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HOW TO DETERMINE THE NUTRITIONAL STATUS OF PRETERM BABIES? – REVIEW OF THE LITERATURE*

JAK OCENIĆ STAN ODŻYWIENIA U DZIECI URODZONYCH PRZEDWCZEŚNIE? – PRZEGLĄD PIŚMIENNICTWA

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Abstract

Prematurity is a high risk factor threatening the well-being of newborns and their somatic and psychological development in the future. Preterm babies need special medical care in which proper nutrition and metabolic control play an evident role. Our review presents the current knowledge concerning the clinical value of different methods investigated in the neonatal unit setting, including: protein markers of nutritional status (albumin, prealbumin, transferrin, and Retinol Binding Protein (RBP) and hormonal markers of nutritional status (somatomedin C, visfatin and ghrelin). Moreover, there is a discussion of the methods used for evaluating body composition. A variety of different techniques based on the physical properties of organisms was tested on neonates, e.g. the Dual Energy X-ray Absorptiometry (DEXA) method and Bioelectrical Impedance Analysis (BIA). Based on the review of the literature, we can speculate that none of the above methods represents a good single marker of the babies' nutritional status, or a prognostic factor for the future development of premature infants and infants born with IUGR. A combination of several methods from different groups seems to be a promising possibility. It is critical to continue looking for markers that will in a simple and efficient way help to optimize the correct nutritional therapy in infants with IUGR and those who were born prematurely.

Key words: nutritional status, biochemical markers, body composition

Streszczenie

Wcześniactwo jest jednym ze znaczących czynników ryzyka nieprawidłowego rozwoju somatycznego i neurofizycznego w późniejszym okresie życia. Noworodki urodzone przedwcześnie wymagają nie tylko specjalistycznej opieki medycznej, ale także odpowiedniego sposobu żywienia i skrupulatnego monitorowania gospodarki energetycznej ustroju.

Poniższy przegląd piśmiennictwa przedstawia aktualny stan wiedzy na temat przydatności klinicznej wybranych danych biochemicznych (albumina, prealbumina, transferyna, białko wiążące retinol) i hormonalnych (somatomedyna C, wisfatyna, grelina) markerów stanu odżywienia u noworodków urodzonych przedwcześnie. Ponadto dokonano ewaluacji technik stosowanych do oceny składu ciała, takich jak: DEXA (Dual Energy X-ray Absorptiometry (DEXA) oraz impedancja bioelektryczna (Bioelectrical Impedance Analysis – BIA). Na podstawie przedstawionego przeglądu piśmiennictwa można stwierdzić, iż aktualnie żadna w w/w metod nie jest dobrym pojedynczym markerem stanu odżywienia ani prognostykiem dalszego rozwoju zarówno noworodków urodzonych przedwcześnie jak i z zahamowaniem rozwoju wewnątrzmacicznego (IUGR). Obiecującą możliwością wydaje się być połączenie kilku metod z różnych grup, co mogłoby pomóc w pogłębieniu wiedzy dotyczącej tego jakże ważnego problemu. Niezwykle istotnym jest zatem prowadzenie dalszych badań ukierunkowanych na poszukiwanie najlepszych metod oceny stanu odżywienia noworodków urodzonych przedwcześnie i dotkniętych IUGR.

Słowa kluczowe: stan odżywienia, markery biochemiczne, skład ciała

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INTRODUCTION

Extreme prematurity represents a significant problem in neonatology. The currently observed development of intensive neonatal care has resulted in the increased survival of ELBW (Extremely Low Birth Weight) babies. Because mortality rates have fallen, problems with nourishing such infants and ensuring their proper physical development have become a major difficulty.

Compared to full-term infants, preterm newborns are more susceptible to malnutrition and extrauterine growth retardation early in life and are more likely to experience skeletal mineral deficiencies [1], growth failure [2], and neuropsychological development restrictions later in life [3]. On the other hand, the increasing prevalence of obesity is becoming an important public health problem in childhood and presents numerous problems. Similarly to the risk of obesity in adulthood, childhood obesity is also a leading cause of pediatric hypertension associated with type II diabetes mellitus, and increases the risk of cardiovascular diseases [4, 5]. Therefore, energy balance and nutritional status are of vital importance in the early stages of preterm infancy.

