Endocrine diseases, perspectives and care in Turner syndrome

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SUMMARY
Turner syndrome is a frequent chromosome disorder in clinical practice. It is characterized by short stature, gonadal dysgenesis and multisystemic involvement, responsible for a high morbidity and reduced life expectancy. The aim of the present paper is to describe the endocrinopathies and major problems at different ages, and to present suggestion for follow-up care in these patients. Arq Bras Endocrinol Metab. 2011;55(8):550-8

Keywords
Turner syndrome; endocrinopathies; rhGH treatment; estrogen HTR

INTRODUCTION
Turner syndrome (TS) is characterized by a female phenotype and loss of the second sexual chromosome. It occurs in about 1:2,500 to 4,000 live female births. The features vary widely, and are associated with short stature, and ovarian failure with sexual infantilism and infertility. Dysmorphisms like cubitus valgus, low hairline, small mandible, multiple pigmented nevi, characteristic face, short fourth toe, high-arched palate, nuchal folds, edema of hands or feet, left-sided cardiac and renal anomalies are commonly observed in the syndrome. The diagnosis is performed by karyotyping, and requires a standard 30-cell karyotype. In routine TS practice, roughly half of the patients have a 45,X karyotype, 20%-30% have mosaicism (45,X plus at least another cell line), and the remainder have structural abnormalities (1). Females with short stature and deletion of the distal region of Xp including the SHOX (short stature homeobox gene) gene are generally not diagnosed with TS. Likewise, individuals with deletions of Xq24, with primary or secondary amenorrhea and without short stature are typically diagnosed with premature ovarian failure (2). The main endocrine problems are short stature, ovarian failure, immune diseases and disturbances of the lipid glucose and bone metabolism (1).

SHORT STATURE
TS patient adult height is in average 20 cm shorter than the mean height of women of the same population (3). This short stature reflects the sum of a normal but small size at birth, decreased growth velocity starting at an early age, and a poor growth spurt during puberty. Several techniques were used to assess the growth hormone (GH) – Insulin-like growth factor (IGF) axis, from stimulation tests (4), to evaluation of the levels of different isoforms, and investigation of IGF-I and IGFBP-3...
generation tests (5,6). All of them show normal values. Presently, the short stature in girls with Turner syndrome is thought to be related to the haploinsufficiency of the SHOX gene, a pseudoautosomal gene (7). Even though the production of growth hormone is normal, treatment with rhGH was approved in the United States in 1996, and is now routine in several countries.

Girls with TS are born with normal but small size, and present slow growth during the first three years of life (8). Davenport and cols. investigated the use of rhGH in this population before 4 years of age, and demonstrated that two years after initiating treatment, patients who received rhGH had an average height of -0.3 SD of the normal population, while patients who did not receive rhGH had a height of -2.2 SD (9).

The gain in height, using expected values prior to initiation of treatment, may be of 8.5 cm above expected height (10). There are few studies comparing treated and control groups. Stephure and the Canadian Growth Hormone Advisory Committee compared adult height of children treated with rhGH to the adult height of a control group who did not receive rhGH, and showed an increment of 7.2 cm in adult height (confidence interval 6.0, 8.4) (11). One important aspect of treatment with rhGH is the quality of life with the treatment (benefits of being taller versus the effects of medicalization – rhGH injection for many years), and two different studies did not find benefits or adverse effects (12). Other aspects of adult height in girls with Turner syndrome is when to start estrogen replacement to optimize growth, and which dose to use. A recently published study compared the effects of rhGH treatment associated with the use of very low doses of estrogen during childhood. Even though the use of ethinyl estradiol alone decreased adult height, when compared with a control group, the use of rhGH alone increased adult height by 5.0 cm, and the association with low doses of estrogen increased adult height by other 2.1 cm (13).

One study published in 1992 reported that the use of oxandrolone, a non-aromatizable androgen, in girls with TS, improved growth (14). Based on the knowledge that estrogen is the hormone responsible for the closure of the ephiphysis, the idea of using oxandrolone and rhGH became popular again, and several recently published studies investigated this topic, with increased adult height of about 4.5 cm, using doses of about 0.05 mg/kg/day (15). Breast development was slower in both studies, and there was no sign of virilization. Menke and cols. had different results. They compared the use of 0.03 mg with 0.06 mg/kg/day or placebo, and found a gain between 2 and 3 cm with the low dose, and no benefits with the use of 0.06 mg when compared with control patients. More patients receiving the higher dose reported virilization (16).

