the more intense the clinical manifestations. Goiter may be absent in atrophic thyroiditis. Lab exams should reveal elevated TSH, low T4 and normal or low T3, depending on the severity of the case. Anti-thyroid antibodies may be present.

The doses of levotyroxine indicated for replacement are 3-4µg/kg/day for individuals aged 10-18 years and 1-2 µg/kg/day for those older than 18. The treatment usually lasts for at least two years, and may be permanent depending on the etiology. Patients with chronic thyroiditis may retrieve thyroid function, showing that treatment should be reassessed every two or three years.

Thyroid nodules

They are rare in adolescents, with a prevalence rate of 0.05 to 1.8%. Seventy percent of the nodules occur alone, and are two or three times more frequent among females. One of the causes of thyroid nodules in adolescents is previous irradiation of the cervical and cranial regions at doses of up to 1,500 rads. Conditions such as endemic goiter, dyshormonogenesis, and CLT also lead to nodule formation. It is important to check family history for the presence of thyroid neoplasms. Every thyroid nodule presents malignancy risk that should not be neglected. On physical examination, large nodules with fast growth, hard and irregular surface, adhered to deep structures, are suggestive of malignancy. These nodules are associated with vocal chord paralysis.
Most nodules present normal thyroid function. If TSH levels are elevated, CLT may be present; normal TSH levels, however, do not rule out the diagnosis of CLT. Thyroid ultrasonography is of paramount importance, confirming or not the existence of small palpated nodules, allowing their classification into solid, mixed, or cystic.

Thyroid scintigraphy with $^{99m}$Tc or $^{131}$I indicates whether the nodules are cold, warm or hot. There is an association between solid, cold nodules and thyroid cancer, although most cold nodules are benign. Finally, FNAB, which is a safe and inexpensive procedure, should be performed since it may guide therapeutic decisions. In a study conducted on 57 patients, younger than 18 years, FNAB proved very accurate and safe, with no false-positive result, and just one false-negative result.

Several authors recommend surgical treatment for each and every isolated nodule, regardless of their characteristics, stating that malignancy risk is twice higher in this age group than in adults. However, the more experience one is with FNAB in children and adolescents, the fewer surgical indications exist. It is common knowledge that solid, colloid nodules may disappear spontaneously or with levotyroxine therapy, and that one third of nodules secondary to CLT may be cured. Conservative therapy may also be proposed for cystic nodules.

Thyroid cancer

Approximately 10% of differentiated thyroid carcinomas affect 20-year-olds, and two thirds affect females. Between 19 and 24% of single nodules contain carcinoma and 70% of them are papilliferous.

Metastatic cervical adenopathy is present in the diagnosis of 30-90% of the cases. In general, thyroid function is normal. Fine-needle aspiration biopsy is extremely important for the diagnosis.

The progression of thyroid neoplasms varies according to their histological type. Papillary carcinoma is the most frequent type, with “benign” progression. It appears as a hard, painless nodule with metastatic potential via lymph nodes, spreading into the cervical ganglia. The progression of follicular carcinoma is similar to that of papillary carcinoma, but its metastases are hematogenic to bones, lungs, brain, and mediastinum. The diagnosis of follicular carcinoma requires histologic criteria for capsular and vascular invasion, which cannot be confirmed by FNAB. Medullary carcinoma, which belongs to multiple endocrine neoplasia (MEN), is rare and results from thyroid parafollicular cells (C cells). The genetic study and the assessment of poststimulus calcitonin levels through pentagastrin allow for early surgical treatment and improve the prognosis. Finally, anaplastic carcinoma presents rapid growth, with large, irregular and compressive goiter that quickly leads to death.

Gynecomastia in adolescents

Gynecomastia is the development of mammary gland in males, with a prevalence rate of approximately 50% during the pubertal stage.

Etiology and pathogenesis

Puberal, physiological gynecomastia is extremely frequent in adolescents, resulting from an increase in the estrogen/androgen ratio, caused by alterations in sex hormone-binding globulins, which, in their turn, increase the absolute levels of estradiol, whereas submaximal testosterone levels are present throughout the day.

