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Body Compartments and Methods of Assesment in Newborns

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Abstract
The aim of the paper is to present different techniques for measuring body composition in neonates and the importance of its assessment for monitoring adequate growth and predicting neonatal- and later-life morbidity. Follow up of neonatal growth is even more important in specific groups of newborns, for example preterm infants, newborns with congenital heart disease and newborns with kidney anomalies. There are several models that divide body into compartments containing specific components. None of the measuring techniques embraces all of the body components, but with accurate and quality assessment of body compartments growth can be followed quite successfully. We believe that measuring body composition in vulnerable and sick neonates can contribute to better enteral support and management resulting in optimal growth and short- and long-term outcomes in these children. **Conclusion** – Optimal growth in infancy has significant impact on neurodevelopment and adult life disease programming. There are several different techniques for measuring body composition and some of them can be easily introduced in everyday clinical practice.

Key Words: Neonatal Body Composition ▪ Growth ▪ Body Compartments ▪ Measurement ▪ Neonate.

Introduction

The period from conception to 2 years of age represents a critical window of opportunity for optimal growth and preventing developmental origins of adult disease, including hypertension, stroke, type 2 diabetes, obesity, and cardiovascular disease (1). The assessment of growth during this early period is mostly based on anthropometric measurements, such as body weight, while the quality of growth and the assessment of body compartments is insufficient in clinical settings. Monitoring body weight is not necessarily the most optimal indicator of lean mass gain since fast body weight gain can represent gain of body fat (2-4). Furthermore, the importance of body composition and total body water assessment in the neonatal period has clinical significance not only in poor weight gain, but also in many different clinical settings and areas of pathology, such as cardiac and renal disorders, where there can be alterations in total body water and other body compartments (5-7).

In the paper we aimed to present the rationale for body composition measurements in neonates to achieve optimal short- and long-term outcomes. Moreover, we discuss several different techniques for measuring body composition, some of which can be easily introduced in everyday clinical practice.

Body Compartments

Body composition can be addressed with several body compartment models that divide body in compartments containing specific components. The most basic division of the body structure is into

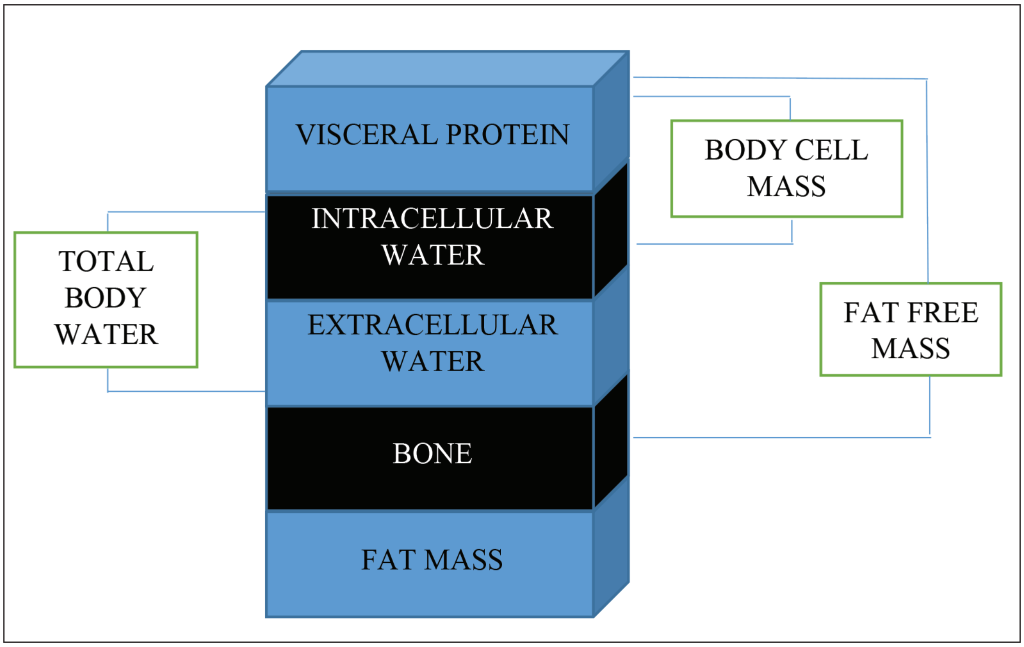

Fig. 1. *Body compartments. Summarized from Kyle et al. (2).*

fat mass (adipose tissue and fat) and fat-free mass that comprises carbohydrates, proteins, water and minerals. This is the so called 2-C compartment model or basic model. 3-C compartment model or nutrition model consists of fat mass (adipose tissue and fat), fat-free mass (predominantly protein and minerals) and water. Expansion of 3-C compartment model, and also most commonly used to asses body composition in children, is 4-C compartment model or metabolic model, where body parts are divided into fat mass (adipose tissue and fat), fat-free mass (body cell mass), extra cellular water and extra cellular solids (Fig. 1) (2). The last model is multi-compartment model or 5-C model that divides body in whole body, tissue, cellular, molecular and atomic compartment. This model has become the standard for body composition research (3, 4).

