正常兒童身體組成的測量: 道德和方法學的限制因素

Body composition measurement in normal children: ethical and methodological limitations

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There are significant ethical, practical and theoretical issues that need to be considered when measuring body composition in normal children. For example, when evaluating the use of techniques that involve ionizing radiation, then the benefit to the volunteer subject, or society at large, needs to be balanced against the likely harm to the subject. For children, the detriment per unit dose may be two to three times larger than that for young adults. At present the decision as to the acceptable radiation dose limit for healthy children undergoing research studies remains debatable. Most techniques for measuring body composition require specific validation of their precision and accuracy when used with small subjects; adaptation of existing methods may thus be necessary in order to measure children. In addition, techniques such as densitometry and dual-energy X-ray absorptiometry may be impractical for use in young children. A major theoretical issue to be considered is that most body composition techniques assume a constant density or chemical composition of the fat-free mass (FFM). However, the FFM in children does not consist of fixed proportions of water, protein and mineral; rather, the proportions of these change during growth, with water content decreasing and protein and mineral content increasing. Caution must therefore be used in the application of adult-derived body composition constants and equations to children.

Introduction

Accurate measurement of body composition in healthy children is important for a number of reasons. Firstly, it enables a better understanding of the major changes in chemical composition of the body that occur as a normal part of growth and development. In so doing, the relationship between easily measured growth parameters and such variables as body protein, potassium and bone mineral content can be determined[1]. Furthermore, measurement of body composition in normal children provides control data which are vital for the interpretation of body composition measurements in children with varying disease processes. However, there are significant ethical, practical and theoretical issues that need to be considered when measuring body composition in healthy children.

Ethical issues

In all clinical research, especially that involving normal subjects, it is vital to consider the benefit that is to be derived from a particular study and to balance this against the possible risks to the subject[2]. These risks include those arising from the use of ionizing radiation as well as from blood sampling.

Ionizing radiation

Several methods for determining body composition involve the use of ionizing radiation including dual-energy X-ray absorptiometry (DEXA)[3], neutron capture analysis[4] and computed tomography[5]. Can any of these techniques be used in assessing children? Are there any established principles that can be used in evaluating the ethical use of ionizing radiation in normal children?

The International Commission on Radiological Protection (ICRP) recently published its report on Radiological Protection in Biomedical Research[2] in which established principles relating to the use of ionizing radiation in research were highlighted[6]. These principles are meant to be applied to all volunteers for medical research, including children. Firstly, it is important to consider why the study is needed; this includes an assessment of the benefit that will result from the study, the extent to which that benefit is to the volunteer or to society at large, and the type of benefit that is likely to arise. Secondly, it is necessary to assess the likely harm to the volunteer from the study.

The biological effects of ionizing radiation can be classified into two categories: deterministic and stochastic[7]. Deterministic effects result from cell or tissue death and are characterized by a severity that increases with dose above a certain clinical threshold. They include such clinical findings as lens opacities, hair loss and reduced fertility. However, a key feature of a deterministic effect is that the dose threshold is well-defined and so can be avoided in biological research. In contrast, stochastic effects result from radiation-induced changes in cell nuclei and lead to cancer induction or to genetic damage (evident only in the next generation). They are effects for which the probability of an occurrence, rather than its severity, is regarded as a function of dose.

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Furthermore, there is an apparent absence of a dose threshold for a stochastic effect; in effect, radiation exposure at any dose results in a probability of induction of harm. It is this biological effect which needs to be considered in any use of ionizing radiation in normal subjects. The risk resulting from the use of ionizing radiation is therefore equivalent to the sum of the probability of fatal cancers caused by the radiation, plus the weighted probability of non-fatal cancers, plus the probability over all succeeding generations of serious hereditary disease resulting from the dose. Of additional specific interest is the fact that at young ages the detriment for a given radiation dose is higher ('2 to 3 times larger') than for young adults[2].

However, before the biological effects of ionizing radiation from a given procedure can be estimated, a reliable assessment of the dose is necessary[2]. This needs to take into account specific age and sex risk factors for different organs[8]. Assessment of dose rates for small subjects is therefore particularly necessary; simple extrapolation from dosimetry estimates for adults will usually be inappropriate. This is very important when using body composition techniques, most of which were initially developed for use in adults[4,9].

The ICRP[2] has modified the original WHO classification of research projects[6] into categories depending on the amount of radiation dose to be received by the subject. Essentially, the categories are defined by the level of risk, and the boundaries between categories may be equated to a level of dose. The lowest risk category (Category I) is of the order of 10^{-6} or less (ie regarded as trivial) and has a corresponding effective dose range of <0.1 mSv (equivalent to a few weeks of background radiation). The level of benefit needed to justify radiation exposure at this level would be only minor. Perhaps it is in this risk category that studies on children can be performed. The highest risk category (Category III) includes risks of approximately 10^{-3} (ie a moderate risk) corresponding to an effective dose range of >10mSv (for comparison, the current annual dose limit for occupational exposure is 20 mSv per year); a substantial level of societal benefit would be required to justify the risks with such a dose. Risk Category II lies between these two extremes of risk and requires an intermediate to moderate level of societal benefit for justification of exposure.