Growth hormone used in patients with TS, probably starting at a very young age, will improve adult height even further, but this has not been shown yet. The use of low dose estrogen during childhood and the use of oxandrolone are still topics of debate.

**OVARIAN FAILURE**

Gonadal function of patients with TS is variable. The ovaries may degenerate during fetal life, in childhood or in early adulthood. Approximately 20% of patients with TS show spontaneous menarche, primary amenorrhea (85%), infertility (98%), and the non-assisted pregnancy rate is 2% to 5% (17).

In most prepubertal TS patients, ovarian failure and reduced ovarian feedback result in significantly elevated FSH and LH levels during early childhood (0-5 years) and adolescence (around 10 years), whereas gonadotropin levels are not significantly elevated at age 5-10 years, compared with healthy girls (18). However, in adulthood FSH and LH increase to menopause levels in gonadal dysgenesis girls (19). Potential spontaneous pubertal development in girls with TS must be monitored by physical examination and assessment of follicle-stimulating hormone levels beginning at about age 10 (20). Inhibit B is secreted by developing follicles, and FSH and inhibit B are markers of remaining ovarian function in girls with TS. However, inhibit B evaluation is not a routine analysis in the follow-up of TS; this analysis is only indicated when testing the possibility of fertility.

When FSH and LH are clearly elevated, and clinical signs of puberty are absent, pubertal induction should be started. The aim of pubertal induction with estrogen in TS is to achieve physical and psychological development similar to that of natural puberty, and to establish adequate peak bone mass in the first two decades of life. However, girls with TS are often introduced to the estrogens late in their lives to prevent stunting of growth. Recent evidence shows that the regimens initiating estrogen treatment at age 12 enable the evolution of puberty without interfering with final height (21). The optimal route of estrogen replacement in TS is unknown. For pubertal induction in girls without spontaneous puberty, the preferred regimen is low-do-
Turner syndrome follow-up

se, transdermal estrogen treatment, with gradual dose increases over approximately 2-3 years until feminization. In these cases, there is a direct correlation between breast stage and gonadotropin levels (22). Optimal estrogen administration seems to be important in preserving bone mass and enhancing trabecular bone volume. Hormone replacement therapy should begin at a normal pubertal age, and be continued until the age of 50. Transdermal estradiol provides the most physiological form of replacement (1). If spontaneous pubertal development occurs, in most cases it is followed by progressive premature ovarian failure (23).

AUTOIMMUNE DISORDERS

Patients with TS are prone to develop autoimmune conditions such as thyroiditis, celiac disease, inflammatory bowel disease, type 1 diabetes, Grave’s hyperthyroidism, ulcerative colitis, Crohn’s disease, juvenile rheumatoid arthritis, psoriasis, alopecia and vitiligo (23). These patients frequently exhibit transient, recurrent and asymptomatic variations in TSH and/or thyroid hormones (24).

The prevalence of Hashimoto’s thyroiditis in these patients ranges from 13.3% to 55%, according to the criteria used for diagnosis, the age range covered, and the technique used to measure antibodies (25).

Moris and cols. (23) showed positive results for anti-TPO in 94% of TS patients with hypothyroidism, and this fact indicated a relationship between autoimmune reactivity and hypothyroidism in this syndrome. However, the authors were not able to say that there was an increase in the number of cases with age, because of the relatively low number of pediatric TS patients in the study (27).

Although the study by Wilson and cols. described the presence of antibody-positive among both patients with TS and their mothers, other study pointed to the opposite direction, and the presence of autoimmune hypothyroidism was associated with the syndrome itself, not the presence of family history (27).

The higher risk of autoimmune diseases in women with TS has been suggested to be due to haploinsufficiency of the X-chromosome (28). However, proinflammatory cytokines, interleukin-6, interleukin-8 and tumor necrosis factor α may be partly responsible for that (29,30). Su and cols. studied the expression of the X-linked FOXP3 gene and the prevalence of autoimmunity in patients with TS, but did not find a positive correlation (30).