Changes in Fluid Compartments after Birth

During fetal life 90% of fetal body mass is water, 60% of this represents extracellular fluid compartment. When approaching term, water content drops to 75% due to natriuresis and diuresis, and extracellular fluid compartment comprises 40%, while intracellular fluid comprises 35%. Water content in preterm neonates is higher, around 80-90%, depending on the level of prematurity. Postnatally, dramatic physiological changes occur; while respiratory and cardiovascular system changes happen immediately after the birth, hepatic, haematological, endocrinological and renal system changes progress more slowly. In the first days of life, when pulmonary vascular resistance falls and pulmonary circulation and venous return increases, atrial natriuretic peptide is increasingly released which effects the establishment of diuresis. Initially urine output in a newborn is limited to 0.5 ml/kg/hour due to poor renal perfusion, which improves with circulatory adaptation. Following initial oliguric phase, a period of natriuresis ensues. Consequently, contraction of extracellular fluid compartment and 5-10% decrease in body mass during the first three days of life is seen (5, 6). Although nephronogenesis is completed at term, the renal tubules are short and consequently the ability to concentrate urine is limited. A limited ability to concentrate urine and the reduced glomerular filtration rate make the neonate susceptible to both, dehydration and fluid overload (5, 7).

Fetal Growth and Neonatal Body Composition

In utero environment has a significant impact on fetal growth. Maternal health, nutrition and weight gain determines normal, over- or undergrowth of the fetus and also metabolic programming, which can later lead to obesity and metabolic syndrome. During embryogenesis DNA methylation is highly dynamic and it partially affects epigenetic regulation and gene transcription. Inappropriate maternal nutrition my lead to abnormal DNA methylation resulting in inappropriate gene silencing. These epigenetic changes may lead to programmed changes in organogenesis, cellular responses and gene expression, which may result in several human diseases later in life (inflammation, cancer, etc.) (8).

The theory of first 1000 days of life emphasizes the importance of appropriate nutrition from the conception to the age of two years. Optimal nutrition of the mother, with all the key nutrients included in the diet, is important for optimal fetal growth and development, while specific nutritional requirements continue also after birth (9).

Estimation of neonatal body composition has become important in the characterization of fetal growth and predicting neonatal, and later life morbidity. Intrauterine growth is influenced by genetic factors, substrate availability and endocrine regulation. Most fetal weight is gained during the last trimester when fat tissue deposition, which is mainly influenced by the intrauterine environment, exponentially increases (10). This was nicely presented in the study of Lapillonne et al. who showed that between 32 and 41 weeks of gestation the body weight increased by 66% (P=0.0001), whereas the lean mass and fat increased by 40% (P=0.000l), and 115% (P=0.0001), respectively. This is consistent with studies showing that the differences in weight at birth of small-for-gestational age, appropriate-for-gestational age and large-for-gestational age infants are caused mostly by fat mass difference, representing up to 46% of the variance in neonatal weight (11, 12). At birth fat-free mass constituted 86% of birth weight and represents 83% of the variance in birth weight in appropriate-for-gestational–age infants, while fat mass constituted 14% of birth weight and accounted for 46% of the variance in birth weight (13).

Hamatschek et al. reviewed accessible literature that reported fat mass and fat-free mass, measured by air displacement pletismography and dual energy X-ray absorptiometry (14). They compared term and preterm neonates at 40, 52 and 60 weeks postmestrual age. Results of the review showed that preterm neonates at 40 weeks postmenstrual age had less fat-free mass, which correlated with worse neurological outcome. On the contrary, they had more absolute fat mass and percentage of fat mass. At 52 weeks postmenstrual age, term and preterm infants had similar percent-fat and the difference in fat-free mass decreased, and, at 60 weeks postmenstrual age fat-free mass almost matched fat-free mass of mature neonates. Their results confirmed the importance of body composition evaluation in preterm neonates since solely the assessment of weight at 40 weeks postmenstrual age can mask fat-free mass deficit (14).