Research that analyzes the correct nutritional approach and monitoring of nutritional therapy in the group of premature babies has a long history. Conclusions from the latest studies confirm that correct physical development in the early period of life is closely associated with appropriate neurological development [6]. Malnutrition during rapid brain growth results in a reduced number of neurons, which might lead to future behavioral problems, difficulties in memorization and learning [7, 8]. Recent studies implicate gut microbiota and diet as key modulators of the signaling pathways between the gut and brain that underlie neurodevelopmental and psychiatric disorders. Sherman et al. suggest that the GBA (gut – brain axis) plays a vital role in adverse neurodevelopmental outcomes in preterm infants [9]. In addition, correct nutrition not only affects neurological development, but also significantly impacts the right proportions of body composition.

Both protein and hormonal markers can help to evaluate the infant's nutritional status, while body composition might be determined by anthropometric methods and a variety of different techniques based on the physical properties of organisms.

Biochemical markers of nutritional status

1. Protein markers of nutritional status
   Biochemical analysis plays a significant role in the assessment of nutritional status and in diagnosing protein-caloric malnutrition, however it is useful predominantly in older age groups. In the population of premature babies their usefulness is limited. Some of the protein markers of nutritional status include albumins, prealbumins, transferrin, and retinol binding protein (RBP).
   a. Albumins – the most commonly used nutritional marker. Albumin serves as a carrier of bilirubin, hormones, drugs and enzymes. The serum half-life of albumin is 17-20 days [10]. Due to its relatively long half-life and its clear association with the hydration status, it is an increasingly challenged marker of nutritional status. In older children and in adults albumin levels of less than 3g/dl are regarded as hipoalbuminemia, however it is difficult to define the appropriate level of albumins in premature newborns. There are studies that demonstrate much lower albumin concentrations in babies born prior to their due date compared to the ones born on time [11, 12]. Albumin concentration increases during pregnancy from about 1.9g/dl (90% CI ~ 1.2 to ~ 2.8 g/dl) at 30 weeks of pregnancy to about 3.1 g/dl (90% CI~ 2.2~ 3.9 g/dl) in the perinatal period [13].
   b. Transferrin – binds and transports iron in plasma. In case of iron deficiency, transferrin concentration increases regardless of the delivery of nutritional products. Only when iron content in the body is appropriate does transferrin become a reliable marker of nutritional status. Its half-life is approximately 8 days, hence if there is a limited energy-calorie supply, it is much sooner reflected in the decrease of serum transferrin concentration as compared to albumins. Transferrin concentration significantly decreases in case of severe protein-calorie malnutrition [14].
   c. Prealbumins – constitute part of transporter proteins. They can form complexes with retinol binding protein, therefore they mediate the transport of vitamin A. In addition, they transport thyroxin and some drugs. Due to their short half-life, i.e. approximately 2 days, they quickly reflect protein deficiencies. Studies demonstrated that prealbumin increase was associated with the length of pregnancy, newborn body mass at birth, calorie and protein supply [15].
   d. Retinol Binding Protein (RBP) – is an alpha-1-globulin that binds and transports vitamin A. RBP is characterized by its short half-life, which is only 12 hours. In comparison to albumins and transferrin, RBP represents the best marker to monitor nutrition therapy [16].
2. Hormonal markers of nutritional status
   a. Somatomedin C – an insulin-like growth factor 1 (IGF-1), a polypeptide structurally similar to insulin. It is a substance whose half-life is extremely short, approximately 2 hrs. IGF-1 synthesis occurs in the majority of body tissues (predominantly in the liver); it is regulated by the concentration of the growth hormone (GH), insulin, age, gender and nutritional status. A decrease of protein supply significantly reduces IGF-1 serum concentration. The significant role of IGF-1 in fetus development is supported by a high, proportional association between IGF-1 levels in the umbilical blood and the newborn's somatic characteristics (17-21). Research studies carried out in prematurely born children with height deficiencies, demonstrated reduced serum somatomedin C concentrations in their later life [22].
   Somatomedin C is released into the bloodstream, where it is associated with specific transporter proteins (mainly IGFBP-3) that stabilize its concentration and regulate its biological activity. A conjugated

form constitutes about 99% of total IGF-1 in blood. In order to obtain reliable results of somatedin C, it is necessary to remove all transporter proteins from the analyzed blood sample. It is an extremely tedious process, which greatly limits general access to the use of this marker in daily clinical practice.

