MEASUREMENT OF BODY COMPOSITION AND ITS SIGNIFICANCE IN TREATMENT OF ONCOLOGICAL PATIENTS

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Summary

Body composition changes could indicate health conditions and potential health risks. Although several methods are currently available for quantitative assessment, each has limitations. Indirect methods are most frequently used because of their availability and simplicity. One of those methods, which found wide use in clinical trials and everyday clinical practice and was found to be of great value in oncology patients, is bioelectrical impedance (BIA). Assessed muscle volume and mass, measured by BIA, were associated with chemotherapy toxicity and overall prognosis, regardless of the primary tumor site. It has been shown that calculated phase angle could be a strong prognostic factor for a particular endpoint and an independent prognostic factor in patients with advanced malignancies. Body composition was also found to correlate with the quality of life (QoL) of patients with cancer, and several studies have shown a significant impact on various QoL subdomains. Measuring body composition and the information it provides could be used for the development of different clinical interventions that can help cancer patients live longer and better lives.

KEYWORDS: body composition; bioelectrical impedance; cancer; sarcopenia

BODY COMPOSITION MEASUREMENT

Body composition assesses the proportion of individual components: water, fat, bone, and muscle tissue in the body. Assessment of the ratio of individual body components and evaluation of nutritional status are essential for physicians because they could indicate the presence of health conditions and potential health risks. Measuring body composition is particularly important in assessing and treating obesity and related diseases, such as metabolic disorders and cardiovascular diseases. Still, it has also been shown to be helpful in the treatment of some other diseases, such as kidney disease, malignancies, and anorexia(1). Repeated measurement of body composition allows monitoring of changes in health status and assessing the effectiveness of dietary and other therapeutic interventions(1,2).

METHODS FOR MEASURING BODY COMPOSITION

Although several methods are currently available for quantitative body composition assessment, each has limitations regarding the technical characteristics and information it provides. All methods are based on assumptions about tissue density, electrolyte and water concentration, and interrelationships between body and tissue components and their distribution in healthy individuals(3). Direct methods analyze the body from the atomic to the cellular level. These methods are not widely available; they have many technical requirements and, therefore, can only be carried out...
in laboratories with adequate equipment (total body water measurement based on isotope dilution, total body measurement based on the measurement of naturally radioactive potassium 40 in the body, etc.) (4–7). Criterion methods measure the properties of the body, such as density, and describe the quantity and distribution of skeletal, muscle, and adipose tissue using X-rays or magnetic fields (densitometry, computed tomography, magnetic resonance) (8–11).

They are less technically demanding than direct body measurement methods but more expensive and often unavailable in everyday clinical practice for this purpose. With indirect methods, we do not measure but only assess the body composition (anthropometric measurements – weighing, height measurements, measurements of the circumference of the abdomen and skin fold, calculation of body mass index, and bioelectric impedance analysis). They are easily performed, inexpensive, and widely available. Individual characteristics and some health conditions could greatly affect the results of indirect measurements. Hence, errors in body composition estimation are expected more often with these methods (12,13).

