

Letter to the Editor

Caucasian or White Phenotype?

The term Caucasian is frequently employed to describe a white individual. Caucasian is used as a synonym for a group of people that share the common character of whiteness. It is frequently used by distinguished researchers when they analyze the differences between various ethnic groups in relation to a phenomenon they have studied. According to the definitions given by *The American Heritage Dictionary of the English Language*, "Caucasus or Caucasia is a region between the Black and Caspian seas that includes Russia, Georgia, Azerbaijan, and Armenia." Caucasian relates to the Caucasus region or its peoples, languages or cultures. It also refers to a major human racial division traditionally distinguished by physical characteristics such as very light to brown skin pigmentation and straight to wavy or curly hair, and including peoples indigenous to Europe, Northern Africa, Western Asia, and India. Thus there are dark and curly haired Caucasians, as there could be very white, light-eyed Latinos or very light to dark skin in other groups. I believe that what scientists who use the term Caucasian are trying to say is that the term refers to a Caucasian, especially of Nordic type or, at least, as defined by the dictionary, "White: A member of a racial group of people having light skin coloration, especially one of European origin." If so, why abandon the term white?

The term Caucasian may intend to reduce a great number of phenotypes into a group that shares other characteristics as well. In a superb, well documented article the significance of the term phenotype is discussed.¹ The current definition of phenotype is: "the complete observable characteristics of an organism or group, including anatomic, physiological,

biochemical, and behavioral traits, as determined by the interaction of both genetic makeup and environmental factors." One realizes that an external character cannot imply, by itself, a necessary similarity between two or more individuals or groups. As the authors state, "The interaction of genes and the environment has the potential to produce a myriad of phenotypes." For example, is it not true that among the Caucasian population in the world there are those who differ greatly in skin hues, ethnicity, and genetic factors? On the other hand a white skinned, light-eyed Latino (or Hispanic as the US Census classifies) may have the appearance, genetic background, behavioral traits, and environmental influences of a Caucasian. If it is melanin that determines the grouping, why not just use the term white?

Cesar Chavarria, MD
Mexico City, Mexico

Reference

1. Catalano PM, Thomas A, Huston-Presley L, Amini SB. *Diabetes Care*. 2007;Supplement 2:156-60.

Editor's Response: *Dr. Chavarria makes a good case to cease using the term Caucasian in describing white patients. The AMA Manual of Style states, "Racial categories should not be used automatically. Authors should explain and justify racial designators. Caucasian is occasionally used to indicate white but is technically specific for people from Caucasus region and thus should be avoided." For several years GGH has used the term white. Unfortunately, the classification of Hispanic and Latino is far more complicated and controversial.*

Fima Lifshitz, MD

REVIEWS & COMMENTS FROM THE LITERATURE

Dosing of Growth Hormone Therapy According to IGF Levels

Cohen and colleagues conducted a 2-year, open-label, randomized, insulin-like growth factor (IGF)-I concentration-controlled trial, administering varying doses of growth hormone (GH) to test whether IGF-I levels achieved during GH therapy are determinants of the growth responses to GH treatment. The 172 subjects (77% male) were pre-pubertal children (mean age 7.53 years) with short stature (mean height SDS -2.64, mean IGF-I SDS -3.56). Subjects were randomized to receive GH treatment following one of 3 regimens: (1)

conventional GH dosing based on the patient's weight (40 mcg/kg/d, n=34); (2) regularly adjusted GH doses to achieve an IGF-I SDS of -0.5 to +0.5 (IGF_(low) group, n=70) or; (3) regularly adjusted GH doses to achieve an IGF-I SDS of +1.5 to +2.5 (IGF_(high) group, n=68). Groups did not differ significantly on demographic or baseline variables such as height, IGF-I levels, peak GH, or bone age.

Baseline data collected included concomitant illness and medications, physical examination, funduscopy, height, weight, determination of IGF-I, pubertal staging,

checks for scoliosis and slipped capital femoral epiphysis (SCFE), blood sampling, and urinalysis. Study visits occurred at months 0, 1, 3, and every 3 months thereafter until 2 years. Adverse event reporting, height, weight, IGF-I, funduscopy, vital signs, and physical examinations for scoliosis and SCFE were conducted at all repeat visits. Laboratory evaluations performed at baseline were repeated annually, and bone age x-rays were obtained at baseline and year 2. Analysis of covariance was used to test for treatment effects, using baseline height-SDS (HT-SDS) as a covariate. Of the 172 enrolled participants, 147 completed the study. An intent-to-treat statistical analysis was performed including all randomized patients who received GH and at least one post-baseline height and IGF-I assessment.