b. Ghrelin – a polypeptide that represents a natural ligand of the receptors for synthetic substances that activate the release of the growth hormone. Ghrelin is generated mostly in the stomach; however its small amounts are also produced in the hypothalamus and other organs. This hormone controls the neuroregulation of appetite and behaviors associated with food consumption. Ghrelin increases the sense of hunger, hence the risk of obesity. The literature reviewed demonstrates that ghrelin regulates intra-uterine development and also the later development of the babies born prematurely [23-25]. Since the expression of the ghrelin gene was shown in the placenta and fetal tissues, and ghrelin peptide was detected in the newborn's umbilical blood [26], it is hypothesized that it plays a significant role in fetus growth, the maturation of the mechanisms that regulate the fetus's energy balance (including protection from hypoglycemia) and facilitates the initiation of sucking by a newborn baby [27].

   Some research studies indicate that ghrelin concentration is higher in newborns characterized as small for their gestational age, SGA [28-30], which suggests its role in the adaptation process to conditions of malnutrition in the uterus. Ghrelin might increase the newborn's craving after birth and stimulate the release of the growth hormone, GH, whose concentration is increased in the babies with intrauterine malnutrition [31] and results in accelerating the growth rate. In recent years, there has been an increasing number of publications that demonstrate the potential role of ghrelin in programming metabolic pathways of the body during fetal life that might affect the baby's health in later life [32].

c. Visfatin – a hormone produced predominantly in the adipose tissue. It displays characteristics similar to insulin. Visfatin directly binds the insulin receptor (however at a different site than insulin), which results in increased glucose absorption both in vitro and in vivo. Visfatin then demonstrates a hypoglycemic profile. There are studies that show a direct link between visfatin and obesity, and the development of type 2 diabetes in adults [33]. There are also some sporadic reports about a potential correlation of the concentration of visfatin serum and insulin resistance during the prepuberty period in children who were born prematurely [34]. Some research shows that the visfatin level is significantly higher in newborns with intrauterine growth restriction, IUGR, compared to babies born with body weight appropriate for their gestational age. Higher visfatin levels in newborns with IUGR might serve as a prognostic marker of later development. The pathology of pregnancy that results in IUGR may be responsible for higher visfatin concentrations in blood, which in turn might become a marker of later development of insulin resistance, type 2 diabetes, and the metabolic syndrome [35].

   Summing up, none of the above biochemical parameters represents a good single marker of nutritional status or a prognostic element to predict the future development of preterm newborns. A great limitation is the cost of the analyses and the lack of possibility to perform them in laboratories not located in big research centers. In the majority of cases, these are not standard tests but only constitute part of research projects. There is also a lack of qualified and experienced laboratory staff to carry out the analyses described above.

Analysis of body composition

One of the methods to evaluate nutritional status and to monitor nutritional therapy is to analyze the body composition. Currently, there are a number of techniques to study body composition, however they are complex and costly, which makes them inaccessible in clinical practice. In epidemiologic (population) studies, anthropometric methods are still most common despite their reduced accuracy.

a. Anthropometric methods

In anthropometric analysis, the basic markers of nutritional status and indirectly body composition are body weight, body height and head circumference. The results of the measurements are compared to the reference values shown on percentile charts for a particular age group. There are also percentile growth charts for the population of babies born prematurely [36].

In addition to the above measurements, there is also an anthropometry of skinfold body test, which allows the analysis of the adipose mass. The measurements are performed at 3 anatomical sites – on the abdomen, over the triceps, and under the scapula. This method is used on assumption that there is a constant fraction of fat tissue under the skin (in those particular locations). Body fat mass is calculated based on the tables characteristic of a particular population. The repeatability of this test is, however, low [37]. Also, there are no developed reference values for the population of preterm newborns; hence this method is of little use in neonatological practice.

b. Dual Energy X-ray Absorptiometry (DEXA) method

It is a reference method to analyze the body composition both in children and in adults (38). The test is based on a whole body scan with the use of two different doses of X-ray radiation. The differences in the absorption of two energies (43 and 110 keV) by soft tissues and bones make it possible to determine bone mineral density (BMD), bone mineral content (BMC), lean body mass (LBM), fat mass (FM), and the percentage of fat in total body mass (%FM).

