DIAGNOSIS OF ENDOCRINE DISEASE

On the need for national-, racial-, or ethnic-specific standards for the assessment of bone maturation

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Abstract

In an attempt to overcome ethnic and racial differences in skeletal maturation, the use of ethnic-specific standards has been suggested. Do we need such standards? Based on a fundamental understanding of phenotypic plasticity and an individual's ability to respond to environmental cues, the author argues that we do not need ethnic-specific standards for bone maturity. I suggest that we use a unified international standard of bone maturity for comparing the health, nutrition, and quality of life of all children, regardless of their race, nationality, and ethnicity.

Introduction

In the dialectics of human anthropometry, bone maturity or 'bone age,' which is usually assessed from hand and wrist radiographs, is considered to be a measure of a child's biological maturity. Pediatricians and endocrinologists use bone maturity for diagnosing disease and height prediction and for recommending the types of physical activity and the timing of orthodontic and orthopedic procedures. Although bone maturity can be assessed by various methods, all methods compare the maturity of hand and wrist bones to a known standard and then average or summarize the maturity scores of several bones before the designation of the bone age.

The two most commonly used methods for assessing bone maturity are the Greulich and Pyle (G&P) and the Tanner and Whitehouse (TW3) standards of bone maturity. Both methods rely on a standard that disregards the child's race, ethnicity, nationality, and geography. In the USA, the most commonly used standard is that which was developed by Greulich and Pyle and was derived from data that were obtained from white children of the upper socioeconomic class in 1931–1942 (1). The most commonly used standard in Europe is the TW3 bone age score, which is based on data that were obtained from children from the UK and Belgian, Spanish, Japanese, Italian, Argentinian, and European-American children (2, 3). In an attempt to overcome ethnic and racial differences in skeletal maturation, standards have been developed for the German, Turkish, East African, and Jamaican populations (4, 5, 6, 7), and the development and use of ethnic-specific standards has been suggested. It was assumed that race-specific bone age tables would improve the accuracy of diagnoses and account for pubertal delay. Do we need such standards?

To determine whether the G&P standard can still be applied to American children of diverse ethnicity in 1996, Ontell *et al*. (8) found that bone maturity in Asian and Caucasian American girls approximated chronologic age

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Table 1 Mean differences between chronological age and bone age by sex, age groups, and study groups. (This is a selective review of data from various races and ethnic groups. For a more comprehensive review, see Tanner *et al*. (3).

Country/Ethnicity	Gender	Early childhood	Middle childhood	Late childhood	Adolescence	Reference
USA						Ontell *et al*. (8)
White	Girls	−0.039	−0.037	0.084	0.330*	
	Boys	−0.317*	−0.533*	−0.669*	0.152	
Black	Girls	0.397*	0.000	0.846*	0.800*	
	Boys	0.055	−0.341	0.374	0.413*	
Asian	Girls	0.143	−0.074	0.334	0.52	
	Boys	−0.347	−1.233*	−0.397	0.788*	
Hispanic	Girls	−0.144	0.482*	0.57	0.739*	
	Boys	−0.399*	−0.497	−0.229	0.956*	
Israel	Girls	−0.090	−0.057	−0.005	−0.099	Soudack *et al*. (13)
	Boys	0.193*	0.451*	0.312*	−0.247*	
India	Girls			−1.61		Kumar *et al*. (12) underweight
	Boys			−1.05		
Korea						Kim *et al*. (34)
By G&P	Girls		0.303	0.108		
	Boys		−0.600*	−0.183		
By TW3	Girls		0.15	−0.005		
	Boys		0.172	0.704*		
Peru						Pawson *et al*. (15) altitude
Nunoa	Girls			−1.65	−1.05	
	Boys			−1.2	−1.15	
Tintaya	Girls			−0.7	−0.37	
	Boys			−0.6	−0.1	
Marquiri	Girls			−0.6	−0.8	
	Boys			−1.2	−0.4	

*$P < 0.05$ for *t*-test correlating the chronological age against bone age. Significance has not been calculated for the Indian and Peruvian studies. In girls, early childhood was defined as 0 to 3 years 10 months; middle childhood: 3 years 11 months to 8 years 4 months; late childhood: 8 years 5 months to 13 years 3 months; and adolescence: 13 years 4 months; to 18 years. In boys, early childhood was defined as 0 to 3 years 9 months; middle childhood: 3 years 10 months to 7 years 6 months; late childhood: 7 years 5 months to 13 years 3 months; and adolescence: 13 years 4 months to 18 years, as defined by Ontell *et al*. (8). Negative values indicate that the child's bone age trails the child's chronologic age. In the Korean study, the bone maturation films were read by both the Greulich-Pyle (G&P) and the Tanner-Whitehouse (TW3) methods.

throughout childhood (Table 1). The only significant discrepancy that they found was in Caucasian adolescent girls, whose bone maturity exceeded their chronologic age by ∼4 months (8). This 4-month difference between the chronological age and the bone age is less than the normal distribution of bone age (1).