The principles stated above can be applied in assessing the ethical use of ionizing radiation in normal children. It is noteworthy that the ICRP does not specify any particular dose limit for children; strict recommendations as to which body composition techniques may or may not be used cannot therefore be given. In essence, the risks should be minimal and the information sought should not be able to be obtained by other means.

Blood sampling

Another ethical issue to be considered in the measurement of body composition in children is blood sampling. Venous access, particularly in well-nourished young children, may be difficult, with the potential for the procedure to be psychologically distressing to both the child and the parent. It is therefore important to firstly consider whether blood sampling is required. For example, collection of urine or saliva samples, rather than blood, would be preferable when estimating deuterium-space in children[10]. However, if blood specimens are required for a study (eg measurement of bromide space[11]) then they need to be collected skillfully. Finger-stick sampling, performed expertly, may be less worrying than a venepuncture although this is not necessarily the case. Furthermore, local anaesthetic creams, applied topically prior to the venepuncture, can minimize much potential distress.

Practical issues in measuring body composition in children

Practical recommendations

Some methods of assessing body composition that are readily used in adults are inappropriate for the assessment of children from a practical point of view. For example, young children are unable to lie still for extended periods of time and thus techniques in which this is a requirement, such as DEXA[3], will be unsuitable for many children in this age range. In practical terms, children below the age of four or five years are rarely suitable as DEXA subjects, except for those under a few months of age who may sleep or lie quietly through the assessment. Measurement of total body potassium by the counting of ^{40}K gamma rays may also be difficult with some facilities. The use of whole body counters which require the subject to lie quietly in a small, lead-lined room is obviously inappropriate for young children. More 'subject-friendly' counters in which the subject is visible at all times have been used for assessment of babies through to adults[12]; such facilities will, however, have higher background levels of radiation. This problem of age-appropriate assessment is also seen with densitometry[13]. Clearly only those who are water-confident can be assessed with this technique; children under the age of six or seven years are therefore not usually suitable as subjects.

Another practical issue relates to the administration of young children of stable isotopes, such as deuterium or ^{18}O, or other tracer substances. Accurate dosing can be challenging in young children who may refuse to drink the tracer, or even spit it out after it has been given! For this reason it is often preferable for an experienced investigator to carefully administer the tracer — in the case of babies, with a fine tube attached to a syringe or, in older infants and toddlers, with a feeding cup[10]. It is also essential to recognize honestly when the tracer has been spilled and to stop the study at that stage without fruitlessly proceeding.

Collection of physiological fluid samples can also be difficult. However, urine bags can be used in babies and toddlers, although these may leak, slip off or become contaminated with faeces. In addition, saliva samples can be collected from infants by swabbing the mouth with a small sponge or absorbent cotton wool[10].

Finally, during any assessment of body composition it is important to ensure that the child remains calm, content and reasonably cooperative. This is most likely to happen if the parents are involved and understand the requirements of the study, if the study takes place in a pleasant environment and if a reassuring and sympathetic approach is used.

Specific validation of techniques for small subjects

Another set of methodological problems is related to the need for specific validation of many techniques for their use in small subjects. For example, in the measurement of nitrogen gamma ray emission with the technique of neutron capture analysis, the smaller the subject then the greater the relative contribution of background counts to the total number of gamma rays measured[4]. The precision of the measurement is therefore likely to be worse in a small subject than it would be

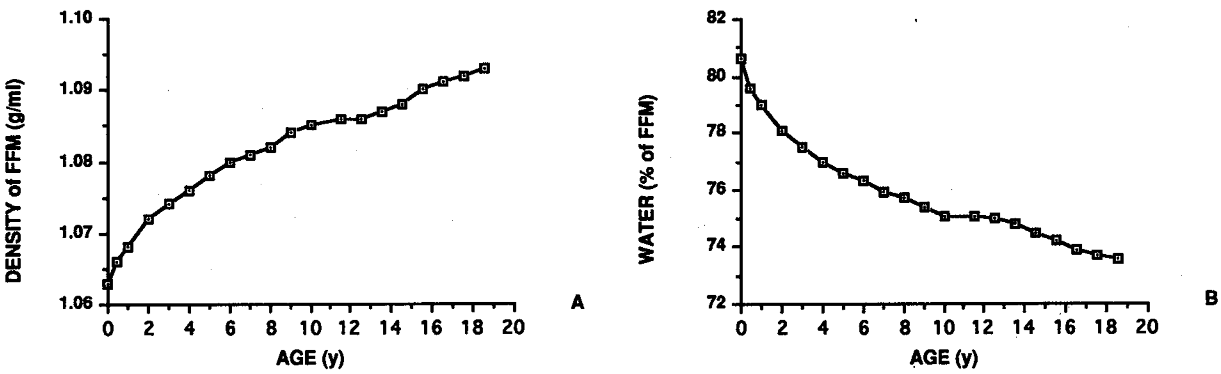

Figure 1. Changes in the density (A) and water content (B) of the fat-free mass (FFM) from birth to 18.5 years in the male reference child and adolescent. Data are those of Fomon et al.[15] and Haschke[16]. These studies show that chemical maturity does not occur until late puberty.