In the general population of women, the diagnosis of thyroiditis is based on clinical evidence of thyroid dysfunction, whereas in patients with TS, functional evaluation is done periodically, regardless the clinical picture, which allows the detection of subclinical changes that cannot always be correlated with disorders of the hypothalamic-pituitary-thyroid axis (25).

The incidence of celiac disease in patients with TS is increased when compared with the general population. Mortensen and cols. found a prevalence of 5% in a cohort of Turner syndrome individuals with 18% of autoantibodies, and revealed a considerable number of silent cases and delayed diagnoses (23).

In Brazil, a 3.6% prevalence of biopsy-proven celiac disease was observed in a group of females with TS, which is 10 times the prevalence among females of the general population in the same geographical area. This result provides additional support to an association between these two disorders, and restates that girls and women with Turner syndrome represent a high risk population for developing celiac disease (31).

CARBOHYDRATE METABOLISM IN TURNER SYNDROME

Glucose homoeostasis is altered in TS, and early reports of diabetes and glucose intolerance have been found. Glucose intolerance has been reported in both TS girls and women, and type 2 diabetes is four times more common (relative risk: 4.4) (32), in addition to increased mortality due diabetes (33), and earlier onset than general population. TS patients present central obesity (34) and a more sedentary lifestyle, and these factors may contribute to the risk of developing diabetes. Additionally, women with TS were at significantly increased risk of certain specific autoimmune diseases, including Hashimoto thyroiditis and type 1 diabetes mellitus (23). Fasting glucose and insulin levels were frequently normal despite the fact that, in adults, glucose intolerance (GI) has been found in 25%-78% during an oral glucose tolerance test (OGTT) (35,36). Glucose homeostasis is not completely understood. There are controversies surrounding insulin sensitivity in TS, and the exact mechanism behind the elevated occurrence of type 2 diabetes and GI remains unclear.
Reduced insulin sensitivity was demonstrated, but not in all patients, and in some of them, impaired insulin secretion was found (37).

**Glucose homoeostasis during hormone replacement therapy (HRT)**

Most of the patients with TS present estrogen deficiency, which results in the loss of the cardio-protector effect of estrogen observed in menopause. Estradiol deficiency can influence several conditions related to glucose homoeostasis, like endothelial dysfunction, decreased insulin production, an abnormal lipid pattern, increased central adiposity, and early atherosclerosis. However, there is no consensus regarding the ideal dosage, route of administration, type of estrogen, type of gestagen, and forms of administration of these hormones for the induction of puberty, and for their use in adolescence and adult life in TS patients (37). For example, when the route of estrogen administration is considered, existing data have not demonstrated important advantages of any form of estrogen administration in TS (38). There is a great probability that the dose, rather than route of administration, is more important in these patients.

**Glucose homoeostasis during rhGH treatment**

Insulin levels increase during rhGH use. Insulin levels decrease after the end of the treatment, but do not return to levels as low as before treatment. GH generally reduces insulin sensitivity in the first 6-12 months of treatment, when it becomes stable. This stabilization could be due to increased lean body mass (LBM) and decreased fat mass (FM). The number of TS patients with GI do not seem to increase significantly during treatment, and HbA1c remains unchanged or even decreases during rhGH therapy. However, the long-term effects of the GH-induced hyperinsulinism and insulin resistance are not known (37).

Finally, adult women with TS require careful medical follow-up. Early medical intervention may decrease the substantially increased morbidity, mortality, and improve the quality of life (39). Many of the problems of adult life in patients with TS are related to obesity (34), partly because of low physical fitness and a sedentary lifestyle. Women with TS should aim at having a body mass index lower than 25 kg/m² and a waist/hip ratio lower than 0.80. Lifestyle education with advice on diet and exercise must be included in a diabetes prevention program. However, exercise programs should be individualized.

There is a need to pay attention to the increased risk of type 1 and type 2 diabetes in TS. Focus on diabetes symptoms and yearly screening of fasting glucose. OGTT is recommended when there is a suspicion of the disorder. Diabetes is often relatively mild and responsive to weight loss or oral monotherapy (37). Recommendations for diagnosis and treatment of diabetes are the same for the general population.

