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Historical Approaches to Human Growth Studies Limit the Present Understanding of Growth Biology

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Growth trajectory · Length increment · Weight gain

Abstract
Background/Aims: Measurements of children's size have (1) provided a biosensor of health and well-being in their environment; (2) provided references for clinical assessment, and (3) informed public health efforts to ameliorate living conditions. Size-for-age measurements offer no information about the growth trajectories by which children achieve size, and growth trajectories offer no information on proximal mechanisms underlying growth biology. Increasing attention to the biological processes themselves, only estimated by anthropometric parameters and statistically based growth proxies, is needed. ***Methods:*** A literature overview of human growth measurement interpretations. ***Results:*** Aspects of study design, analysis and reliance on common conventions contribute to limitations in growth biology knowledge. Examples include conflating both the concepts of size and growth and incremental gains in either weight or length as manifestations of growth; nonuniformity in the use of growth trajectory-derived clinical categories, and conventional approaches to data collection and analysis. ***Conclusions:*** Intensive studies of individuals hold promise for expanding normal growth biology knowledge. Focusing on growth (not merely size), length (not weight alone) and individual growth patterns (not growth chart phenotypes) are important tactics. Benefits include clarification of mechanisms by which nutrition and metabolism influence growth, new solutions to abnormal growth states and improvements in long-term health consequences.

Introduction

Historically, growth measurements of children have provided a biomarker of children's health. Auxological epidemiology [1] has documented how population level trends in children's height and weight provide a snapshot of general health and well-being [2]. Commonly, these studies compare size-for-age measurements of children within the study sample to either growth references (a statistical distribution describing a specific group of children) [3] or growth standards (a statistical distribution of size-for-age measurements that proposes to show how children should grow under ideal circumstances) [4, 5]. Specifically, studies associating stunting (failure to gain height) and wasting (weight loss) with factors including,

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but not limited to, poor nutrition, infectious disease burden, low status of women and poor water quality [6] have identified changes in the percent of stunted (below minus two standard deviations from median height-for-age measurements of a reference population) [6] and wasted (below minus two standard deviations from median weight-for-height measurements of a reference population) [6] children as useful population level outcome measures of public health efforts to increase energy intake, improve micro- and macronutrient intake, provide medical treatment and ameliorate local circumstances aimed at reducing disease burden [7]. Likewise, there are clinical situations in which size-for-age and weight-for-length/height measurements are useful biomarkers of individual well-being. One such circumstance is among preterm infants in the neonatal intensive care unit, where weight-for-age and weight gain have provided a primary clinical indicator of health status and are strong predictors of mortality [8].

Size versus Growth

The factors that mechanistically underlie size as a proxy for health are less clear. At any single time point, a measurement represents the size of the individual at that moment. By inference, this signifies how much growth has occurred previously. A single measurement, however, has no information on growth itself or the path by which a child got to that size: whether growth previously occurred rapidly and then slowed; languished, followed by a recovery; or progressed by an even pace is not known without repeated measures, collected in a longitudinal study design. This is important as it is the biological processes that underlie variable growth patterns across age that hold the key to the mechanisms by which growth is a proxy for individual level health and well-being. Such details are required to advance the field of growth biology, moving research away from correlational studies and into a realm that investigates the molecular and cellular basis of child growth.

A rapid assessment of the size of any individual at one age relative to their peers provides an inference regarding their previous relative growth rates. This is accomplished by comparing one individual's measurement to a statistical distribution of size for age derived from similarly aged children: bigger children of comparable age have previously grown more. This type of comparison is useful when clinicians want to know something about the relative 'normality' of an individual or in cases where community health workers seek to assess the relative 'health' of children, as noted above. Both cross-sectionally collected data among children of different ages, where each child is measured only once, and longitudinally collected data, with repeated measurements on the same children as they get older, have been the basis for such comparative references and standards [3, 5]. Often, these data are not only presented in tabular form but are prepared such that percentile distributions at consecutive ages are sequentially connected by mathematically smoothed curves. These charts are commonly referred to as 'growth charts' or 'growth curves'. While useful visual tools for the purpose of comparative size-for-age estimates, caregiver [9] and healthcare worker [10] comprehension of the information presented can be limited and these charts are not necessarily representative of the growth trajectories followed by individuals [11]. Instead, the curves are interpolations, or mathematical inferences, of growth rates. This can be the case even for data that have been collected longitudinally [12, 13].

