

High BMI in Teens Predicts Heart Disease Risk

VITALS

Major Finding: An elevated BMI during adolescence, even within the range currently considered normal, strongly predicted the diagnosis of CHD on angiography by the age of 45 years.

Data Source: A prospective cohort study of 37,674 healthy military men who were followed from approximately age 25 years for a median of 17 years for the development of angiography-proven CHD and type 2 diabetes.

Disclosures: The Chaim Sheba Medical Center, Tel-Hashomer, Israel, and the Israel Defense Forces Medical Corps supported the study. The authors reported that they had no conflicts of interest.

BY MARY ANN MOON

FROM THE NEW ENGLAND JOURNAL OF
MEDICINE

Among males, an elevated body mass index during adolescence was a strong predictor of angiography-proven coronary heart disease in young adulthood, according to large, prospective study.

Male adolescents who were in the top

10% of body mass index had a risk for developing coronary heart disease at ages 25-45 years that was nearly seven times higher than the risk in adolescents in the lowest 10% of BMI, according to Dr. Amir Tirosh of the division of endocrinology, diabetes, and hypertension at Brigham and Women's Hospital, Boston, and his associates (N. Engl. J. Med. 2011;364:1315-25).

“Although obesity in adulthood is a

Norditropin® Cartridges [somatropin (rDNA origin) injection], for subcutaneous use

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BRIEF SUMMARY: Please consult package insert for full prescribing information

INDICATIONS AND USAGE: Pediatric Patients: Norditropin® is indicated for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone (GH). Norditropin® is indicated for the treatment of children with short stature associated with Noonan syndrome. Norditropin® is indicated for the treatment of children with short stature associated with Turner syndrome. Norditropin® is indicated for the treatment of children with short stature born small for gestational age (SGA) with no catch-up growth by age 2–4 years. **Adult Patients:** Norditropin® is indicated for the replacement of endogenous GH in adults with growth hormone deficiency (GHD) who meet either of the following two criteria: Adult Onset (AO): Patients who have GHD, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or Childhood Onset (CO): Patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients who were treated with somatropin for GHD in childhood and whose epiphyses are closed should be reevaluated before continuation of somatropin therapy at the reduced dose level recommended for GHD adults. According to current standards, confirmation of the diagnosis of adult GHD in both groups involves an appropriate growth hormone provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic growth hormone deficiency.

CONTRAINDICATIONS: Acute Critical Illness: Treatment with pharmacologic amounts of somatropin is contraindicated in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n=522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3–8 mg/day) compared to those receiving placebo [see Warnings and Precautions]. **Prader-Willi Syndrome in Children:** Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment [see Warnings and Precautions]. There have been reports of sudden death when somatropin was used in such patients [see Warnings and Precautions]. Norditropin® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome. **Active Malignancy:** In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since GHD may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor. **Diabetic Retinopathy:** Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy. **Closed Epiphyses:** Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses. **Hypersensitivity:** Norditropin® is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Localized reactions are the most common hypersensitivity reactions.

WARNINGS AND PRECAUTIONS: Acute Critical Illness: Increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin [see Contraindications]. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients experiencing acute critical illnesses should be weighed against the potential risk. **Prader-Willi Syndrome in Children:** There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If, during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively [see Contraindications]. Norditropin® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome. **Neoplasms:** Patients with preexisting tumors or GHD secondary to an intracranial lesion should be monitored routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence. Patients should be monitored carefully for potential malignant transformation of skin lesions, i.e. increased growth of preexisting nevi. **Glucose Intolerance:** Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity, Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored

closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients. **Intracranial Hypertension:** Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome may be at increased risk for the development of IH. **Fluid Retention:** Fluid retention during somatropin replacement therapy in adults may frequently occur. Clinical manifestations of fluid retention are usually transient and dose dependent. **Hypothyroidism:** Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with GHD, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated. In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered. **Slipped Capital Femoral Epiphysis in Pediatric Patients:** Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including GHD and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated. **Progression of Preexisting Scoliosis in Pediatric Patients:** Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated patients with Turner syndrome and Noonan syndrome. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy. **Otitis Media and Cardiovascular Disorders in Turner Syndrome:** Patients with Turner syndrome should be evaluated carefully for otitis media and other ear disorders since these patients have an increased risk of ear and hearing disorders. Somatropin treatment may increase the occurrence of otitis media in patients with Turner syndrome. In addition, patients with Turner syndrome should be monitored closely for cardiovascular disorders (e.g., stroke, aortic aneurysm/dissection, hypertension) as these patients are also at risk for these conditions. **Confirmation of Childhood Onset Adult GHD:** Patients with epiphyseal closure who were treated with somatropin replacement therapy in childhood should be reevaluated according to the criteria in *Indications and Usage* before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults. **Local and Systemic Reactions:** When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site. As with any protein, local or systemic allergic reactions may occur. Parents/Patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur. **Laboratory Tests:** Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-I may increase after somatropin therapy. **Pancreatitis:** Cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain.

ADVERSE REACTIONS: Most Serious and/or Most Frequently Observed Adverse Reactions: This list presents the most serious^a and/or most frequently observed^d adverse reactions during treatment with somatropin: ^aSudden death in pediatric patients with Prader-Willi syndrome with risk factors including severe obesity, history of upper airway obstruction or sleep apnea and unidentified respiratory infection [see Contraindications and Warnings and Precautions]; ^bIntracranial tumors, in particular meningiomas, in teenagers/young adults treated with radiation to the head as children for a first neoplasm and somatropin [see Contraindications and Warnings and Precautions]; ^cGlucose intolerance including impaired glucose tolerance/impaired fasting glucose as well as overt diabetes mellitus [see Warnings and Precautions]; ^dIntracranial hypertension [see Warnings and Precautions]; ^eSignificant diabetic retinopathy [see Contraindications]; ^fSlipped capital femoral epiphysis in pediatric patients [see Warnings and Precautions]; ^gProgression of preexisting scoliosis in pediatric patients [see Warnings and Precautions]; ^hFluid retention manifested by edema, arthralgia, myalgia, nerve compression syndromes including carpal tunnel syndrome/paraesthesias [see Warnings and Precautions]; ⁱUnmasking of latent central hypothyroidism [see Warnings and Precautions]; ^jInjection site reactions/rashes and lipoatrophy (as well as rare generalized hypersensitivity reactions) [see Warnings and Precautions]; Pancreatitis [see Warnings and Precautions]. **Clinical Trials Experience:** Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials performed with one somatropin formulation cannot always be directly compared to the rates observed during the clinical trials performed with a second somatropin formulation, and may not reflect the adverse reaction rates observed in practice. *Clinical Trials in Pediatric GHD Patients:* As with all protein drugs, a small percentage of patients may develop antibodies to the protein. GH antibodies with binding capacities lower than 2 mg/L have not been associated with growth attenuation. In a very small number of patients, when binding capacity was greater than 2 mg/L, interference with the growth response was observed. In clinical trials, patients receiving Norditropin® for up to 12 months were tested for induction of antibodies, and 0/358 patients developed antibodies with binding capacities above 2 mg/L. Amongst these patients, 165 had previously been treated with other somatropin formulations, and 193 were previously untreated naive patients. *Clinical Trials in Children with Noonan*

well-documented risk factor for both type 2 diabetes and CHD, it [has been] unclear whether a longer history of relative overweight, starting earlier in life, poses an additional risk,” Dr. Tirosh and his associates said.

“Given the current obesity pandemic, it is important to determine whether elevated BMI in childhood [or] adolescence ... contributes independently to the risk of disease,” they noted.

Dr. Tirosh and his colleagues examined the issue with the use of

data from the Israel Defense Forces’ ongoing Metabolic, Lifestyle, and Nutrition Assessment in Young Adults study.

All men in the Israeli military are examined every 3-5 years, beginning at about age 25 and continuing throughout their military careers, and the information is recorded in a database.

Also recorded are the weight and height measurements obtained during the men’s medical examination at induction into the military, usually at age 17.

The researchers used those data to calculate body mass index in adolescence.

For this study, Dr. Tirosh and his associates analyzed data on 37,674 male military personnel who were followed prospectively for a mean of 17 years, starting at about age 25, and whose body mass index during adolescence was tracked retrospectively. At that time, body mass index ranged from 15 to 36 kg/m².