**CARDIOVASCULAR RISK**

The population with Turner syndrome has an increased risk for cardiovascular and cerebrovascular disease of ischemic origin (40). The existence of dyslipidemia in patients with TS is controversial. In some studies, the levels of cholesterol and triglycerides are comparable to controls, as well as the numerical superiority of HDL (41). However, most studies demonstrate that there is abnormal lipid profile with increased LDL cholesterol, decreased HDL cholesterol, and high triglycerides, especially because of altered body composition, leading to insulin resistance. Low-density lipoprotein cholesterol and triglycerides are elevated, and lipid particle size is reduced in women with TS compared with women with normal karyotype and ovarian failure matched by age and body mass index, suggesting that the X chromosome deletion per se, apart from the effects of premature ovarian failure, is associated with dyslipidemia (42). Our group, in a recent, unpublished study, noted that patients with TS have higher postprandial triglycerides than controls, and this fact was not influenced by the route of estrogen replacement.

There is no consensus on the treatment of dyslipidemia in patients with TS. Some studies have reported the improvement of some lipid profile parameters, such as decrease in lipoprotein A, apoprotein A-I and increase in HDL cholesterol after the beginning of estrogen replacement. The administration of rhGH also improves the lipid profile by reducing total cholesterol and LDL cholesterol and increasing HDL (41,43). Androgen replacement therapy presents controversial effects on lipid metabolism in patients with TS. Zuckerman-Levin and cols. have shown that the administration of methyl-testosterone had improved the lipid profile, not only with a reduction in total cholesterol, LDL cholesterol and triglycerides, but also with a decrease in HDL cholesterol (44). However, Wilson and cols. did not observed any change on lipid profile after administration of oxandrolone (45).
BONE MASS GAIN AND PREVENTION OF FRACTURES IN TURNER SYNDROME

Estrogens and gestagens play a crucial role, and several reports suggest that during puberty and late adolescence normal gonadal function is required in TS girls for adequate skeletal mineralization, as well as attainment and posterior maintenance of normal bone mass peak (46). Genetic factors are important determinants of adult bone mass, but no inheritable variables, including body mass, calcium nutrition, vitamin D, sex steroids, and activity may strongly influence whether maximal bone mineral is achieved. These risk factors contribute to the osteopenia associated with delayed puberty, TS, and growth hormone deficiency (47).

Osteopenia is a common complication among adult patients and may be related to the delayed pubertal development and hypoestrogenism. In addition, prepupal estradiol secretion may also play a role in bone mass acquisition during this period. Adolescents girls with TS and spontaneous puberty have bone mineral density (BMD) in the normal range, while in TS girls who underwent induced puberty (48) and young TS patients do not attain peak BMD despite proper HRT and growth hormone therapy (49).

In girls with TS, transdermal E2 resulted in faster bone accrual at the spine, and increased uterine growth compared with conjugated oral estrogen. Neither BMI, nor calcium intake, karyotype, nor concomitant rhGH therapy appear to be significant factors accounting for these differences. Inadequate availability of estrogens to bone tissue from infancy to adulthood, caused by early prepubertal ovarian dysfunction, delayed puberty, therapeutic estrogen/gestagen regimens, and treatment compliance, should be considered as major factors responsible for the low BMD values observed in our puberty-induced patients. However, unknown genetic factors related to bone mineralization, or disturbances in other calcium-regulating hormones cannot be ruled out. In addition, it has been reported that rhGH therapy increases bone calcium availability, and enables adequate bone mass peak in adolescent Turner syndrome patients (50).

Several studies have shown decreased BMD in girls, as well as in younger and middle-aged women with TS (51,52). This finding may be largely due to the two-dimensional nature of dual energy x-ray absorptiometry (DEXA) scans (53), which fails to account for the reduced height in TS, leading to lower BMD a priori. Studies of volumetric BMD, taking actual body height into account, have shown largely similar volumetric BMD in TS and controls (54).