Several drugs may cause gynecomastia, including growth hormone, GnRH analog, metochlopramide, and anabolic steroids. Other possible etiologies are use of heroine, marijuana, and alcohol, exogenous contamination, and continuous use of foods that contain estrogen (milk, poultry, veal or beef).

Gynecomastia may also result from refeeding after malnutrition, secondary to several causes (pulmonary tuberculosis, diabetes mellitus, anorexia nervosa, ulcerative colitis and other chronic diseases), and also after a long period of exhausting exercises.

The presence of malignant breast lesions in adolescence is extremely rare. Approximately 10% of patients with prolactinoma develop gynecomastia, which occurs with or without spontaneous galactorrhea or after stimulation.

Estrogen-producing tumors (supra-renal and testicular) and hCG-producing tumors (testicular, hepatic, pleural) are other causes of gynecomastia. Among congenital disorders, we have androgen resistance, anorchism, defects of enzymes.
involved in testosterone biosynthesis, true hermaphroditism and, especially, Klinefelter's syndrome. This syndrome is characterized by abnormal karyotype (more commonly, 47, XXY), azoospermia, elevated FSH, atrophy and increase of testicular consistency, and is usually diagnosed in adolescence due to the presence of gynecomastia, which is present in 40% of the cases.

Other causes of gynecomastia are acquired testicular injury (surgery, trauma, irradiation, and infection), systemic disorders (renal and hepatic failure, thyrotoxicosis) and increased activity of tissue aromatase.

Clinical status

The most common symptom is enlarged breasts (usually bilateral), sometimes associated with moderate pain and epithelial erosion. Galactorrhea is observed in 4% of the cases. Local pain and discomfort normally disappear within a year. Gynecomastia with less than 3cm in diameter recedes spontaneously within a few months, but if it is greater than 10cm, surgical treatment is usually required.

Additional assessment

Although puberal gynecomastia is the most frequent etiology, specific lab examination should be made in order to rule out other causes.

- Hepatic and renal exams: AST, ALT, alkaline phosphatase, GT gamma, prothrombin time, creatinine.
- Hormone evaluation: estradiol, testosterone, T4, TSH, prolactin, LH, FSH, b-hCG.
- Chromosome evaluation: karyotype, if there is suspicion of Klinefelter's syndrome and androgen resistance.
- Radiological exams: breast ultrasonography and mammography when there is suspicion of malignant neoplasia; magnetic resonance for examining the hypothalamo-hypophyseal axis, in cases of hyperprolactinemia. If b-hCG levels are elevated, chest x-ray and abdominal ultrasonography should be made.
- Histological examination: fine-needle aspiration guided by breast ultrasonography, in case of tumor, to determine diagnosis.

Psychosocial aspects

Protuberant gynecomastia cause apprehension and insecurity in adolescents and their parents. For that reason, a psychologist should inform them about the disease and of the necessary procedures.

A solid doctor-patient relationship is of paramount importance. Sometimes, psychologists should also participate, helping adolescents to retrieve their self-esteem and overcome the problem. Special attention should be given to the possibility of chemical addiction to drugs, whose incidence among adolescents has alarmingly increased in the last decades. We also suggest that sexual orientation be carefully assessed, since, in some cases, some adolescents can use estrogen to enlarge their breasts. In short, the best approach to adolescents with gynecomastia consists of availability and understanding.

Treatment

The treatment of gynecomastia usually consists of clinical follow-up and psychological support, eliminating the need for drug therapy, except, of course, in the case of specific diseases. The use of tamoxifen is a good option. Testosterone and hCG are not efficient and may even enhance breast enlargement. Surgical treatment is recommended for protuberant gynecomastia or when its presence causes psychological problems that are difficult to control; surgery is indicated when gynecomastia has been present for more than two years and only for patients older than fifteen years.

References


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