During follow-up, there were



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CHD risk was sevenfold higher in young men whose teen BMI had been in the top 10%, vs. the lowest 10%.

Syndrome: Norditropin® was studied in a two-year prospective, randomized, parallel dose group trial in 21 children, 3–14 years old, with Noonan syndrome. Doses were 0.033 and 0.066 mg/kg/day. After the initial two-year randomized trial, children continued Norditropin® treatment until final height was achieved; randomized dose groups were not maintained. Final height and adverse event data were later collected retrospectively from 18 children; total follow-up was 11 years. An additional 6 children were not randomized, but followed the protocol and are included in this assessment of adverse events. Based on the mean dose per treatment group, no significant difference in the incidence of adverse events was seen between the two groups. The most frequent adverse events were the common infections of childhood, including upper respiratory infection, gastroenteritis, ear infection, and influenza. Cardiac disorders were the system organ class with the second most adverse events reported. However, congenital heart disease is an inherent component of Noonan syndrome, and there was no evidence of somatropin-induced ventricular hypertrophy or exacerbation of preexisting ventricular hypertrophy (as judged by echocardiography) during this study. Children who had baseline cardiac disease judged to be significant enough to potentially affect growth were excluded from the study; therefore the safety of Norditropin® in children with Noonan syndrome and significant cardiac disease is not known. Among children who received 0.033 mg/kg/day, there was one adverse event of scoliosis; among children who received 0.066 mg/kg/day, there were four adverse events of scoliosis [see *Warnings and Precautions*]. Mean serum IGF-I standard deviation score (SDS) levels did not exceed +1 in response to somatropin treatment. The mean serum IGF-I level was low at baseline and normalized during treatment. *Clinical Trials in Children with Turner Syndrome:* In two clinical studies wherein children with Turner syndrome were treated until final height with various doses of Norditropin®, the most frequently reported adverse events were common childhood diseases including influenza-like illness, otitis media, upper respiratory tract infection, otitis externa, gastroenteritis and eczema. Otitis media adverse events in Study 1 were most frequent in the highest dose groups (86.4% in the 0.045–0.067–0.089 mg/kg/day group vs. 78.3% in the 0.045–0.067 mg/kg/day group vs. 69.6% in the 0.045 mg/kg/day group) suggesting a possible dose-response relationship. Of note, approximately 40–50% of these otitis media adverse events were designated as “serious” [see *Warnings and Precautions*]. No patients in either study developed clearcut overt diabetes mellitus; however, in Study 1, impaired fasting glucose at Month 48 was more frequent in patients in the 0.045–0.067 mg/kg/day group (n=4/18) compared with the 0.045 mg/kg/day group (n=1/20). Transient episodes of fasting blood sugars between 100 and 126 mg/dL, and, on occasion, exceeding 126 mg/dL also occurred more often with larger doses of Norditropin® in both studies [see *Warnings and Precautions and Adverse Reactions*]. Three patients withdrew from the 2 high dose groups in Study 1 because of concern about excessive growth of hands or feet. In addition, in Study 1, exacerbation of preexisting scoliosis was designated a serious adverse reaction in two patients in the 0.045 mg/kg/day group [see *Warnings and Precautions*]. *Clinical Trials in Children Born Small for Gestational Age (SGA) with No Catch-up Growth by Age 2–4 Years: Study 1 (Long-Term):* In a multi-center, randomized, double-blind study, 53 non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) to final height for up to 13 years (mean duration of treatment 7.9 and 9.5 years for girls and boys, respectively). The most frequently reported adverse events were common childhood diseases including influenza-like illness, upper respiratory tract infection, bronchitis, gastroenteritis, abdominal pain, otitis media, pharyngitis, arthralgia, and headache. Adverse events possibly/probably related to Norditropin® were otitis media, arthralgia, headaches (no confirmed diagnoses of benign intracranial hypertension), gynecomastia, and increased sweating. One child treated with 0.067 mg/kg/day for 4 years was reported with disproportionate growth of the lower jaw, and another child treated with 0.067 mg/kg/day developed a melanocytic nevus [see *Warnings and Precautions*]. There were no clear cut reports of exacerbation of preexisting scoliosis or slipped capital femoral epiphysis. No apparent differences between the treatment groups were observed. In addition, the timing of puberty was age-appropriate in boys and girls in both treatment groups. Therefore, it can be concluded that no novel adverse events potentially related to treatment with Norditropin® were reported in long-term Study 1. *Study 2 (Short-Term):* In a multi-center, randomized, double-blind, parallel-group study, 98 Japanese non-GHD children with short stature born SGA with failure to catch-up were treated with 2 doses of Norditropin® (0.033 or 0.067 mg/kg/day) for 2 years or were untreated for 1 year. The most frequently reported adverse events were common childhood diseases almost identical to those reported above for Study 1. Adverse events possibly/probably related to Norditropin® were otitis media, arthralgia and impaired glucose tolerance. No apparent differences between the treatment groups were observed. However, arthralgia and transiently impaired glucose tolerance were only reported in the 0.067 mg/kg/day treatment group. Therefore, it can also be concluded that no novel adverse events potentially related to treatment with rhGH were reported in short-term Study 2. As with all protein drugs, some patients may develop antibodies to the protein. Eighteen of the 76 children (~24%) treated with Norditropin® developed anti-rhGH antibodies. However, these antibodies did not appear to be neutralizing in that the change from baseline in height SDS at Year 2 was similar in antibody positive and antibody negative children by treatment group. In both Study 1 and Study 2, there were no clear cut cases of new onset diabetes mellitus, no children treated for hyperglycemia, and no adverse event withdrawals due to abnormalities in glucose tolerance. In Study 2, after treatment with either dose of Norditropin® for 2 years, there were no children with consecutive fasting blood glucose levels between 100 and 126 mg/dL, or with fasting blood glucose levels > 126 mg/dL. Furthermore, mean hemoglobin A_{1c} levels tended to decrease during long-term treatment in Study 1, and remained normal in Study 2. However, in Study 1, 4 children treated with 0.067 mg/kg/day of Norditropin® and 2 children treated with 0.033 mg/kg/day of Norditropin® shifted from normal fasting blood glucose levels at baseline to increased levels after 1 year of treatment (100 to 126 mg/dL or > 126 mg/dL). In addition, small increases in mean fasting blood glucose and insulin levels (within the normal reference range) after 1 and 2 years of Norditropin® treatment appeared to be dose-dependent [see *Warnings and Precautions and Adverse Reactions*]. In both Study 1 and Study 2, there was no acceleration of bone maturation. A dose-dependent increase in mean serum IGF-I SDS levels within the reference

