**Bioelectrical spectroscopy impedance phase angle is not associated with nutritional status in a stable cohort of paediatric inflammatory bowel disease patients**

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**Abstract**

**Background-** Nutritional assessment in paediatric inflammatory bowel disease (IBD) is key to supporting growth whilst minimising adiposity. Bedside assessment using bioelectrical impedance spectroscopy (BIS) has previous identified patients with declining cellular and nutritional health. We aimed to assess BIS measures in stable paediatric IBD patient.

**Methods****-** Stable IBD patients were recruited at routine hospital visits. All patients underwent BIS, anthropometry and disease activity assessment. Multivariable regression and receiver operator curve (ROC) analyses were undertaken to assess the utility of BIS phase angle 50KHz (PA-50) and 200/5KHz impedance ratio (IR) in nutritional assessment.

**Results-** There were 140 study visits from 97 patients, mean age 14.49 years, 62.9% Crohn’s disease. Mean BMI Z-score (BMIZ) was 0.31 (range -2.97 to 3.99), 33% of patients were overweight (BMIZ>1) and 13.8% of patients were underweight (BMIZ<-1). Crohn’s disease patients had a lower mean BMIZ score 0.14, compared to ulcerative colitis, 0.68, p=0.007.

There was no relationship between PA-50 and BMIZ or disease activity. IR was not related to disease activity but was negatively related to BMIZ in a multivariable regression, accounting for age, sex and disease subtype (beta -0.331, p=0.001). ROC did not identify a clinically useful cut off for either PA-50 or IR to identify patients with active disease, biologic use or BMIZ>1 or <-1.

**Conclusion-** BIS appears to have limited added value in nutritional assessment of stable paediatric IBD patients. Nearly 1/3 patients were overweight and personalised approach to supplementation is vital to avoid overnutrition.

**Keywords:** phase angle, children, bioelectrical impedance, nutrition, inflammatory bowel disease

**Introduction**

Inflammatory bowel disease (IBD) is a relapsing and remitting inflammatory condition, comprising Crohn’s disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU). The incidence and compound prevalence of paediatric and adult-onset IBD is increasing worldwide1,2. Historically, children presenting with CD were often malnourished resulting in linear growth delay and poor weight gain3,4. Improvement in medical therapy, including better nutritional management, timely immunosuppression and widespread use of anti-TNF agents has resulted in improved disease contol and early indications of restored growth5,6. Additionally, contemporary data indicates that at the time of diagnosis, patients with IBD appear to have less severe growth deficits than previously reported, and these recover over the course of treatment7. Despite improvements in medical therapy, nutritional support remains based on the premise of a malnourished CD phenotype, resulting in continued widespread use of oral nutritional supplements (ONS)8. With improved control of underlying inflammation, including transmural and mucosal healing of the small bowel the need for ubiquitous nutritional supplementation may be diminishing, with targetted nutritional support being more important. There is an emerging body of evidence pointing towards increased prevalence of overnourishment in IBD, associated with adverse outcomes9. Simple bedside anthropometry and accurate body composition assessment is likely to improve our ability to personalise nutiritonal and improve outcomes in paediatric disease10,11.