Growth from the 14th intrauterine week and until the two years of age was also widely studied by INTERGROWTH-21st project. The goal of this global multidisciplinary project that included several countries was to study nutrition, growth, health and neurodevelopmental outcome from birth until two years of age. Anthropometric measurements of the newborns were done (body mass, body length and head circumference), and body composition was evaluated by using air displacement plethysmography within 96 hours of age. Results of the project showed that there is a moderate increase in fat mass when approaching term, both in girls and boys. The main reason for weight gain from the 34th week of gestation is the increase in fat-free mass, which is slightly higher in boys, whereas body fat percentage is somewhat higher in girls. In this study preterm newborns, which were mostly older than 34 weeks of gestation, had significantly lower values of fat mass and fat-free mass comparing do their mature peers. In the cohort of small and large-for-gestation newborns the body mass reduction or increase was due to fat mass reduction or increase comparing to appropriate-for-gestation newborns, whereas difference in fat-free mass in these two neonatal groups were less pronounced (15).

Importance of Growth Evaluation in Vulnerable Groups of Newborns

Special groups of newborns, such as newborns with congenital heart disease, renal anomalies, preterm and small-for-gestational-age newborns are facing specific nutritional and caloric requirements. As well as prenatal growth, also postnatal growth is closely regulated by interaction of genetic, hormonal and environmental factors. Normal growth is an indicator of the child's physical and emotional well-being.

Premature birth coincides with the most rapid body growth and brain development. Although a number of studies have evaluated the influence of nutrition and growth on brain development in preterm infants, optimal nutrition that would mimic fast nutrients accretion during the last trimester is still not defined (16). To achieve appropriate postnatal growth, preterm newborns require a high protein formula. Although sufficient postnatal growth correlates with better neurodevelopmental outcomes, the preterm infant with accelerated postnatal growth have higher risk for cardiovascular disease and obesity later in life (8). Bell et al. studied the association between postnatal physical growth, brain size and body composition at term in preterm neonates (17). Growth that is sufficient and directed towards gaining fat-free mass appears to be protective for brain development. Measurements of brain volume in preterm babies at term were compared with fat-free mass and fat mass accretion. Gaining fat-free mass was positively associated with brain size, whereas gaining fat mass was not. Therefore, growth aimed at gaining lean mass is associated with bigger brain volume that is correlated with better neurodevelopmental outcome (17).

Small-for-gestational-age newborns are a group of newborns predisposed to fast catch-up growth, especially if there is also a component of genetic predisposition. Fast postnatal growth directed towards fast fat mass instead of fat-free mass gaining is likely to influence adult disease programming, and increasing the risk for developing central adiposity. Central adiposity later in life is a key risk factor for the development of cardiovascular disease and type 2 diabetes (8).

Neonates with congenital heart defects may have higher caloric intake requirements to achieve appropriate growth. Moreover, feeding difficulties are more prevalent in this population, which additionally predispose these infants to growth failure. Insufficient growth has been associated with prolonged wound healing, myocardial dysfunction, endothelial damage, increased risk for postoperative infection and long-term cognitive delay (18). Problems with feeding and weight gaining are more pronounced in newborns with cyanotic heart anomaly as compared to acyanotic heart anomaly, which additionally alters infant's recovery, as well as short- and log-term outcomes (19). Moreover, heart anomaly can lead to heart decompensation and therefore fluid retention that must be considered when evaluating a newborn with congenital heart anomaly. Assessment, whether weight gain in this group of children is due to increase/accretion of lean mass, fat mass or water retention, is very important in clinical management.

Anomalies of kidneys and urinary tract represent 20-30% of all birth defects (7, 20). Some of these patients may develop chronic kidney problems. Faltering growth and insufficient weight gain in newborns with renal disorders is thought to be the consequence of uremic milieu, higher circulating levels of cytokines and alterations in amino-acid balance which all lead to poor appetite (21). Deterioration of renal function later in infancy can further influence nutritional status, leading to malnutrition (22). Therefore, monitoring of body composition and adequate nutrition from the newborn period further leads to better prognosis of the disease.

Neonates born to mothers with gestational diabetes are at increased risk of acquiring higher body fat during intrauterine development due to maternal hiperglycemia and consequently fetal hyperinsulinism. The study from Wiechers et al. showed statistically higher fat mass and fat mass/ total body mass in this group of neonates (23).