range (but including a substantial number of children with serum IGF-1 SDS > +2) was observed after both long-term (Study 1) and short-term (Study 2) Norditropin® treatment. *Clinical Trials in Adult GHD Patients:* Adverse events with an incidence of ≥5% occurring in patients with AO GHD during the 6 month placebo-controlled portion of the largest of the six adult GHD Norditropin® trials are presented in Table 1. Peripheral edema, other types of edema, arthralgia, myalgia, and paraesthesia were common in the Norditropin-treated patients, and reported much more frequently than in the placebo group. These types of adverse events are thought to be related to the fluid accumulating effects of somatropin. In general, these adverse events were mild and transient in nature. During the placebo-controlled portion of this study, approximately 5% of patients without preexisting diabetes mellitus treated with Norditropin® were diagnosed with overt type 2 diabetes mellitus compared with none in the placebo group [see *Warnings and Precautions and Adverse Reactions*]. Anti-GH antibodies were not detected. Of note, the doses of Norditropin® employed during this study (completed in the mid 1990s) were substantially larger than those currently recommended by the Growth Hormone Research Society, and, more than likely, resulted in a greater than expected incidence of fluid retention- and glucose intolerance-related adverse events. A similar incidence and pattern of adverse events were observed during the other three placebo-controlled AO GHD trials and during the two placebo-controlled CO GHD trials.