Dosage and Growth. All 3 treatment groups demonstrated increased HT-SDS scores at the end of the study (median of 24 months), with the IGF_(high) group showing the greatest increase (1.58 SDS) compared with the IGF_(low) group (1.08 SDS) and the conventional dosing group (1.00 SDS). Annualized growth velocities for the IGF_(low), IGF_(high), and conventional groups were 9.71, 11.20, and 9.01 cm/year at 12 months, and 8.38, 10.03, and 8.16 cm/year at 24 months, respectively. Mean IGF-I SDS showed a rapid increase in all 3 groups during the first month after initiation of GH treatment; the target IGF-I values were generally reached within 6 to 9 months. The IGF_(high) group had a target IGF-I SDS value of 2.0 (1.5–2.5) and the IGF_(low) 0 (–0.5 to 0.5). IGF-I SDS values for the IGF_(high) group were significantly higher than for the IGF_(low) and the conventional groups from 6 months onward; no differences were found between mean IGF-I SDS for IGF_(low) and conventional groups. Mean daily GH doses for the 3 treatment groups were 110 (median 98, range 20 to 346) mcg/kg/day for the IGF_(high) group, 33 (median 28, range 9 to 114) mcg/kg/d for the IGF_(low) group, and 41 (median 41, range 34 to 45) mcg/kg/day for the weight-based GH dosing comparison group. The IGF_(high) group received a substantially larger mean GH dose than the other 2 groups, but no significant differences in the mean dose between the IGF_(low) group and the comparison group were found. For all participants, the change in HT-SDS from baseline was positively correlated with both the IGF-I SDS change from baseline and with the cumulative GH dose. Multivariate analysis revealed that height outcome was significantly related to treatment group (accounting for 42% of the variance), inversely related to baseline peak GH level (39%), and inversely related to baseline IGF-I SDS (15%).

Safety. Over the 2-years, treatment-emergent adverse events were reported in 95.7% of participants in the IGF_(low) group, 86.6% of patients in the IGF_(high) group, and 82.4% in the conventional treatment group; most commonly, upper respiratory tract infection, headache, fever, coughing, and injection site hematomas. There was no occurrence of intracranial hypertension or malignancy. There was one case of SCFE in the IGF_(high) group and 11 cases of

worsening scoliosis (3 in the conventional, 4 in the IGF_(low) group, and 4 in the IGF_(high) group). Change in fasting serum insulin levels from baseline in the IGF_(high) group was significantly greater than in the other groups, although mean serum insulin remained within the normal range for all groups. Bone age was delayed by approximately 2 years in all 3 groups at baseline, and after 2 years of treatment, bone age showed an increase of 2.45 to 2.82 years with no differences identified among the 3 groups.

The authors concluded that the IGF_(high) group, titrated to the upper portion of the normal range, demonstrated significantly greater height gains than the IGF_(low) and conventional groups. Expressed in height benefit, the IGF_(high) group gained approximately 3 cm more in height than the comparison groups after 24 months of GH treatment. The study lacked sufficient power to detect the safety of IGF-based dosing in terms of rare side effects. No information regarding the long-term safety of such a regimen, especially in terms of cancer risk, was provided.

Cohen P, Rogol AD, Howard CP, Bright GM, Kappelgaard AM, Rosenfeld RG; American Norditropin Study Group. IGF-based dosing of growth hormone therapy in children. *J Clin Endocrinol Metab.* 2007;92:2480-6.

Editor's Comment: *This study provides evidence for the feasibility of IGF-based GH dose titration; however, the increased height gains compared to the conventional treatment dosing were only significant for the IGF_(high) group. The authors were circumspect by restricting interpretation of the findings to a demonstration of the feasibility of IGF-I GH dose titration and not as a recommendation for clinical practice. Important considerations to explore before implementing such a strategy in regular practice include: (1) GH doses administered to this group were as high as 346 mcg/kg/day (mean 110), compared to the mean conventional weight-based dose of 41 mcg/kg/day; this represents as high as a 9-fold increase compared to previously studied values; (2) given the lack of safety data beyond the length of 2-year study, movement toward increasing GH above the conventional dosing should be discouraged. An editorial by Baron accompanying this paper stressed that the principle of primum non nocere dictates that weight-based dosing remain the standard of care.¹*

Although there is a dearth of information to inform us about the possible negative side effects that may be associated with prolonged treatment with high doses of GH, there is certainly a theoretical basis for concern. A growing body of epidemiological data suggests that high levels of circulating IGF-I constitute a risk factor for the development of breast, prostate, colon, and lung cancer.² This study by Cohen and colleagues demonstrated a height gain of 3 cm for the IGF_(high) group compared to the IGF_(low) and conventional weight-based dosing groups. Even if the substantial excess cost of the additional GH administration of higher dosages is not considered, does the potential (not guarantee) for taller adult height justify potentially increasing a child's risk of developing cancer?