Since adequate nutrition and fat-free mass gain enable proper growth and brain development, the need to properly asses body composition of patients from neonatal period onwards has become of increased importance.

Different Techniques for Measuring Body Composition

The least invasive and most widely used techniques for growth monitoring are measurements of weight, length and head circumference. These anthropometric measurements are easy to perform, but on the other hand are not optimal for a thorough assessment of growth, since accurate analysis of relative body compartments, such as fat mass and fat-free mass is needed for exact evaluation of nutritional status. Fat mass compartment can be assessed by skinfold thickness. Skinfold thickness measurement is simple and inexpensive, and helps to determine neonatal subcutaneous fat and distribution of fat mass in specific areas of the body. Its disadvantage is the size of the instrument which makes the measurements in this vulnerable population quite invasive (24).

Body composition can be analysed by many different methods. Air displacement pletismography is considered a golden standard for the body compartment measurements. It is based on the estimation of the volume of air that the body displaces inside an enclosed chamber. After body volume and mass is measured the density of the body is calculated and the two-compartment model is derived, assuming fixed density of fat and age-, and sex- specific estimation of fat-free mass (25). To perform the measurement, the newborn has to be removed from the incubator or bed and placed and immobilized inside the device, which is the main downside of the method (24).

Dual-energy X-ray absorptiometry (DXA) is a method primarily used for bone density measurement. It uses spectral imaging with two X-ray beams containing high and low photon energies that depend on the properties of the underlying tissue. DXA is considered to accurately measure mineral content and lean soft tissue, but it's estimation of fat mass could be overestimated in small infants. The disadvantage of this method is also radioactive exposure and need for sedation, since the movement of the newborn has to be prevented during the investigation (26-28).

Isotope dilution technique is based on the dilution principle, where the amount of total body water can be estimated if the concentration of the ingested and excreted isotopes are known. For the purpose of the measurement the newborn has to ingest isotope-labeled (^{18}O and/or ^{2}H) water, and then post-dose urine samples are collected (the collection of saliva or plasma is also possible). The concentrations of ^{18}O and ^{2}H in the urine samples are measured using gas isotope ratio mass spectrometry. Body composition is then assessed by assessing fat-free mass from the estimated total body water. The disadvantage of this method is that the amount of ingested isotope must be accurate, which is sometimes difficult in a newborn, because of spitting and vomiting. Accurate collection of the urine may be challenging as well. Since variations in total body water in the neonatal period can be great, sometimes the estimation of body compartments can be difficult (29, 30).

Magnetic resonance imaging and newer technique, chemical-shift MRI is the technology that uses different resonance frequencies of protons in fat versus water. An image of fat versus non-fat tissues in the body is produced by shifting the MRI read-out gradient. Dyke et al. showed that chemical-shift MRI measurements can be performed without sedation in naturally asleep and properly prepared neonates (placed in vacuum immobilization pack with ear covers). The method is without radiation, accurate, repeatable and rapid but again, neonate has to be placed outside the incubator or bed, and has to be immobilized and asleep. The accessibility of the MRI may be another disadvantage of the technique (31).

The foundations of bioelectrical impedance analysis (BIA) were established by 1970s, but it is in the last decade that it is more widely used in the neonatal units. It is a safe, minimally invasive bedside technique, and the results are easily reproducible (2). The method is based on the prediction of the electrical conductive properties of the body, since the lean tissue that consists of water and electrolytes is a good conductor, whereas fat is a poor conductor. The method uses the passage of painless, low amplitude, low and high frequency electric current through the body. The resistance of homogenous conductive material of uniform cross-sectional area is proportional to its length and inversely proportional to its cross sectional area. Since the body is not a uniform cylinder and the conductive length, which represents the distance from wrist to ankle, is in practice difficult to measure, the patients's height is used for standard length in this method. The body offers two types of resistance: capacitative resistance, which is called reactance, and resistive resistance, which is called resistance. Capacitative resistance arises from cell membranes, whereas the resistive resistance comes from extra- and intracellular fluid. Values of reactance and resistance are then used to calculate impedance and phase angle. At very low frequency, the current does not penetrate the cell membrane and therefore passes through the extracellular fluid. At very high frequency the capacitor behaves as a perfect capacitor. The total body water is then estimated in addition to the quantity of extracellular and intracellular water. On the assumption that total body water is a constant part of the fat-free mass, other body compartments can also be estimated (2, 32).