Increased fracture risk is a feature of TS. However, the reasons for this finding are unclear. It is not entirely clear whether a primary bone defect exists in TS (55), perhaps due to skeletal dysmorphogenesis caused by haploinsufficiency of the *SHOX* gene (7). In addition, deletions of the Xp11.2-p22.1 region of the X chromosome have been identified in non-mosaic TS patients, and were related to the presence of phenotypical traits such as short stature, ovarian failure, high-arched palate, and autoimmune thyroid disease. Whether the presence of functional mutations in unidentified genes related either to factors that regulated bone mass acquisition, or to intrinsic bone defects in TS patients, play a role in the differences observed in BMD values in our patients, is something that should also be considered. Some authors observed reduced BMD at the femoral neck; QCT data suggests that cortical density is reduced with sparing of trabecular bone. This differential of cortical and trabecular BMD may predispose to fracture (56). There is an approximately 25% increase in fracture risk, most of which is related to medium or high-impact trauma. Longer bones, especially of the forearm, are predominantly affected. This fact may be due to a selective cortical bone deficiency in TS, which is unrelated to hypogonadism. In addition, lack of adequate estrogen replacement can lead to trabecular bone deficiency, and increase vertebral compression fractures after the age of 45.

Although DEXA evaluation is important, it should be used judiciously in TS in view of its inherent tendency to underestimate the bone density of people with short stature. Bone size-independent methods, such as QCT or volumetric transformation of DEXA data, should be used in individuals shorter than 150 cm. Achieving optimal bone density is of critical importance for fracture prevention in TS, and should be pursued by timely introduction of hormone replacement therapy, adequate dose of estrogens during young adult life, optimal calcium and vitamin D intake, and regular physical exercise (57).

Assays on bone turnover markers show evidence of increased bone turnover. Bone deficiency is most marked at the femoral neck and seems correlated with serum testosterone and estradiol levels (58).

On the whole, bone health represents a main clinical issue for the management of persons with disorders of sex differentiation, and well-designed longitudinal studies should be developed to improve their bone health.
health and well-being. In addition, early detection of osteopenia in prepubertal age and early instauration of preventive measures, such as adequate calcium intake and optimal physical activity, should be considered mandatory in the health care of TS patients. Bone health can be maintained in most women with TS when appropriate information is given, and proper HRT, as well as vitamin D and calcium supplementation, is recommended (21).

PERSPECTIVES IN TURNER SYNDROME

The main perspective in TS is related to the fertility problem. Pregnancy is an exceptional event, but is possible in 2% of cases. It can occur in patients with structural anomalies of the X chromosomes in which the Xq13-q26 region, containing the genes that are thought to control ovarian function, is spared; or in patients with a mosaic karyotype containing a 46, XX cell line, which preserves ovarian function (59). In vitro fertilization with donor oocytes and subsequent embryo transfer has been the predominant fertility option for such patients (60). Women with Turner mosaicism (46XX/45XO) and normal FSH levels may have an adequate ovarian reserve and undergo attempts at traditional assisted reproduction. At the time of retrieval, an ovarian biopsy may be performed in order to directly evaluate the ovarian karyotype. A successful pregnancy results from oocytes retrieved from the gonad demonstrating a normal karyotype (61). The combination of ovarian tissue cryobanking and immature oocyte collection from the tissue, followed by in vitro maturation and vitrification of matured oocytes represent promising approaches to fertility preservation for young women with mosaic Turner syndrome (62,63).

CARE OF TURNER SYNDROME

The presence of Y-chromosome material in patients with dysgenetic gonads increases the risk of gonadal tumors and/or nontumoral androgen-producing lesions, and the risk increases with age (64). The gonads should, therefore, be removed, even if they appear inconspicuous on ultrasound.

Otherwise, adults with TS have a 4- to 5-fold increased rate of premature mortality, which is attributed mainly to complications of congenital heart disease (CHD) and premature coronary artery disease. TS patients with congenital anomalies indicating involvement of the cardiovascular system should be followed up by a cardiology specialist. In young girls, transthoracic echocardiogram is sufficient, if it enables clear visualization of the cardiac anatomy. If not, or if otherwise indicated, cardiac magnetic resonance (CMR), with sedation if necessary, may be advised. In addition to echocardiogram, CMR is recommended as a screening test for older girls and for all adults, ideally, adults with TS (20). Similarly, TS patients should be followed up by other specialists, such as nephrologists, gastroenterologists, gynecologists and others, besides the endocrinologist. Table 1 summarizes the problems, and table 2, the care at different ages of TS patients.