Body mass index (BMI) is routinely used as a marker of nutritional status. However, it is a crude measure of body habitus, does not represent body compsition, and is recognised as being insufficient to identify all children with malnutrition presenting to acute services12. Simple assessment of nutritional status and body composition in patients is desirable. Using techniques such as computerised tomography (CT), dual energy X-ray absorptiometry (DXA) or air-displacement plethysmography (ADP) to assess body composition are not easily accessible in a clinical setting, with the additional exposure to radiation associated with CT and DXA13. Bioelectrical impedance spectroscopy (BIS), a simple bedside test that measures the resistance and reactance of a subject to a weak alternating electrical current, can be used to provide a derived measure of body composition and, through assessment of the phase angle measure, cellular health14. This then allows the potential for identification of those children at risk of declining physiological and functional reserve. Whilst BIS measures of resistance and reactance as raw values are accurate, estimates of fat mass (FM) and fat-free mass (FFM) derived from proprietary equations are device and population specific, and predicted measures of body composition using BIS have shown poor agreement with reference methods of determining body composition, especially in children15. Phase angle (PA), a measure of the relationship between resistance and reactance, have previously been shown to predict health status, with higher PA values predictive of increased functional reserves and resilience as well as being associated with improved nutritional status in infants and older children14,16. Low measures of PA at a frequency of 50Khz have been reported to occur earlier in children than changes in anthropometry, suggesting the use of BIS in a clinical setting may identify children with nutrition risk earlier, providing the opportunity for timely intervention14. An alternative approach is to use a composite measure of PA such as PA 200KHz/5KHz- the impedance ratio (IR). In children with renal disease who had a normal BMI, an IR ratio of <1 in children was associated with changes to cellular permeability and tissue hydration, including an increased extracellular fluid component and lower muscle mass as found in poor nutritional status17,18. Similarly, higher IR values at 200KHz/5KHz, have been associated with abnormal body composition and poorer overall health, including increased oedema in breast cancer patients, and increased mortality chronic obstructive pulmonary disease19,20.

We hypothesised that patients with poorer nutritional status, as measured by a BMI Z-score (BMIZ) <-1 (undernutrition) or >1 (overweight), or higher disease activity, would have lower phase angle at 50KHz or abnormal IR values. The primary aim of this study was to assess the relationship between BIS-PA, anthropometry and disease activity in a cohort of prospectively recruited stable paediatric IBD patients. Secondary aims were to characterise the growth and body habitus of this cohort.

**Methods**

Study Design and patient population

Patients were recruited from the paediatric gastroenterology service at Southampton Children’s Hospital. To be eligible patients must have had a diagnosis of IBD in line with the modified Porto criteria21, have been aged under 18 years of age and attending routine appointments at Southampton Children’s Hospital. Patients were prospectively enrolled from September 2018 to February 2020. BIS measurements were collected at baseline and then at subsequent visits (follow up 1 and 2).

Bioelectrical impedance measurements

Patient measurements occurred at routine hospital appointments. BIS measurements were conducted with the ImpediMedSFB7 (Pinkenba, QLD 4008 Australia) device as previously described14. Briefly, this is a single-channel tetra-polar device measuring resistance, reactance and phase angle across up to 256 frequencies. PA is a directly measured variable. The machine was calibrated before use with a circuit of known impedance, as per manufacturer’s guidelines. Measurements were taken in triplicate, with the mean used in downstream analysis. Measurements were conducted in unfasted subjects using a standard tetrapolar electrodes distribution whilst the patients were supine. Standardised anthropometric and BIS measures were performed by a small group of trained researchers.

*Data processing*

BIA measurement files were processed using Bioimp software (ImpediMed). Measurements were rejected if all values were zero (presumed failure of measurement). PA values at a current frequency of 5KHz, 50KHz and 200KHz were used for analysis. The impedance ratio (200KHz/5KHz) was calculated as previously described18.

Anthropometric measurement

At each study visit patients had their height and weight measured in line with local standard operating procedures, as previously described7. Measurements were performed and recorded in accordance with local Standardised Operating Procedures and World Health Organisation (WHO) guidelines. Children were weighed with minimal clothing and no shoes; weight was measured to the nearest 0.1kg using a digital scale. Height was measured to the nearest 0.1cm in children under a stadiometer (Seca 213: Birmingham, UK).

Definitions of malnutrition

Z-scores were calculated using WHO Anthro software version 3.3.3 2011 for participants <5 years and WHO AnthroPlus 3.2 for those ≥5 years. WHO growth reference interpretation of cut offs for malnutrition were used. Mild under-nutrition was defined as body mass index Z score (BMIZ) <-1, with moderate malnutrition was defined as a BMIZ for age ≤-2. Overweight and obesity were defined as BMIZ >1 and >2, respectively.