There are several types of BIA: single frequency BIA, multi-frequency BIA, bioelectrical spectroscopy and segmental BIA. In the single frequency BIA the frequency of 50 Hz passes between electrodes in comparison to multifrequency BIA, where multiple frequencies are used and then total body water is differentiated into extracellular and intracellular water. Bioelectrical spectroscopy uses mathematical modelling to generate relationship between resistance (R) and body fluid, and is suitable for measuring fluid shifts and hydration status, whereas segmental BIA constitutes of placing electrodes on different body parts and has been used to determine fluid shifts and fluid distribution (2, 32, 33).

First studies using BIA in neonatal population aimed to assess total body water in preterm and mature neonates. These first studies made by Modi et al. estimated total body water by comparing the method of isotope dilution technique ($^2H^{18}O$) and BIA. They concluded that the BIA method can be applied in neonatal population since it is accurate in estimating total body water and changes in body water (34, 35). The BIA research in neonatal population expanded over the next years. Besides total water estimation it was used to study fat and fat-free mass in different groups of neonates, such as small- and large-for–gestational-age neonates, mature and preterm neonates (32, 36, 37). Moreover, the study from Mol and Kwinta included critically ill newborns and showed that BIA is suitable for measurement of body composition in term and preterm infants, where differences in fat mass, fat free mass and body water are seen (37).

There are several considerations when performing BIA. There are important changes in total body weight and body water in the first few days of life that were detected with BIA (38) and must be taken into consideration when performing the measurements. Physiological factors that can influence BIA are supine position of the newborn, likewise measurement is supposed to be done when the subject lies still, which is sometimes difficult to accomplish. Additionally, the feeding in the first week of life and varying body temperature can influence bioelectrical impedance values. The literature is still inconsistent about the distance between the electrode placing, since minimal separation between electrodes is not defined yet. BIA is not influenced by cardiorespiratory monitoring (32).

Comparison of Different Techniques and Their Application in Clinical Practice

The indication for body composition measurement is neonatal growth monitoring with special attention to fat-free mass. Advantages and disadvantages of previously described methods for body

Table 1. Comparison of Different Techniques for Measurement of Neonatal Body Composition (32)

Technique	Advantages	Disadvantages
Skinfold thickness measurements	- Easy to perform - Noninvasive - Bedside technique - Possible repeated measurement	- Skillful examiner is needed - The need for accurate tools - Repeated handling of the neonate
Air displacement pletismography	- Golden standard measurement - Very accurate measurement of body composition - Quick, safe, non-invasive	- Expensive - Neonate has to be removed from bed/incubator - Not suitable for neonates on ventilatory/ continuous intravenous support
Dual x-ray absorptiometry	- Accurate measurement - Quick	- Possible overestimation of fat mass - Radioactive exposure - Need for sedation
Isotope dilution technique	- Accurate measurement	- The need for accurate amount of ingested isotope - Problems with collecting urine/saliva/plasma samples for calculation - Daily variations in total body water- inaccurate calculation
Magnetic resonance imaging	- Without radiation - Accurate - Repeatable and rapid	- Neonate has to be immobilized - Neonate has to be removed from bed/incubator - Problems with accessibility
Bioelectrical impedance analysis	- Without radiation - Accurate - Repeatable and rapid - Bedside technique	- Neonate has to lie still - Possible problems with electrode placement

composition evaluation are listed in Table 1 (32). According to published researches none of them is ideal while air displacement pletismography is currently the golden standard. When applying body composition measurement in everyday practice, the technique used should be bedside, simple, noninvasive, repeatable and accurate. Nagel et al. compared different body composition measurement techniques and their clinical implications and concluded that air displacement pletismography and BIA are suitable for stable neonate in the neonatal intensive care unit or outpatient care, while measuring skinfold thickness is more useful in the outpatient care (39).

Measurements of body composition in vulnerable neonates are currently used for assessing different diets in research settings, while studies on clinical management are still missing. Studies suggest the use of different methods to asses nutritional intervention mostly in preterm babies while the experience based on BIA is very limited (40).

Conclusion

Optimal growth in infancy has significant impact on neurodevelopment and adult life disease programming. Monitoring of neonatal growth and adjusting neonatal and early infant nutrition for appropriate lean mass expenditure, which is the optimal indicator of adequate growth, has become increasingly important. There are several different techniques for measuring body composition and some of them can be easily introduced in everyday clinical practice.

Conflict of Interest: The authors declare that they have no conflict of interest.

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