Measurement Specificity

Historically, assessments of growth have relied on weight, as it is the relatively easiest assessment to take, and together with height (or infant length) they comprise the two most commonly measured body dimensions. In spite of the convenience, weight alone is not the measurement of choice for a growth study aiming to understand growth biology. The processes of increasing length or height, expanding head circumference, increasing subcutaneous fat and gain in body weight are biologically distinctive. Gain in body weight is a nonspecific summary of increasing mass that represents bone elongation and density accumulation, muscle expansion and organ enlargement, together with the accumulation of fatty tissue as energy intake exceeds utilization. The latter is neither a sensitive nor a specific reflection of 'growth' in the developmental sense of progress on the path to maturity and is particularly problematic with the expanding global obesity epidemic [14].

Growth of the skeleton is a clear marker of development as the incremental gain in dimensions of individual bony elements progress, with intramembranous ossification along the sutural margins of the skull, and elongation and replacement at the endochondral plate among long bones [15]. Skeletal growth occurs during a time-limited period of life; limb length increases from gestation until chondrocytic proliferation senesces and the epiphyseal

growth plate thins and fuses to the long bone [16]. This is highly age variable. Final femoral and tibial epiphyseal fusion, for example, occurs between 14 and 22 years of age [17], depending on methodology, sex and population [18, 19]. This process is an organized sequence of events involving the coupled activity of osteoblasts and osteoclasts as they create and mineralize new bone and remodel old bone, mediated by the effects of factors such as insulin-like growth factor-1, growth hormone and sex steroids, among others [20]. The conflation of the term 'linear growth' with growth in length, a reflection of skeletal growth processes, further obscures the specificity of body compartments.

By contrast, body weight does not represent a single aspect of an individual's physiology but is rather a summary of the mass of different body constituents and metabolic activities. Weight is a nonspecific marker of energy balance reflecting the relationship between caloric consumption and expenditure; it is highly responsive to environmental conditions and behaviors [21]. Underweight and low weight-for-height remain a central health issue among populations living in developing regions, as well as those experiencing extreme impoverishment in developed countries. In contrast, overweight and high weight-for-height among children is increasing globally with the availability of so-called 'cheap' calories and reductions in physical activity, among other factors [22].

More specific aspects of body composition can be assessed using a number of methods including anthropometry, bioelectrical impedance analysis, dual-energy X-ray absorptiometry and air displacement plethysmography. Each of these methods holds benefits and limitations, particularly for children [23, 24]. The human variability in body composition due to sex, race and ethnicity [18, 25, 26], the ratio of lean to fat mass and the specific sites of fat mass accrual [27, 28] identifies the complex and nonspecific meaning of 'weight'. Importantly, low body weight does not indicate low adiposity, as described by the 'thin but fat' individuals from Pune, India [29]. Likewise, the simpler estimates of phenotype commonly employed, ponderal index (weight/length^3) and body mass index (weight/height^2), describe the shape of the body without taking into account either body fat percentage or distribution.

Additionally, while skeletal growth is a terminating process, both weight and body composition change over the life course [30, 31]. During development, physiological cues determine whether mesenchymal stem cell differentiation prefers muscle, adipocytic or osteoblastic lineages [32]. With age, the regeneration potential of muscle satellite cells decreases [14, 33], resulting in a gradual decline in lean muscle mass [34]. At all ages, the relative ratio of fat to muscle mass can be modulated through diet and physical exercise [15–17]. Thus, neither a stable weight across time nor patterns of weight gain and/or loss reliably reflect body composition, and none are specific and sensitive indicators of growth. In summary, the biology of growth is complex and not readily represented by either size alone or changes in summary variables of mass, such as weight.