Bioelectrical impedance (BIA) in clinical practice

Basic principles of bioelectrical impedance are based on two assumptions. The first one relies on the fact that the human body mainly comprises water (around 55% of total body water is intracellular, and about 45% is extracellular) and ions, which are good electrical conductors (14). Muscles and bones are less conductive, while adipose tissue is the least conductive part of the body and provides the most significant resistance to electric current (15). This method measures different body components’ resistance (impedance) when conducting an alternating electric current of very low strength. In practice, body impedance is defined by a drop in voltage recorded when a constant current of low power and constant frequency (800 μA, 50 kHz) passes between two electrodes in contact with the subject’s palms and/or feet. Lean tissue rich in water and electrolytes has the lowest impedance. In contrast, adipose tissue has the highest, and the amount of lean tissue and body fat can be indirectly calculated from this difference (16). The obtained resistance index is proportional to the total body water volume and is used as an independent variable in regression equations to predict body composition. The final result of bioelectrical impedance analysis (BIA) is an estimation of the amount of total body water (TBW), fat-free body mass (FFM), and total body fat (17–19). The second basic principle of the BIA model is based on the assumption that the human body behaves as a cylindrical ion conductor with a homogeneous composition, constant cross-sectional area, and uniform distribution of current density (20). BIA measures the resistance to the flow of an electric current through the total body fluid. Thus, the total conductive volume – V (represented by TBW or FFM) is directly related to the square length of the conductor – S and inversely correlated with the resistance of the cross-section area of the conductor – R. At the same time, p stands for the specific receptiveness of the conductor, which generates the equation: \[ V = p \times S^2/R \]. Based on this presumption, solely arms and legs contribute to 47-50% of the total body resistance (despite contributing only 4-17% of body weight), while the trunk, which carries 50% of the body weight, contributes only 5-12% of the total body resistance (14). The main disadvantage of this method in everyday practice is that bioelectrical impedance analyzers use equations based on biological relationships within the particular population to describe statistical associations (21). The relationship between the obtained bioelectrical data and TBW, including the validity of the method itself, can be influenced by gender, age, race, ethnicity, phase of the menstrual cycle, type of disease, amount of fat in an individual, etc. Produced BIA equations are population-specific and useful only in subjects who match the comparative (reference) population by the size and shape of their body. When used in a population with different characteristics, these methods could yield wrong results with an average error of up to 8% (22,23). In a review article by Heyward and Wagner, who examined the reliability and validity of different equations when measuring BIA, it was shown that BIA results are incorrect when generalized equations are applied in different ethnic groups (24). Body composition diversities between ethnic groups could be explained by different adipose tissue quantity and distribution, average body weight, and different body proportions (25–27). Other factors influencing BIA results are food and beverage intake, physical activity before measurements, health conditions that impact fluid and electrolyte balance, environmental factors, and the subject’s characteristics (28–34). Considering the above, the
BIA method is unsuitable for measuring body composition in extensive international epidemiological studies involving a heterogeneous population of subjects, given that predictive equations have not yet been defined for individual ethnic groups. Therefore, the validity of the results obtained is questionable. In smaller studies including homogeneous populations (same ethnicity, sex, age, level of physical activity, or health status), it is possible to assess the body’s composition with a high-reliability level with this method(35). BIA advantages are low cost, simple conduction of measurements with minimal requirements for the subjects, and safety (it is not recommended in patients with pacemakers).

MEASUREMENT OF BODY COMPOSITION IN ONCOLOGICAL PATIENTS

Body composition has relatively recently begun to be studied as part of oncological studies in different types of tumors in the context of metabolism of various anti-tumor drugs, assessment of the response to treatment and its tolerability and, consequently, the overall prognosis of malignant disease depending on the proportion of individual body components(36-38).

Skeletal muscles and adipose tissue estimation using computed tomography (CT) imaging became popular in larger oncology centers because of its availability, high accuracy, and moderate expenses, especially in patients with metastatic disease, mainly because most of these patients undergo initial CT or MRI staging before cancer treatment, on which body composition can be measured(39). CT has become the preferred standard for providing information on body compositional changes, especially those associated with cancer cachexia(40). In particular, fat and muscle area at the L3 vertebra level are highly correlated to other measures of body composition, and serial imaging enables longitudinal assessment of changes in body composition following treatment that cannot be captured by conventional anthropomorphic measurements(41,42). One of the measures recently highlighted as relevant in predicting outcomes is myosteatosis, or fat deposition in muscle. A meta-analysis identified that patients with lymphoma, gynecologic, renal, pancreatic, hepatocellular, gastroesophageal, and colorectal cancers who had higher myosteatosis had worse overall survival(43).

In everyday clinical practice, the body composition of an oncology patient is assessed by conducting simple anthropometric measurements of body height and mass and calculating the body mass index and body surface area, which is used to estimate the dose of predicted antineoplastic therapy.

Body surface area (BSA) calculation is used in oncology to derive the required dose of a cytotoxic drug for an individual patient. It was introduced in clinical practice due to mutual agreements, more than scientific research work, and it is often questioned(44-46). This method is based on the assumption that body size is proportional to organ size and function. Still, it is considered that BSA, which is obtained as a function of body height and mass, is not an ideal parameter for such a correlation(47). The volume and type of tissue in the human body in which cytotoxic drugs are distributed and metabolized could significantly affect their bioavailability and, ultimately, their efficacy. Most cytotoxic drugs are metabolized and excreted through the liver, and BSA, in this case, is not a good indicator because hepatic function, unlike renal, correlates poorly with body size (45).

Assuming that fat-free body mass (FFM) represents the distribution volume for most cytotoxic medications, it is estimated that single variations in FFM could lead to significant changes in chemotherapy distribution volume applied by the unit of body surface(36). Few recent studies performed on drugs such as carboplatin, fluorouracil, and paclitaxel identified the levels of exposure beyond which unacceptable toxicity occurs after BSA-based dosing. This variability reflects differences in the way individual patients clear drugs, which underscores the need for an alternative to BSA-based dosing(48-51).