Baron reminds the reader that "risk must be weighed against benefit" and states that "although short stature may be quite unpleasant for some individuals and carry social disadvantages, it generally does not cause death, serious physical dysfunction, or probably even serious psychological dysfunction."¹ This opinion is grounded in empirical evidence.³

Baron also encourages careful evaluation of the etiology of short stature before prescribing a costly and invasive procedure to which greater than 80% of children experienced some adverse side effects. Although Cohen et al used GH therapy in children with GH deficiency as well as in children with other categories of non-GH deficient short stature, the situation may be more complex and different among the various types of patients. As an example, it is well known that decreased IGF-I levels reflect nutritional status, not necessarily GH deficits,⁴ yet no attempts were made to distinguish patients who

may have had nutritional growth retardation, nor were the body weights of the patients defined. It has been shown that a subgroup of children with idiopathic short stature show decreased weight for height,⁵ which is not typical of GH deficiency, suggesting their decreased growth and IGF-I may reflect insufficient nutrition. In such cases, lifestyle and dietary changes would be a more expedient, safer, and cost-effective treatment for the child.⁶

David E. Sandberg, PhD

References

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2. Le Roith D, Roberts CT. *Cancer Lett.* 2003;195:127-37.
3. Sandberg DE, Colsman M. *Horm Res.* 2005;63:275-83.
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IGFs and Cytokines in Celiac Disease

The interesting study reported in this paper is the result of one of the few productive collaborations between pediatric endocrinologists and their gastroenterologist colleagues. This endocrine group from Parma, Italy has already published papers on the interaction of the cytokine and insulin-like growth factor (IGF) systems in Crohn's disease and cystic fibrosis. Growth failure is a well known feature of childhood celiac disease, however the precise mechanisms are not established and the possible influences of pro-inflammatory cytokines have not been well explored. The patients studied had "atypical" celiac disease, ie, they presented after the classical period of infancy. These patients were not extremely short at diagnosis but BMI SDS was decreased and both height and BMI increased significantly after treatment with a gluten-free diet.

Baseline values of IGF-I were reduced compared to controls ($P < 0.05$) and interleukin (IL)-6 and tumor-necrosis factor (TNF)- α values were significantly elevated. IGF binding protein (IGFBP)-2 acts as an acute phase protein and, as reported in inflammatory bowel disease and childhood malignancy, values were elevated in affected subjects compared to controls. On treatment with a gluten-free diet, IGF-I and IGFBP-3 normalized and IL-6

and TNF- α decreased significantly. This study provides indirect evidence that cytokines may be involved in the abnormalities in the IGF system and when mucosal inflammation is suppressed, as occurs with treatment of celiac disease, and leads to the increases of IGFs and IGFBP-3 which facilitate normalization of linear growth.

Street ME, Volta C, Ziveri MA, et al. Changes and relationships of IGFS and IGFBPS and cytokines in coeliac disease at diagnosis and on gluten-free diet. *Clin Endocrinol (Oxf).* 2008;68:22-8.

Editor's Comment: *The celiac disease debate remains as to whether it is improvement in nutrition or suppression of inflammation which drives the recovery of growth. Both factors probably contribute, however as shown in Crohn's disease,¹ suppression of inflammation can independently result in increase of serum IGF-I, therefore the contribution of active inflammation may be subtle, but should not be discounted.*

Martin O. Savage, MD

Reference

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Aortic Dilatation and Dissection in Turner Syndrome

The cardiovascular phenotype in Turner syndrome (TS) is largely defined on clinical signs such as aortic valve abnormalities and aortic coarctation. Investigation in asymptomatic patients has revealed a far more complex phenotype. Combined echocardiography and MRI have shown that up to 75% of adult women with TS have significant cardiovascular abnormalities. In parallel there have been reports of a high rate of aortic dissection in

TS and dilation of ascending aorta could be among predisposing factors. It is still unknown whether aortic dilatation precedes dissection in these patients and what specific diameter predicts impending deterioration.

The purpose of this study by Matura et al was to reliably identify girls and women at risk for such acute aortic events. This study included 166 adult volunteers with TS, aged more than 18 years, who