European Journal of Clinical Nutrition (1996) 50, 335–339
 0954-3007/96 $12.00

Altered body water distribution in subjects with juvenile rheumatoid arthritis and its effects on the measurement of water compartments from bioelectric impedance

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Objective: To assess the reliability of bioelectric impedance analysis (BIA) for predicting total body water (TBW) and extracellular water (ECW) in children affected by juvenile rheumatoid arthritis (JRA).
Subjects: Thirty-nine children affected by JRA and 23 healthy children of similar age (11.0 ± 3.6, range 3.0–19.0 y) were recruited for the study.
Methods: TBW and ECW were measured by deuterium oxide and bromide dilution, respectively. Bioelectric impedance (Z) was measured at frequencies of 5, 50 and 100 kHz. The prediction of TBW and ECW from BIA was based on the impedance index (ZI = height$^2/Z$, cm$^2/\Omega$).
Results: TBW standardized per kg of body weight and ECW standardized per litre of TBW were significantly higher in JRA as compared to control patients (59.7 ± 2.4 *vs* 57.7 ± 2.7% and 44.5 ± 4.6 *vs* 38.1 ± 7.9%, with $P < 0.005$ and $P < 0.0001$, respectively). Moreover, intracellular water standardized per litre of TBW was significantly lower in JRA than in control subjects (55.5 ± 4.6 *vs* 62.5 ± 8.1, with $P < 0.0001$). In both controls and patients, the use of ZI at 5 kHz offered the more accurate prediction of ECW. However, the use of ZI at 100 kHz did not offer a better prediction of TBW as compared to its value of 50 kHz. Control-generated formulae for predicting water compartments from BIA [TBW = 0.716 × ZI at 100 kHz–1.504, r = 0.934, s.e.e. = 2.2 l; ECW = 0.430 × ZI_5–3.652, $r = 0.869$, s.e.e. = 1.7 l] underestimated TBW and ECW in JRA patients. However, population-specific formulae [TBW (l) = 0.766 × ZI at 100 kHz–0.053, $r = 0.939$, s.e.e. = 2.8 l; ECW (l) = 0.399 × ZI at 5 kHz–0.283, $r = 0.886$, s.e.e. = 1.7 l] allowed an accurate prediction of TBW and ECW in JRA patients, taking into account their altered body water distribution.
Conclusions: Altered water distribution impedes the use of formulae developed on healthy children to predict TBW and ECW from BIA and JRA patients. It is hypothesized that chronic inflammation and subclinical malnutrition may be responsible for the altered body water distribution of JRA patients. Traditional body composition models may require adjustments for use in JRA children due to their altered body hydration and water distribution.
Sponsorship: The study was supported by MURST (Ministero Università Ricerca Scientifica e Technologica) '60%' grants.
Descriptors: juvenile rheumatoid arthritis, body composition, total body water, extracellular water, bioelectric impedance analysis

Introduction

Juvenile rheumatoid arthritis (JRA) is the most common rheumatic disease of childhood. It is one of the more frequent chronic illnesses and an important cause of disability in children (Cassidy, 1990). JRA is a chronic immuno-inflammatory disorder of joints which may nonetheless involve other organs. Extra-articular involvement is absent in oligo-articular JRA while it may be present in poly-articular JRA. However, it is always present in systemic JRA (Cassidy *et al*, 1986).

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Received 2 September 1995; revised 30 September 1995; accepted 5 October 1995

Abnormalities of growth and development are common in JRA patients (Bernstein *et al*, 1977). These abnormalities are generally related to the immuno-inflammatory activity of the underlying disease (i.e. they are more severe in the systemic type of JRA) (Cassidy, 1990). Moreover, prolonged use of corticosteroids (CS), which are commonly employed for the treatment of JRA, may further compromise growth and development of the affected children (Sturge *et al*, 1970).

It is therefore clear that nutritional status assessment should be an integral part of the clinical evaluation of JRA patients (Bacon *et al*, 1990). Unfortunately, biochemical indexes of nutritional status, eg plasma albumin and serum ferritin, are not suitable for use in JRA patients since their levels may be altered by inflam-

mation (Gibson, 1990). The assessment of body composition by means of clinically suitable techniques may nonetheless provide a simple method to establish nutritional status in patients with JRA.

Bioelectric impedance analysis (BIA) is a simple and expedite method for the assessment of total body water (TBW) and extracellular water (ECW). It is also commonly employed for the assessment of fat-free mass (FFM) (Heitmann, 1994). The prediction of water compartments from BIA relies largely on the ECW to intracellular water (ICW) ratio (Deurenberg *et al*, 1989, 1995*a*). While BIA has a great potential to be employed for assessing body composition in JRA, no study has been performed yet (as far as is known) to assess its accuracy in patients with this disease.