Several systematic reviews have summarized the literature on cancer survival in relation to BMI at the time of diagnosis. A meta-analysis that involved studies for 15 cancer sites recently reported a modestly increased risk of overall mortality as well as cancer-specific death in obese patients (BMI≥30) with breast, colorectal, and uterine cancer. A decreased risk of death was found among lung, renal cell carcinoma, and melanoma cancer survivors(52). The Global Cancer Update Program group studied the relationship between a number of anthropometric measures of adiposity and breast cancer outcomes and found that elevated
BMI was associated with more significant all-cause mortality and breast-cancer-specific survival, recurrence, and incidence of second primary cancers(53). Generally, similar findings have been reported in a recent review of studies focused on colorectal cancer survivors. The risk of death from any cause was elevated at the extremes of the BMI range (BMI <18.5 or ≥35). However, those in the overweight range displayed the lowest risk of death (obesity paradox). Similar patterns were observed for disease-free survival and colorectal cancer-specific deaths(54).

Bioimpedance measurement for body composition assessment has also been shown to be valuable in oncology patients(55). During BIA measurements, cell membranes produce resistance to the electric current flow, causing electric charge accumulation and increased capacitance, which causes the current to lag behind the voltage, consequently creating a phase shift. This shift is geometrically quantified as phase angle, defined as the calculated ratio of capacitance and resistance, and expressed in degrees.

It has been shown that phase angle could be used as a strong prognostic factor for a particular endpoint in patients with advanced pancreatic cancer and an independent prognostic factor in stage III B and IV non-small cell lung cancer patients(55-60). There are some reports that BIA can be used in the assessment of sarcopenia, and one systematic review of this topic found that sarcopenia identified by BIA was associated with poor clinical outcomes(61). Although the accuracy and clinical value of the BIA results are frequently debated, newer multifrequency BIA technology is more promising and may have more significant correlations with computed tomography (CT) scan–based body composition measurements(62).

**BODY COMPOSITION SIGNIFICANCE IN TOLERABILITY OF CANCER TREATMENTS**

In recent decades, the prevalence of overweight and obesity has been rising, and so is the number of obese cancer patients. Obesity is a known strong predictor of worse outcomes, but it can also complicate drug dosing(63). In obese patients, it was common to empirically lower the full-weight-based dosage to prevent excessive toxicity (dose capping). However, there was no evidence that toxicity was increased among obese patients receiving full-weight-based chemotherapy doses, while some studies suggested compromised survival outcomes(64-67). Therefore, in 2012, the American Society of Clinical Oncology (ASCO) released clinical practice guidelines recommending full-weight-based chemotherapy doses in obese patients(68). A recent study of early breast cancer patients showed that obese patients (in which no upfront dose capping was applied) treated with adjuvant docetaxel-containing chemotherapy received a lower relative dose intensity (RDI) compared to lean patients.

Obese patients had shorter disease-free survival and overall survival compared to lean patients, which was also the case when only patients with an RDI of 85% or higher were analyzed. Therefore, it appears that obese patients tolerate full-weight-based docetaxel chemotherapy less well compared to lean patients, which negatively influences survival outcomes(69). Differences in body composition could be one of the reasons for differences in chemotherapy tolerability. Still, this parameter is not used for chemotherapy dose calculation and adjustments in everyday clinical practice. Studies found that adipose tissue distribution and higher visceral fat levels affect cancer patients’ overall survival (70). On the other hand, sarcopenia is characterized by a reduction in skeletal muscle volume and mass, and it is associated with more significant chemotherapy toxicity, a higher risk of other medical conditions and death, and a worse overall prognosis, regardless of the primary tumor site(37-38). It is a common finding in cancer patients in general, and recently published meta-analysis data have suggested that 19-74% of patients with solid tumors have sarcopenia, which correlates with worse overall survival, not only in patients with metastatic but also in patients with non-metastatic disease(71). Most recent studies conducted on patients with gastric cancer have confirmed this statement, demonstrating that sarcopenia is a significant predictor of chemotherapy toxicity and worse overall survival(72-75). In a clinical trial conducted on patients with metastatic breast cancer treated with capecitabine, 25% of patients were classified as sarcopenic, and 50% had pronounced side effects of treatment, unlike non-sarcopenic patients in whom the incidence of adverse reactions was 20%. 
Time to disease progression was also significantly shortened in sarcopenic patients. Data analysis showed that sarcopenia was the only significant predictor of toxicity. In contrast, other variables previously known to have an impact on toxicity prevalence (age, BSA, performance status, and albumin level) were not(76).

Supposed sarcopenic obesity, which includes both risk factors – sarcopenia and high visceral fat level – was presumed to be the predictor of the worst outcome in multiple analyses(36,77). In their research, Prado et al. have demonstrated that sarcopenic obesity (diagnosed by lumbar CT scans) reduces survival chances by half(36). One of the assumed theories is that in obese patients, a tiny percentage of loss of total body mass could potentially mask a significantly more considerable proportional loss of skeletal muscle mass(78). In this case, calculating chemotherapy dose based on total body mass, without correction according to body composition, could lead to higher chemotherapy dose exposure and, consequently, higher toxicity rates. Meta-analysis of twenty-six studies analyzing outcomes in gastrointestinal surgical oncology found that patients with sarcopenic obesity showed increased incidences of total and significant complications. Sarcopenic obesity was particularly associated with the incidence of cardiac complications, leak complications, and organ/space infection and was predictive of poor overall survival and disease-free survival(79). However, some studies show no association between sarcopenic obesity and mortality, where patient weight acted as a protective factor against mortality, supporting the obesity paradox(80).