Almost 20 years later, Cole *et al*. examined ethnic differences in the pattern of skeletal maturation in South African adolescents using a novel longitudinal analysis technique, superimposition by Translation and Rotation (SITAR) (9). No ethnic differences were found in the pattern or timing of skeletal maturity in the girls, while skeletal maturity in white boys was reached 7 months earlier than black boys. They concluded that the delayed maturity of black boys, but not black girls, implied that black boys are more sensitive to environmental factors than black girls. Because these sex and race differences imply the existence of environmental constraints, we should be using unified standards of bone maturation in the clinical analysis of a given patient.

Human variation is mostly adaptive

The ability of the genotype to produce different phenotypes in response to different environments is termed 'adaptive plasticity.' Developmental plasticity is maximal in the fetus and progressively declines from fetal life to adolescence (10).

Early life nutrition and stress are among the best documented examples of environmental cues that can influence phenotypic plasticity, and the secular trends in child growth and puberty are dazzling examples of adaptive plasticity (11). European men are now 13 cm taller than they were 150 years ago, and this increase is ∼50% of the variation in the stature height of contemporary men (10). This increase in height over approximately six generations is not long enough to be the result of changes in the DNA sequence. Over the same six generations, the age of menarche in most western industrialized countries has decreased by 4 years. As a consequence of constantly changing life conditions and

environment, today's children in different countries and societies exhibit a continuum from being very short to very tall, adapt their body composition and energy metabolism, and modulate their bone maturation, longevity, and other quantitative traits.

In a 1996 study of bone maturity in US children of diverse ethnicity, the differences between bone age and chronologic age were calculated (Table 1) (8). Asian and white girls did not differ much, and the average difference was smaller than 4 months. In black girls, bone age exceeded mostly chronologic age, and in Hispanic girls, bone age exceeded chronologic age only during adolescence. Preadolescent Asian boys showed significant delays in bone age, particularly in middle childhood, when bone age lagged behind chronologic age by nearly 15 months. Children from Israel in 2013 and or from Korea in 2015 (12) with similar economies show remarkably similar results to those of white Americans (13), whereas undernourished Indian children show a much-retarded bone maturity (14).

The bone maturation of children living in high-altitude communities associated with an active copper mine in southern Peru showed strong association with the altitude and nutrition (Table 1) (15). In the Tintaya community, nutritional and health conditions were believed to be relatively favorable as a result of the substantial mine-related infrastructure that had developed. Almost 60% of the children were born at an altitude of over 3000 m, and about 50% were defined as malnourished. In contrast, the Marquiri community has minimal infrastructure and limited part-time labor at the mine; 82% of the children were born at an altitude of over 3000 m, and 70% were considered malnourished. In all these parameters, the Nuñoa were worst off, and their children were significantly shorter than the other two communities. There were significant differences between the three communities, with those in the mining community exhibiting significantly smaller differences between bone maturity and chronological age (Table 1).

Multiple studies show how the effect of emigration overshadows racial differences. Asian refugee children, who emigrated to the USA under 5 years of age, showed a progressive and significant decline in the prevalence of low height-for-age and low weight-for-age, while those nutritional indices remained stable for low-income white children and black children. By 1993, the growth status of Asian refugee children was comparable with that of other ethnic groups (16).

Growth and maturation are the foremost measures of health, nutritional status, and quality of life of an individual child but are also used as measures of the health-related quality of life of an entire population. The use of national-, ethnic-, or racial-specific charts of growth and maturation would abrogate the use of growth and bone maturity measures as part of the assessment of the health-related quality of life in children.

Race and ethnicity

Humans come in many different sizes, shapes, and colors, and different forms of eyes, hair, nose, and lips. These differences are immediately apparent, and thus some people assume they must be highly significant genetically. Yet, race and ethnicity are but two descriptions of human subjects and are mostly historical and not biological. These two descriptive terms are typically used in a mechanical and uncritical manner as a proxy for unmeasured biological, socioeconomic, and/or sociocultural factors (17). Physiological traits, the rates of morbidity and mortality from particular diseases, growth, and maturation are not uniformly distributed among socially defined racial and ethnic groups throughout the world (18).

The genetic variation among humans, which is continuous, complexly structured, constantly changing, and predominantly within races, cannot be fully explained by race and ethnicity. Trait variations, which are usually based on social, familial, and environmental differences, are much greater within races than between races (19, 20). Both historical evidence and the results of contemporary genetic research suggest that 'racial profiling' in medicine can lead to serious medical errors; morbidity and death from particular diseases are not uniformly distributed among socially defined racial and ethnic groups (21). To monitor physical and health inequalities, we need to keep health records that include a description of the ethno–racial category. Descriptive statistics, which were derived from population surveys and used racial definitions that were based on self-identity, are not biological or attributive categories that are appropriate for an individual's medical assessment (21).