Challenges to Increasing Understanding of Growth Biology

Clarifying the biological processes underlying growth is central to understanding individual level growth variability and designing positive intervention strategies. Historical approaches that have contributed to our present gaps in understanding include, but are not limited to, (1) the conflation of change in weight and length as parallel representations of growth, (2) the nonspecific clinical terminology for interpreting individual growth and (3) the methods employed to both collect and analyze growth data.

Changes in Weight and Length/Height

The conflation of changes in weight with changes in length/height as markers of 'growth' has historically limited the progress in the science of growth biology. One example of consequences attendant to this practice is our present incomplete understanding of the energetic requirements needed to grow. The commonly cited estimation for energy costs of infant growth was based on weight accrual. Median infant weight-for-age measurements from the 1977 National Center for Health Statistics growth references, with infant weight velocities assessed from formula-fed infants, were used to infer the calories needed for growth: Weight gain was partitioned into estimated percent of tissue fat and protein, which was then converted to associated calories per gram [35]. These calculations were subsequently updated to include estimations partitioning infant weight gain into experimentally assessed fat and lean body mass components, with added considerations for physical activity and energy expenditure [36]. Based on weight gain, it is unclear how well this approach actually captures the reality of growth as distinctive from excess caloric storage. Moreover, variability in metabolic rates due to influences ranging from genetics [37] to the mi-

crobiome [38], and tissue heterogeneity in fat type and location [39–41] raise questions as to the validity of such estimates.

A second example is the commonplace use of birth weight as a proxy for 'fetal growth'. Hundreds of epidemiological studies report an association between birth weight and risk of adult chronic disease [42–44]; causality has been inferred to reflect aspects of growth, with little clarity in terms of mechanisms. Reliance on birth weight is rooted historically in the absence of a methodology for assessing growth in the womb until the emergence of ultrasound in the last 30–40 years [45]. Birth weight is an outcome of complex developmental processes and provides no insight into changes as they occur across the prenatal period. Repeated ultrasonography demonstrates the importance of variability in growth trajectories overall, and time-specific events in particular, for understanding biology. Ethnic and sex-specific differences in fetal growth trajectories [46, 47] highlight the degree to which birth weight is misleading as a meaningful summary of the process by which size at birth is attained, and weight reveals nothing about body composition [48]. It is likely that the salient biology underlying fetal and birth weight predictions of subsequent health reflects both the timing of growth rate variability [49–52] and specific organ growth trajectories, rather than gross body mass [53, 54].

Interpretation of Individual Serial Data Plotted on Growth Curves

Phenotypic growth trajectory patterns that appear when an individual's serial size measurements are plotted on growth charts have led to concepts that are not necessarily accurate reflections of growth biology. Repeated measures of an individual's size with increasing age need not track along single percentile channels, but may cross percentile lines. These changes in size relative to peers of similar age are a normal occurrence as an expression of regression to the mean [55]. While the change in relative size among individual children is a reflection of the inter-individual variability in the timing and magnitude of growth, the 'percentile crossing' apparent on the charts attendant to these 'shifting growth rates' has been adopted by public health surveillance approaches to growth monitoring. In this capacity, 'percentile crossing' has become both a marker indicating pathological or abnormal growth and proposed as a useful indicator for clinical interventions in contexts that include altering infant feeding patterns in relation to breast-feeding when downward percentile crossing occurs or curbing early weight gain in response to upward percentile crossing [56].

Interpretations of individual biology from patterns on a growth chart are widespread. Unfortunately, they are inconsistently applied. The varying usage of the term 'catch-up growth' is illustrative. This was first used by Prader et al. [57] to describe the occurrence of changes in the graphical patterns of weight- or height-for-age measurements seen among some children as they recover from insults and regain their pre-insult growth trajectory. In the original definition, catch-up growth *followed a documented growth faltering* and was a clinical marker of improvement. Subsequently, the concept of catch-up growth has been used more generally in reference to both height and weight trajectories, with several definitions. Catch-up growth has been used variously to describe upward percentile crossing growth trajectories of different body parameters [58] with [59] or without [60] specific criteria for the magnitude of change. This inconsistency has consequences for clinical decision making at the individual level, and leads to divergent interpretations of health and well-being at the population level [61, 62]. A specific case in point is failure to thrive, which does not have a single diagnostic criterion [63]. This lack of standardization inhibits clarification of the biological bases of poor growth and limits efficacy of intervention strategies [64, 65].

