Short Commentary

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Clinical Implications of a Novel Biomarker of Growth

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Description

Growth is a complicated phenomenon that begins in utero and is completed after puberty. Growth is regulated by numerous factors including nutrition, which dominates prenatally through age 2 years, endocrine modulators such as thyroid hormone, Growth Hormone (GH), insulin-like growth factor-1 and sex steroids, and other genes that regulate growth, including direct effects on the growth plate. Normal growth is a global indicator of child health, and variants of growth can be normal or pathologic. Environmental causes of poor growth include malnutrition, social determinants of health, and severe psychological stress. Primary causes include genetic diseases and syndromes. Acquired causes are common, including chronic disease, late effects of cancer treatment and endocrine dysfunction. Growth concerns including growth failure (abnormal growth rate) and short stature (<3rd%ile for age/gender) comprise about 20% of all referrals to paediatric endocrinologists. Clinical evaluation may reveal a primary cause (e.g., familial short stature), an acquired cause (e.g., hypothyroidism) or constitutional delay of growth and puberty, which is a normal variant and a common reason for referral [1].

Our best tool for assessing growth is a child's height and growth velocity, both of which require serial measurements of height from birth until after puberty. However, in a slow-growing child, determining an accurate growth rate requires height measurements at least 6 months apart. Screening all slowly growing or short children for pathologic causes is costly and has a very low positive predictive value. A "real time" biomarker of growth that could identify normal variants from pathologic disorders and indicate response to a growth-promoting treatment would be an ideal clinical tool. This biomarker may have been found. A recent study by Coghlan and colleagues describes data supporting the potential use of collagen X biomarker (CXM) as a real time marker of growth [2]. CXM is a degradation by-product of type X collagen that is produced by hypertrophic chondrocytes during endochondral ossification, which in children occurs almost exclusively at growth plates. It is released into the circulation in proportion to overall growth plate activity and can be measured in blood. The authors' original study [3] revealed that CXM concentrations plotted vs. age displayed a pattern similar to established height velocity (HV) curves, suggesting a relationship between CXM and HV. The goals of the follow-up study were to confirm initial observations supporting the utility of CXM as a HV biomarker in a larger number of subjects and establish reference ranges.

CXM was assessed in 302 normally growing children with no known risk factors for impaired growth and 10 healthy adults yielding a total of 961 CXM measurements. With these samples, the CXM assay was optimized. Based on 432 measurements plotted by age, sex-specific reference ranges were generated. Cross-sectional CXM data with percentile curves for each sex were plotted in a scatterplot by age and then superimposed on established HV curves [4], revealing remarkable similarity between peak HV during and after puberty in girls and boys. Additionally, there was strong correlation between blood CXM levels and HV (Pearson's r=0.80) based on serial measurements from 110 participants. The data also showed that CXM values in girls peaked at breast Tanner stage III, corresponding to the timing of the pubertal growth spurt as well as being statistically different from girls at all other Tanner stages ($p<0.05$). This association was not found in pubertal boys; however, we suspect this is attributable to the small sample size.

These results support the conclusion that CXM is indeed a biomarker of growth and provide a foundation for reference ranges. The authors acknowledge that while these data were from an expanded data set compared to their original study, the reference ranges are based on a small number of children.

Additional CXM samples are needed in growing children of all ages to establish definitive norms, especially normally growing males to delineate CXM values by Tanner staging. A larger number of serial samples of CXM plotted against observed HV are necessary to strengthen the correlation between CXM and observed HV, delineate the time period over which CXM reflects "real-time" HV, and establish to what degree single vs. serial CXM levels predict growth velocity, especially during times of slowing growth before puberty and increased growth during puberty.

CXM has the potential to significantly improve our ability to evaluate growth in children with short stature. While newer consensus statements suggest laboratory tests should be guided by clinical features rather than routinely applied to all patients with short stature [5], the standard approach and previous consensus statements recommend routine laboratory screening for occult disease in asymptomatic short children. However, this is costly (>$300,000) with very low yield [1]. If a one-time CXM measurement could be used to differentiate healthy normally-growing short children (e.g., constitutional delay and familial short stature) from those with intrinsic or acquired growth disorders, it could save significant costs by avoiding unnecessary screening evaluations, serial height measurements over many months, and decrease referrals to pediatric endocrinologists for normal variants of growth.

The clinical implications of a growth biomarker would also improve our ability to monitor treatment with growth promoting agents such as GH. How CXM values differ in patients with GH deficiency, treated or untreated, compared to normally growing children or children with constitutional delay are still to be determined. The treatment of classic GH deficiency is well established; however significant controversies exist regarding the expanded and increased use of recombinant GH in children with idiopathic short stature such as whom to treat, how to monitor growth response and cost vs. benefit of height gained [6-8]. If accurate CXM reference ranges are established, then CXM could be used to better monitor response to GH therapy and avoid unnecessary treatment in those patients with poor responses.

While there is still a need for further investigation, this compelling study suggests that CXM is a biomarker for growth and has the potential to become a valuable tool in the clinical setting, both in the diagnosis of growth disorders and in response to treatment.

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