How should physicians treat individuals who present with a perceived race, but do not display the average characteristics of a studied population? Racial categories, with their shifting meanings and culturally determined parameters, have always shaped medical practice and thinking, and debates about their use in epidemiology and public health have been vigorous. No standard definition of race exists in medical, epidemiological, or health services research (22). The assumption that race reflects

an 'underlying genetic homogeneity' has been now replaced by the term 'shared social experience' (17). Racial categories originally suggested a scale of inferiority and superiority; today such groupings continue to imply notions of human hierarchy (21). The use of the terms African, Chinese, or Swedish origin to describe an individual does not sufficiently capture the complexity of human history, migrations, artificial boundaries, and genetic drift to be of much scientific or medical use. In an era of individually tailored treatment, race and ethnicity should not be used to medically define a patient.

The case of African Americans

African American children are a special case study with respect to body growth and composition. On average, puberty and skeletal maturation of African American children occurs earlier and their BMI is higher than those of Caucasian children (23). However, the variation within each of these groups is greater than the racial difference. In a US study, investigators confirmed that skeletal age in African Americans was more advanced than that of Caucasian Americans and that the advancement in skeletal maturation was due to the greater BMI of African Americans (24). After correction for lean body mass and either BMI, BMI SDS, or dual X-ray absorptiometry (DXA) fat mass, the difference between bone age and chronological age (BA – CA) and the ratio of bone age to chronological age (BA/CA) of African American and Caucasian children were no longer significantly different (24).

The skeletal microarchitecture of African Americans and their children is denser than that of Caucasian Americans and their children (25, 26), and this increase in density is also correlated with their greater BMI. A unified standard for skeletal maturity allows for that conclusion, which would have been missed if a race-specific standard of bone maturity were used.

Based on such arguments, the Center for Disease Control and Prevention (CDC) promotes one set of growth charts for all US racial and ethnic groups. Racial- and ethnic-specific standards of bone maturity are not recommended because the results of studies support the premise that differences in growth among various racial and ethnic groups are due to environmental factors and genetic differences between children (27).

The WHO growth charts

Many countries have developed their own growth charts to describe the national, racial, and ethnic distribution of its child population. For example, the racial and ethnic distribution of the reference population in the US CDC growth charts for the USA is representative of the US population at the time when the National Household Education Survey (NHES) and National Health and Nutrition Examination Survey (NHANES) were conducted. However, the US CDC's growth charts and the growth charts of most other countries rely on data that were collected from children who live in urban zones, and the validity of these data for children who live in rural zones has not been addressed. The growth and maturation of children who live in rural zones is different than those of children who live in urban zones, and this difference is very exaggerated in children who live in developing countries (28). That does not mean that urban or rural, privileged or underprivileged, this or another ethnic group require their own reference. Many of them will change their living places and conditions. Rather, I claim that children grow very differently due to their living conditions; the same growth standards are recommended for them precisely because the difference is down to plasticity in relation to the environment, not genetics.

In developing its international growth charts, the WHO working group has used a similar rationale (29). It recommended an approach that described how children should grow when they are healthy and well provided (the standard) rather than describing how children grow in their current milieu (the reference) (30). Their main finding was that 'child populations grow similarly across the world's major regions when their needs for health and care are met.' Greulich and Pyle designed their Atlas project in a similar way by selecting white children from the upper socioeconomic classes (1).

Conclusions

Environments change continuously, and we adapt our phenotype to the prevailing environment, even when the environmental changes are disruptive or even catastrophic. Adaptive plasticity has enabled individuals and societies around the globe to respond to environmental changes to survive and reproduce and may manifest itself as a continuous variation in traits (31). Adaptive responses override the 'canalization of development' (32) and the inheritance of acquired characteristics. The notion that genes are the primary determinants of physiognomy, which also includes growth-related traits, has been repeatedly disproved. Based on a fundamental understanding of phenotypic plasticity and an individual's

ability to respond to environmental cues, we do not need ethnic-specific standards for bone maturity.

Clinicians are aware of the multitude controllers of bone maturation (33). Maturation is delayed in children with constitutional delay of growth, malnutrition, chronic illness, high altitudes, and hormonal deficiencies. Often, several of these occur in the same child, and the clinician contemplates the combination. It is therefore still important to gather data on how and why the maturation rate varies and how this varies between populations. The potential implication for the diagnosis of using a single reference dataset, in which the whole population differs significantly from that reference, is part of that clinical contemplation.

What we need is an international standard for assessing bone maturity. The current gold standards for assessing bone maturity—the G&P Atlas and the TW3 tables—are globally used to assess the bone maturity of children of different nationalities, races, and ethnicities. The appropriateness of these two methods explicitly needs testing as a priority, and new standards need to be developed if these data are found to be inadequate. Until a unified standard is developed and accepted, these two methods should remain the international standard for comparing the health, nutrition, and quality of life of children.

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