Clinical data collection

At the time of BIS measurements all patients had standardised collection of clinical data, including an appetite questionnaire, disease activity index score (paediatric Crohn’s disease activity index- PCDAI or paediatric ulcerative colitis activity index- PUCAI, as appropriate), medications and nutritional supplementations. PCDAI was used for IBDU patients. Each BIS measurement was linked with the clinical data at that visit.

Data and statistical analysis

Patient anthropometry was grouped by WHO classification and graphically represented, mean values were compared between groups using a T-test. Analysis of disease subtypes and BMIZ were performed using a χ2 test. We performed correlation between PA at 50KHz, the impedance ratio 200KHz/5KHz (IR), BMIZ and disease activity. Additionally, multivariate linear regression was performed to determine the factors associated with both disease activity (PCDAI or PUCAI) and BMIZ, whilst accounting for potential confounding variables. PA at 50KHz, and the IR were assessed in separated models. Co-variants were accounted for including medications, age and disease subtype.

Using a receiver operator curve (ROC) analysis for binary outcomes, including disease activity ≥15 and biologic use, we determined whether PA 50KHz, or the IR (200KHz/5KHz), were useful classifiers to determine these outcomes. All data were analysed using SPSS v25 (IBM).

Ethical approval

Ethical approval was granted by the London (Westminster) research ethics committee (18/LO/1457). All patients, or caregivers, gave signed informed consent prior to participation in the study.

**Results**

Ninety-seven patients were recruited to the study with 146 independent visits. Mean age at inclusion was 14.49 years, 85.6% of patients were of Caucasian ethnicity and 40 patients (41.2%) were female The median time from diagnosis to recruitment was 1.9 years (range 0.2-11.5 years). Twenty-two patients had one follow-up visit, 14 patients had two follow-up visits, supplementary figure 1. The remaining 61 patients had a single study visit. Across the visits there were 140 BIS measurements following quality filtering, with 6 study visits excluded for failure of BIS (all values 0). Each individual BIS measurement was included in the analysis as an individual timepoint.

Regarding CD, there were 89 study visits from 61 patients. Anthropometry was available at 86 (96.6%) of these visits. For UC there were 46 study visits from 31 patients. Anthropometry was available at 43 (93.5%) of these visits. The remaining 5 patients had IBDU, each of whom had a single study visit and 100% had anthropometric data available.

Disease activity was generally low, median disease activity index score 5 (range 0-40). Only 25 study visits (17.8%) corresponded to a disease activity score of ≥15 or more, indicating active disease and only 7 study visits corresponded to a disease activity score of 30 or greater, indicating moderate-severe disease activity. Only 5% of visits involved patients on steroids, whereas 67.9% of visits had patients on thiopurines and 35% had patients on anti-TNF therapy (infliximab or adalimumab).

Anthropometry across cohort

Considering all study visits across the cohort, the mean BMIZ was 0.34 (range -2.97 to 3.99). Mean BMIZ in CD was 0.14, compared to 0.68 for UC patients, p=0.007. Histograms were constructed to view the distribution of BMIZ across the entire cohort, and individually for CDand UC, figure 1. BMI, height and weight Z-scores are available in supplementary data 1.

Considering individual patients at the initial study visit only (94 patients had available data), the mean BMIZ was 0.31 (range -2.97 to 3.99). Seven patients (7.5%) had a BMIZ >2 and 24 patients (25.5%) had a BMIZ between 1 and 2. In contrast, 5 patients (5.3%) had a BMIZ <-2 and 8 patients (8.5%) had a BMIZ between -1 and -2.

In the BMIZ >1 group, 19 patients had CD, 10 had UC and 2 had IBDU. Comparing the expected number of patients in this group to the overall cohort did not show that a specific disease subtype was overrepresented in the overweight group, p=0.82. In the BMIZ <-1 group, 11 patients had CD and 2 had UC, again compared to the overall cohort no disease subtype was significantly overrepresented in the underweight group, p=0.15.

Phase angle 50KhZ is not related to BMI Z-score or disease activity

PA-50KHz data were correlated with disease activity (PCDAI or PUCAI) and BMIZ. There was no significant correlation between either disease activity, Pearson correlation coefficient (PCC) r2=0.086, p=0.32, or BMIZ score, PCC r2=0.02, p=0.78. All phase angle measures are available in supplementary data 2.