in a bigger subject[4]. In fact, many methods which are used in adult body composition measurements may need to be modified and specifically validated if they are to be used in children.

Theoretical issues

There are also major theoretical issues to be considered when measuring body composition, even in normal children. It is vital to understand the assumptions that underlie many techniques, and any specific problems associated with their use. Fundamental to many body composition techniques is the assumption that the fat-free mass (FFM) is of constant density and chemical composition.

The concept of chemical maturity was first introduced in 1923 by Moulton[14]. He defined it as 'The point at which the concentration of water, proteins and salts becomes comparatively constant in the fat-free cell...' Moulton suggested that mammals reach chemical maturity at approximately 4–5% of their total life span, and proposed this to be at about 4 years of age in humans. At chemical maturation the FFM was estimated to be 70–75% water, 18–20% protein and 5–9% mineral ('ash'). However, Moulton's conclusions were based upon observations of a limited number of carcass analyses in foetuses, infants and adults.

Detailed calculations of the body composition of the growing child and adolescent were first published by Fomon, Haschke and co-workers in the early 1980s[15,16]. These were based upon estimates of total body water, total body potassium and total body calcium (from single-photon absorptiometry) obtained from both their own work and a review of the literature[15,16]. Using these data and a number of assumptions, the body composition of 'reference children' at different ages was able to be determined. These estimates allowed the change in the composition of the FFM with growth to be assessed. Fomon and co-workers[15,17] estimated that the FFM of the term infant is 80.6% water (61% of the water mass being extracellular), 15.0% protein and 3.7% mineral. Subsequently there is a decrease in the percentage of water, an increase in the proportion of intracellular to extracellular water and an increase in the percentage of protein. Increasing mineralization of the FFM also occurs, particularly during adolescence. The composition of the FFM in the adult male quoted by Haschke[16] consists of 72.6% water (43% of the water mass is extracellular), 20.1% protein and 6.7% mineral, this being a significant change from the FFM composition of the infant. Figure 1 is a graphical representation of these changes in the density of the FFM (calculated from the chemical constituents), and the water content of the FFM, based upon the data of Fomon et al.[15] and Haschke[16] for male children and adolescents. Other workers have found similar changes in density and body water content by employing different techniques[18,19]. In addition we have demonstrated, using direct measurements of total body nitrogen in normal children, that the protein content of the FFM increases with age[20]. Such findings confirm that chemical maturity of the FFM does not occur until at least puberty.

The concept of chemical maturity has great significance for the measurement of body composition in childhood and adolescence; this aspect was reviewed in detail by Lohman in 1986[19]. It is essential to recognize that the assumption of constant density or of constant water, protein or mineral content is often routinely used in the estimation of FFM by such techniques as densitometry, deuterium-space analysis, gamma ray spectrometry (for measurement of total body potassium), skinfold thickness measurement, bioelectrical impedance analysis and DEXA[13]. In the usual analysis of data obtained using these techniques, adult-derived constants are used. However, it may be appropriate to modify these basic assumptions, for example by using age- and sex-adjusted constants[19]. Finally, the use of more than one method to assess to body composition in children has the potential to allow a more precise and accurate assessment to be performed. There are many models of body composition, from the basic two-compartment model of fat mass and FFM, which tends to be the one most commonly used in paediatric measurements, to more complex models, usually derived from the use of two or more different techniques. Multi-compartment models are increasingly used in adult body composition measurements[21]; their use in the assessment of children may allow body composition to be determined by means that are less dependent on non-validated assumptions.

Conclusion

Therefore, in measuring body composition in normal children a number of factors need to be recognized. The major ethical issue to be considered relates to the balance of the level of benefit to be derived from the study versus the level of risk to which the subject may be exposed from the study. When dealing with children these risks should be minimal. While ionizing radiation may be a significant factor with some methods for measuring body composition in childhood, it should be realized that there other forms of risk such as those associated with blood sampling. A number of practical issues should also be recognized. For example, some techniques for measuring body composition may be inappropriate for use in small children while others may require specific validation in order to be used for the accurate and precise assessment of small subjects. Finally, many body composition techniques assume a constant density or chemical composition of the FFM, an assumption that is not valid in children. Caution must therefore be used in the application of adult-derived body composition constants and equations to children.

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