It is important to note that the relationship between sarcopenic obesity and cancer outcomes is complex and varies depending on the type of cancer and the stage of the disease. Studies performed use considerable variations in definition, cutoffs, and assessment methods for sarcopenic obesity, which translates to complicated clinical practice(81).

**BODY COMPOSITION AND CANCER PATIENTS’ QUALITY OF LIFE**

Body composition measurement analyses in correlation with the quality of life (QoL) have shown a significant impact on health-related quality of life (HRQOL) as on other QoL subdomains in several studies. Most described is the effect of low skeletal muscle mass on HRQOL. A meta-analysis of 14 studies with 2776 participants showed that low muscle mass was associated with poorer global HRQOL scores and poorer physical functioning subdomain but not social, role, emotional, or cognitive functioning subdomain scores(82). A cross-sectional study performed in 2018 on patients with non-small cell lung cancer showed that low muscle mass negatively impacted physical and role-functioning HRQOL subdomains in both genders and overall HRQOL in male patients(83).

Similarly, a cross-sectional study of patients with incurable lung and gastrointestinal cancers found that low skeletal muscle was associated with worse overall HRQOL and more significant symptoms of depression (84). Fat body mass also significantly impacted QoL in cancer patients and survivors. Higher fat-body mass proportion and poor physical functioning interrelationships have been described(85-87). A meta-analysis that investigated the QoL of endometrial cancer survivors showed that obese subjects had significantly poorer physical functioning, social functioning, and role-functioning subdomains when compared to non-obese women. Emotional and cognitive functioning subdomains did not show significant differences(88). Fatigue is one of the important domains of HRQOL, and patients with higher body fat percentages were significantly more tired than the ones with higher muscle mass percentages(89). Multiple factors probably cause changes in the sexual functioning domain throughout cancer treatment. However, the correlation between higher body fat percentage and poor sexual functioning has been described. It is assumed that patients with a higher rate of body fat have disturbed body image as well, which significantly impacts both sexual performance and sexual desire(89,90).

**FUTURE PERSPECTIVES**

Early screening to identify patients with occult muscle loss, combined with multimodal interventions that include nutrition therapy and exercise training combined with pharmacotherapy, is necessary to prevent or slow down the cancer-related process of tissue wasting and reduce the incidence of poor clinical outcomes. Simple and cost-efficient methods to measure metabolic processes’ essential body components should be inte-
grated into large-scale clinical workflows. The interest of the oncology community in body composition measuring is growing, and today represents one of the very provocative areas, given that it opens up additional possibilities for interventions that could help oncology patients to live longer and better lives.

REFERENCES


Sažetak

MJERENJE SASTAVA TIJELA I NJEGOV ZNAČAJ U LIJEČENJU ONKOLOŠKIH BOLESNIKA

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Promjene u sastavu tijela mogu ukazati na postojanje određenih zdravstvenih stanja i rizika. Iako su trenutno dostupne brojne metode za kvantitativnu procjenu sastava tijela, svaka od njih ima svoja ograničenja. Najčešće se upotrebljavaju indirektna metode zbog njihove dostupnosti i jednostavnosti. Jedna od tih metoda, koja je našla široku primjenu u kliničkim ispitivanjima i svakodnevnoj praksi, a pokazala se i vrlo vrijednom u onkološkim bolesnika, je bioelekttrična impedanca. Pokazalo se da se procijenjena masa i volumen mišića mjereni bioelektričnom impedancom mogu povezati sa toksičnošću kemoterapije i ukupnom prognozom bolesnika, nezavisno od sijela primarnog tumora. Pokazalo se da se izračunati fazni kut može koristiti kao snažan prognostički faktor za određene ishode, kao i nezavisni prognostički faktor u bolesnika sa uznapredovalim malignom. Sastav tijela je također povezan i s kvalitetom života onkoloških bolesnika, a brojna istraživanja su pokazala značajan utjecaj na različite poddomene kvalitete života. Mjerenje sastava tijela i informacije koje ono pruža mogu se upotrijebiti za razvijanje različitih kliničkih intervencija koje mogu pomoći onkološkim bolesnicima da žive duže i kvalitetnije.

KLJUČNE RIJEČI: sastav tijela; bioelekttrična impedanca; rak; sarkopenija