Phase angle 50KHz is not predictive of disease activity in a multivariable linear regression

To account for confounding variables two linear regression models were performed, for disease activity and BMIZ. There were no significant independent variables associated with disease activity, table 1. Disease subtype was associated with BMIZ, indicating CD patients had a lower BMIZ, as expected from anthropometric data above but PA-50 was not associated with BMIZ, table 2.

Impedance ratio negatively correlates with BMI Z-score, but not disease activity

The IR did not correlate with disease activity, PCC r2=0.02, p=0.84. There was a significant negative relationship between IR and BMIZ, PCC r2=-0.19, p=0.02, indicating those with lower BMI had a higher IR, potentially reflecting poorer cellular health.

Impedance ratio is negatively related to BMI Z-score in a multivariable linear regression model

As for PA-50, two linear regression models were performed for IR, with disease activity and BMIZ as the dependent variables. There were no significant independent variables associated with disease activity, table 3. For the BMIZ regression model, IR was negatively associated with BMIZ (standardised beta= -0.33, p=0.001). Additionally, age was negatively correlated with BMIZ, indicating older patients were more likely to have lower BMIZ, when all dependant variables were accounted for, table 4.

Receiver operator curves do not identify a significant phase angle 50KHz or impedance ratio associated with biologic use or active disease.

For binary outcomes we assessed whether clinically useful cut-off values for PA-50 or IR could be determined using ROC. Biologic use at time of measurement, active disease (PCDAI or PUCAI ≥15), overweight (BMIZ >1) and underweight (BMIZ <-1) were assessed. Neither PA-50, nor IR, produced a significant area under the curve (AUC), preventing a useful cut-off value from being determined, figure 2. IR AUC for BMIZ <-1 was 0.64 (95% CI 0.50-0.77), indicating borderline significance for identifying underweight patients using IR.

**Discussion**

In this cohort of stable paediatric IBD patients we found no evidence of significant nutritional deficient, although a third of patients were overweight or obese. BIS measures of PA and the IR were of limited usefulness in identifying malnutrition or active disease. However, whilst PA-50 was not significantly related to either BMIZ or disease activity index, IR was negatively associated with BMIZ, indicating that those with a higher IR were more likely to be underweight, however ROC analysis was unable to determine a clinically useful cut off value associated with undernutrition. Overall, our ambulatory cohort of paediatric IBD patients was stable, with good disease control. Overweight/obese patients (31 patients, 32%), as defined by a BMIZ >1, were more common compared to underweight patients (13 patients, 13.4%), BMIZ <-1. This pattern remained consistent for both CD and UC patients. This high prevalence of overweight patients within our ambulatory paediatric IBD cohort points towards personalised nutritional care being even more important. Obesity in IBD is associated with worse outcomes and increasingly paediatric clinical teams should be ensuring healthy eating occurs and avoiding routine supplementation9. Previous data also indicates that CD patients do not have a higher resting energy expenditure when they are well, providing additional evidence that routine nutritional supplementation is not required in this group22,23. There is an increasing need to reduce the prevalence of paediatric obesity within the general childhood population, and our data highlight the need to consider those with chronic disease in this strategy.

Despite the propensity of patients to be overweight or have a normal BMI, we did observe a higher IR in patients with a low BMIZ. Previous data indicates a higher IR may be associated with worse cellular health and increased intracellular fluid24. Studies looking at IR in disease have determined that higher values are associated with abnormal body composition such as lymphoedema in breast cancer patients, and increased all-cause mortality in patients with chronic obstructive pulmonary disease, although in patients with gastrointestinal malignancies the converse is true19,20. As such measures outside a “normal range” may be indicative of declining nutritional and physical health. Whilst this cohort was largely well and stable patients, these data indicate that IR may be a useful screening tool for undernutrition in IBD patients, although further validation of this is required in a cohort with higher prevalence of acute malnutrition and higher disease activity. Disease activity or biologic use was not associated with either PA-50KHz or IR. Despite this, previous data from hospitalised paediatric IBD patients did identify a significantly lower PA compared to healthy controls25. A similar increase in PA was also observed in patients treated with anti-TNF therapy, compared to conventional immunomodulation, in a study of adult CD patients26. As most patients in our study were in remission we may have lacked the power to differentiate between patients with inactive disease and those with modest disease activity. Our data suggest that BIS has limited use in identification of malnutrition in patients with stable disease and clinical and biochemical measures may be more effective27.