### Table 1. The natural history of Turner syndrome and its associated problems

<table>
<thead>
<tr>
<th>Birth and neonatal period</th>
<th>Growth: often borderline small for gestational age</th>
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<tbody>
<tr>
<td>Lymphoedema</td>
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<td>Cardiac abnormalities: e.g. coarctation of aorta, aortic stenosis, bicuspid aortic valve</td>
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<td>Infancy</td>
<td>Growth: length — usually close to and parallel to the 3rd percentile</td>
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<td>Feeding difficulties with weight faltering</td>
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<td>Poor sleeping pattern</td>
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<td>Preschool</td>
<td>Short stature: growth velocity usually low/normal</td>
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<td>High activity levels</td>
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<td>Behavioral difficulties with exaggerated fearfulness</td>
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<td>Recurrent middle ear infections; otitis media with effusion (glue ear); variable conductive hearing loss; sensorineural deafness in a minority</td>
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<tr>
<td>School</td>
<td>Growth: height — gradually falling away from 3rd percentile</td>
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<td>Middle ear disease (see above)</td>
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<td>Obesity</td>
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<td>Specific learning difficulties: e.g. mathematics, visuospatial tasks</td>
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<td>Social vulnerability</td>
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<td>Foot problems: e.g. toenail involution, cellulitis</td>
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<td>Renal anomalies: e.g. horseshoe, duplex, unusually shaped kidneys</td>
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<tr>
<td>Adolescence</td>
<td>Growth: impaired pubertal growth spurt even with estrogen induction</td>
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<td>Ovarian failure: absent/incomplete puberty</td>
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<td>Increased prevalence of immune disorders:</td>
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<td>Young adulthood</td>
<td>Need for counseling in relation to:</td>
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<td>Long term estrogen replacement</td>
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<td>Visuospatial difficulties</td>
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<td>Sensorineural deafness</td>
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(adapted from Donaldson and cols. (65)).
Table 2. Guideline of care for the management of Turner syndrome

At the time of diagnosis
- Height, weight, blood pressure and complete physical examination
- Bone age
- Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
- Renal and pelvic ultrasound; echocardiogram
- Audiometry
- Bone mineral density (prepubertal and after ages)
- Refer to cardiology, ENT, ophthalmologist and orthopedist

Annual evaluation until 10 years of age
- Height, weight, blood pressure and complete physical examination
- Thyroid function tests

At the ages of 4, 6, and 8 years, the following should be added to routine annual evaluation
- Bone age
- Blood cell count, fasting glucose, renal and hepatic function tests, lipid profile, and antithyroid antibodies

At 5 years of age, the following should be added to routine annual evaluation:
- Echocardiogram and audiometry
- Refer to cardiologist, ENT, ophthalmologist and orthopedist

At 10 years of age, the following should be added to routine annual evaluation
- Special attention to pubertal staging
- Careful exam of Nevi
- Bone age
- Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
- Renal and pelvic ultrasound; echocardiogram
- Audiometry
- Bone mineral density
- Refer to cardiologist, ENT, ophthalmologist, orthopedist and orthodontist

Annually, between 11 and 14 years of age
- Height, weight, blood pressure and a complete physical examination
- Special attention to pubertal staging
- Careful exam of Nevi
- Bone age
- Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
- Pelvic ultrasound

At 15 years of age
- Height, weight, blood pressure and a complete physical examination
- Special attention to pubertal staging
- Careful exam of Nevi
- Bone age
- Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
- Pelvic ultrasound
- Bone mineral density
- Refer to gynecologist

Annual evaluation after 16 years of age
- Weight, blood pressure and a complete physical examination
- Careful exam of Nevi
- Blood cell count, fasting glucose, renal and liver function tests, lipid profile, TSH, T4, antithyroid antibodies, estradiol, LH, FSH
- Refer to gynecologist

Evaluation every 2 years after 16 years of age, to be added to routine annual evaluation
- Bone density and body composition if previous exam was abnormal

Evaluation every 5 years after 15 years of age, to be added to routine annual evaluation
- Echocardiogram
- Audiometry
- Bone density and body composition if previous exams were normal
- Refer to cardiologist, ENT, ophthalmologist

ENT: Ear, nose and throat specialist.

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REFERENCES