This method has been widely employed in the analysis of body composition of babies born prematurely. The first large study which evaluated the size, body composition, and

distribution of fat tissue in preterm babies was published in 2009 by Cook and Griffin [36]. The authors showed that on discharge from the hospital preterm babies not only had reduced body mass, but also incorrect proportions of body composition, such as reduced lean body mass and increased fat percentage, in particular peritoneal fat. These data appear to support the theory of obesity as an inborn disease [39, 40]. They suggest that newborns with very low and extremely low body mass are in the group with a higher risk of developing insulin resistance [41, 41]. Analyses of body composition of newborns born prematurely provide a lot of information on how to provide them with nutritional support both during infancy and in the early childhood period. Poor somatic development along with the decrease of lean body mass and parallel increase of fat tissue mass suggest that babies born prematurely receive nutrition in which the protein content is too small as related to total calorie intake [39]. There were a few studies which tested the above theory by comparing the body composition of newborns born prematurely that were fed with either infant formula for preterm infants or infant formula for infants born at term. The results of those studies still require further verification [43].

The advantage of the above method is its ability to determine the composition of both the entire body and its separate parts, which is not possible with the use of other methods, i.e. BIA. The analysis is relatively common due to its ease of performance, good accuracy, reproducibility of the results, and short scan times, which last approximately several minutes. However, the disadvantage of the DEXA scan is its use of X-ray energy with a relatively large dose of radiation, which requires special consideration, particularly in infants born prematurely (44).

c. Bioelectrical Impedance Analysis, BIA

This is a method based on the measurement of body tissue resistance to electric current at low voltage (≤1mA) and at the frequency 50 kHz, or a variable range of frequencies [45]. It allows the measurement of impedance components, such as electrical resistance (R) and the capacity resistance/reactance (Xc) of the analyzed tissues [46]. Adipose tissue includes a small amount of water and electrolytes, therefore it is a weak electric transducer, and it shows high impedance, in other words resistance. In contrast, lean body mass includes a large amount of both extra- and intracellular water, which makes it a good electric transducer, and demonstrates low resistance. A proper selection of electric current frequencies makes it possible to calculate volumes of water in the intracellular (ICW, intracellular water), and extracellular (ECW, extracellular water) spaces [47]. Such measurements allow the indirect estimation of total body water (TBW), fat free mass (FFM) and fat mass (FM) [37, 48]. BIA analysis is non-invasive, safe and quick, since the measurements take from a few seconds to few minutes. BIA does not require the patient's cooperation. The cost is relatively low, and the measurements are reproducible, therefore many authors consider it to be ideal for the analysis of body composition, also in children. The disadvantage of this method is the lack of possibility to determine the amount of regional fat tissue, i.e. peritoneal fat. There are still very few reports on the use of the BIA method in newborns, in particular premature newborns [49].

SUMMARY AND CONCLUSIONS

None of the above methods represents a good single marker of nutritional status or prognostic factor of the future development of premature infants; however a combination of several methods from different groups seems to be a promising possibility. It is critical to continue searching for markers that will help to optimize correct nutritional therapy in prematurely born infants in a simple and efficient way.

Analysis of nutritional status of a preterm infant – recommendations of management:

1. Regular measurements of body mass, body length, head circumference along with the evaluation of these parameters relative to the appropriate age reference values visualized on growth charts are critical.
2. Biochemical methods, which include proteins with short half-lives, such as prealbumin, RBP, IGF-1 can be used to monitor nutrition therapy; however none of these substances constitutes a good single marker of nutritional status.
3. Analysis of body composition with BIA or DEXA is not a standard approach, mostly due to the limited access to the right equipment; however many reports also question the safety and accuracy of those scans.
4. High hopes are raised by clinical studies that investigate new hormones controlling a widely defined energy metabolism, such as ghrelin, visfatin, leptin, relaxin, irisin, which might provide some prognostic value to future approximate body metabolism.

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