There are mixed results for the utility of BIS in assessment of body composition in IBD patients. Data from Dung *et al* assessed different equations for prediction of fat-free mass (FFM) in children with CD, demonstrating that body composition could be estimated from BIS measurements28. Similarly, data from our own group showed a significant correlation between psoas muscle cross-sectional area and BIS estimates of FFM, as a proxy of lean mass29. Whilst BIS can be used to assess other studies have pointed to significant inaccuracies and suggest that the primary BIS outputs, including PA and IR, are more useful in determining overall nutritional health of an individual17. We chose to use the primary BIS outputs to assess cellular health, rather than the derived measures of fat mass (FM) and FFM. Whilst these estimates may be clinically useful there are also large variation in the results from different equations used to calculate the FM and FFM, calling into question the validity of these for clinical practice, especially in patients with excess fat mass or abnormal hydration status15. Alternative research methods for ascertaining true body composition in children with IBD will be increasingly important. Utilising routine measures of lean mass from MRI or CT scans, alongside specific measures such as ADP, are likely to be useful in identification of patients who are overweight but have a lean muscle deficit11. Directing personalised nutritional care towards these patients is vital, and body composition toolkits must be developed to avoid untargeted supplementation.

All patients and study visits were prospectively recruited, with data captured at each visit. Standardised anthropometric and BIS measures were performed by a small group of trained researchers. Despite this we accept there are several limitations of this study, firstly the patients were largely well and stable, meaning we were unable to capture a broad spectrum of disease activity. Additionally, we did not include newly diagnosed patients which may have led to fewer underweight individuals being studied. However, the aim was to ascertain BIS measures and assess the utility in a group of stable IBD patients, representing the majority of children under follow-up. We acknowledge that BIS may be of use in differentiation of an inflammatory state in patients with active disease.

These data indicate that up to a third of stable paediatric patients with IBD are overweight. Recent ECCO-ESPGHAN guidance recommends maintenance enteral nutrition as a strategy for prolonging remission in patients with low CD activity30. Careful nutritional consideration must be undertaken in these patients to ensure supplemental nutrition is included in the entire daily calorific requirement for these patients, as energy supplementation beyond normal baseline requirements is not needed in CD. A higher IR may be able to identify those at increased risk of undernutrition. Thoughtful nutritional intervention in well IBD patients is vital and these data provide the framework to avoid routine supplementation whilst identifying those at increased risk of both over and undernutrition.

**Tables and figures**

Table 1- Enter multivariable linear regression, dependant variable disease activity (PCDAI or PUCAI)

Table 2- Enter multivariable linear regression, dependant variable BMI Z-score

Table 3- Enter multivariable linear regression, dependant variable disease activity (PCDAI or PUCAI)

Table 4- Enter multivariable linear regression, dependant variable BMI Z-score

Figure 1A- BMI Z-score distribution for the entire IBD cohort demonstrating a majority of patients have a BMI Z score >0, 1B- BMI Z-score distribution for patients with Crohn’s disease, 1C- BMI Z-score distribution for patients with ulcerative colitis.

Figure 2- Receiver operator curves (ROC) for biologic use, disease activity (PCDAI >10), BMI Z-score >1 and BMI Z-score <-1, determined by phase angle 50Khz and impedance ratio (200/5KHz). None of the ROC analyses demonstrate statistical significance.

**Supplementary data**

Supplementary figure 1- Flow chart of patient recruitment and study visits

Supplementary data 1- Height, weight and BMI Z scores for entire cohort at all time points

Supplementary data 2-­ Aggregated phase angle measurements for entire cohort at all time points

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