Analytic Methods

The history of both sampling strategies and data-analytic approaches has obscured a true understanding of individual level growth physiology. A reliance on generalizing infrequently collected individual data by descriptive statistics across age at the sample level followed by curve fitting, foundational to the development of growth reference curves, led to the view that individuals of similar size for age grow at a similar pace across ages, thus maintaining their status within a percentile channel. Abundant evidence documents greater variation among individuals across age than this model captures. The adoption of multilevel modeling approaches in more recent years permits the variability in individual growth trajectories to be appreciated in group data analyses as the between-individual variability in both size and growth rate can be assessed [66].

Towards an Understanding of Individual Growth Biology

From a historical perspective, the reliance on curve fitting infrequently collected data at the level of the sample has had a profound effect on the basic tenets of growth biology [67]. Individual growth does not progress at the

slow and steady pace implied by the curvilinear graphics of the customary growth chart curves. Instead, growth is discontinuous and episodic [68] with daily saltatory bursts separated by intervals of no significant growth. Specifically, both endochondral and intramembranous bone growth occur by episodic saltatory increments of variable amplitude, punctuating unequal intervals of stasis, and these characteristics vary both within and between individuals [68, 69]. This saltation and stasis process has a very different underlying biology than a continuous growth process [67]. More work is needed to clarify the mechanisms that control the timing and amplitude of discrete growth saltations. This is important as this pulsatility is a manifestation of the fundamental biological program driving normal growth and the processes by which the temporal program is implemented. Acknowledging that continuous growth is not the process by which normal growth occurs is central to improving abnormal growth intervention strategies, for which a disruption of quiescence is a promising target for therapeutics [70, 71].

Expanding scientific understanding of growth biology requires not only time-intensive serial data collection but also leveraging new technologies to temporally assess in vivo cellular level changes in relation to anthropometric indicators and their interrelationships. As the skeleton is intricately involved in whole-body energy homeostasis [72], scientific understanding of growth biology will be advanced by an integrated approach clarifying relationships between body parameters. Knowing when discrete skeletal growth events actually occur permits the documentation of temporal relationships between weight gain and bone elongation [73], or bone elongation and sleep [74], for example. These relationships generate hypotheses regarding more specific mechanisms regarding metabolic characteristics of individual level growth biology.

Conclusions

It is clear that early growth is fundamental to lifelong health [42–44]. Our understanding of what it is about growth that is causal in these relationships is less clear. The escalating profile of multiple chronic diseases associated with aging [75] requires a greater focus on the mechanisms that drive these descriptive relationships. Additionally, the global obesity epidemic [14] calls for increased attention to the relationships between growth of the skeleton and soft tissue. A secular increase in average height has not been observed at the same pace as average weight, and a high prevalence of obesity among youth has emerged [76]. In the broader global health perspective, health promotion programs in low- and middle-income countries often utilize weight gain as the primary target outcome. As rapid weight gain after 2 years of age, especially in the absence of relative increases in height, are not associated with improvements in human capital, but instead with an increased chronic disease risk [77], attention should shift to the promotion of skeletal growth accompanied by moderation of weight gain, in alignment with 2015 Millennium Development Goals [78]. The science of growth biology will expand with changes in aspects of research design and enhanced understanding of individual growth tracking, which hold benefits for efforts to improve lifelong health. A focus on growth (not merely size), length (not weight alone) and individual growth patterns (not growth chart phenotypes) is important to advance knowledge.

Disclosure Statement

The authors have no conflicts of interest to report.

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