Table 1 – Adverse Reactions with ≥5% Overall Incidence in Adult Onset Growth Hormone Deficient Patients Treated with Norditropin® During a Six Month Placebo-Controlled Clinical Trial

Adverse Reactions	Norditropin® (N=53)		Placebo (N=52)	
	n	%	n	%
Peripheral Edema	22	42	4	8
Edema	13	25	0	0
Arthralgia	10	19	8	15
Leg Edema	8	15	2	4
Myalgia	8	15	4	8
Infection (non-viral)	7	13	4	8
Paraesthesia	6	11	3	6
Skeletal Pain	6	11	1	2
Headache	5	9	3	6
Bronchitis	5	9	0	0
Flu-like symptoms	4	8	2	4
Hypertension	4	8	1	2
Gastroenteritis	4	8	4	8
Other Non-Classifiable Disorders (excludes accidental injury)	4	8	3	6
Increased sweating	4	8	1	2
Glucose tolerance abnormal	3	6	1	2
Laryngitis	3	6	3	6

The adverse event pattern observed during the open label phase of the study was similar to the one presented above. **Post-Marketing Experience** Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The adverse events reported during post-marketing surveillance do not differ from those listed/discussed above in children and adults. Leukemia has been reported in a small number of GH deficient children treated with somatropin, somatrem (methionylated rhGH) and GH of pituitary origin. It is uncertain whether these cases of leukemia are related to GH therapy, the pathology of GHD itself, or other associated treatments such as radiation therapy. On the basis of current evidence, experts have not been able to conclude that GH therapy *per se* was responsible for these cases of leukemia. The risk for children with GHD, if any, remains to be established [see *Contraindications and Warnings and Precautions*]. Pancreatitis: cases of pancreatitis have been reported rarely in children and adults receiving somatropin treatment, with some evidence supporting a greater risk in children compared with adults. Published literature indicates that girls who have Turner syndrome may be at greater risk than other somatropin-treated children. Pancreatitis should be considered in any somatropin-treated patient, especially a child, who develops abdominal pain [see *Warnings and Precautions*]. The following additional adverse reactions have been observed during the appropriate use of somatropin: headaches (children and adults), gynecomastia (children), and pancreatitis (children).

OVERDOSAGE: *Short-Term:* Short-term overdosage could lead initially to hypoglycemia and subsequently to hyperglycemia. Furthermore, overdose with somatropin is likely to cause fluid retention. *Long-Term:* Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone.

More detailed information is available upon request.
For information contact: Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540, USA, 1-888-NOVO-444 (1-888-668-6444)
Date of Issue: December 7, 2010
Version: 13
Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark
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327 incident cases of angiography-proven CHD, which were diagnosed when the subjects were aged 25-45 years. After the data were adjusted to account for potential confounders such as subject age, presence or absence of a family history of CHD, blood pressure, physical activity level, smoking status, and lipid profile, elevated adolescent body mass index was a significant predictor of CHD across the entire BMI range, reported Dr. Tirosh and his colleagues..

The nearly 4,000 subjects whose body mass index was in the 90th percentile and above had a hazard ratio of 6.85 for developing CHD, compared with those

‘Our study may help to redefine what constitutes a “normal” or “healthy” BMI in adolescence and to highlight the role of elevated BMI at different ages in the pathogenesis’ of diseases.

subjects who were in the 10th percentile and below.

The excess CHD risk was present even at BMIs that are “well within the range currently considered to be normal,” rising 12% for every 1-unit increment in BMI, Dr. Tirosh and his associates reported.

“Our study may help to redefine what constitutes a ‘normal’ or ‘healthy’ BMI in adolescence and to highlight the role of elevated BMI at different ages in the pathogenesis of different diseases,” the researchers said.

In contrast to CHD risk, the risk of type 2 diabetes did not correlate with adolescent body mass index once the data were adjusted to account for potential confounders.

Diabetes was more influenced by recent BMI and weight gain, “suggesting that BMI in adolescence has a more reversible or shorter term effect on the risk of diabetes as compared with its effect on the risk of CHD,” they reported.

“Our results might be explained by the fact that diabetes represents a more functional pathomechanism than CHD, which relies on anatomical changes (atherosclerosis),” Dr. Tirosh and his colleagues said.

Because the study involved only young Israeli military men, the findings may not be generalizable to other patient populations, they added. ■



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