There are some reasons for which body water distribution may be altered in patients with JRA. First, there is both clinical and experimental evidence that chronic inflammation may lead to an expansion of ECW (Chrousos, 1995). Second, non-steroidal anti-inflammatory drugs (NSAIDs) and CS, which are commonly employed for the treatment of JRA, have well known sodium- and water-retaining effects, which may be responsible for the expansion of ECW (Rose, 1994). Lastly, nutritional status may have an independent effect on ECW. In fact, ECW may expand as a consequence of both under- or over-nourishment (Shetty, 1995; Battistini *et al*, 1995).

It follows that a validation of BIA is surely needed in order to ascertain its applicability to patients with JRA. The present study aimed at assessing body hydration and water distribution in subjects with JRA and the accuracy of the BIA method for predicting body water compartments in this disease.

Materials and methods

Subjects

Thirty-nine children affected by JRA were recruited for the study. They were followed as outpatients at the Third Paediatric Clinic of the Second University of Napoli (Italy). Twenty-three healthy children of comparable age served as controls. The age of all the subjects was comprised between 3.0 and 19.0 y. Informed consent was obtained from all the subjects participating into the study. For subjects < 18 y of age, informed consent was obtained from parents. The study protocol had previously been approved from the Ethical Committee at the Second University of Napoli. Diagnosis and classification of JRA were based on the criteria established by the American Rheumatologists Association (Cassidy, 1990). Since the study protocol required that patients had no evidence of cardiac, hepatic and renal disease, patients with systemic JRA were excluded from the study. However, no selection was made on the basis of the pharmacological therapy eventually followed by the children. This was done in order to ascertain if pharmacological therapy would affect with ECW : ICW ratio in patients with JRA. All subjects were on a free diet.

Anthropometry

Body weight, height, arm circumference (AC) and triceps skinfold (TSF) were measured following the Anthropometric Standardization Reference Manual (Lohman *et al*, 1988). Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Arm fat area (AFA), arm muscle circumference (AMC) and arm muscle area (AMA) were calculated as described by Frisancho (1990).

TBW and ECW assessment

TBW and ECW were measured by deuterium oxide (D_2O) and bromide (Br) dilution, respectively. A preliminary study aimed at establishing the equilibration time of D_2O and Br was done on the plasma of five unselected JRA patients. Both tracers reached the equilibrium 3.0 h after their administration, a time comparable to that observed in healthy children (Battistini *et al*, 1992, 1995). Subjects had fasted for at least 8 h and voided the bladder before receiving orally a precisely weighed solution made up of D_2O, NaBr and drinkable water. Plasma samples were collected before the administration of this solution and 3.5 h later, as described in detail elsewhere (Battistini *et al*, 1992, 1994). Deuterium concentration in plasma samples was measured by FT-IR spectrophotometry according to the method of Lukaski & Johnson (1985). TBW was calculated as deuterium dilution space $\times$ 0.95, taking into account non-aqueous distribution of D_2O. Bromide concentration in plasma samples was measured by HPLC according to the method of Wong *et al* (1989). ECW was calculated as bromide dilution space $\times$ 0.90 $\times$ 0.95, taking into account non-extracellular distribution of bromide and Donnan's effect, respectively. The final concentration in plasma was below one-tenth of the value regarded as toxic (6 mM) (Goodman & Gillman, 1970). TBW was standardized per kg of body weight in order to obtain body hydration (TBW%). ECW and ICW were standardized per litre of TBW and expressed as a ratio to obtain indexes of water distribution (ECW%, ICW% and ECW : ICW ratio, respectively).

BIA

The determination of bioelectric impedance (Z) was made with a tetrapolar impedance plethysmorgraph (Human IM Scan, Dietosystem, Milano, Italy) at frequencies of 5, 50 and 100 kHz, as described in detail by Segal *et al* (1991). The impedance index or ZI was calculated as the ratio between height^2 (cm^2) and Z (Ω).

Statistics

Statistical analysis was performed on an Apple Macintosh computer using the Statview 4.01 and Super-ANOVA 1.1 software packages (Abacus Concepts, Berkeley, USA). Differences in body composition between controls and patients and within patients were evaluated by one-way ANOVA. Partial correlation coefficients were calculated in order to identify the frequencies at which ZI was significantly correlated with TBW after correcting for ECW and vice versa. This method is described in detail by Deurenberg *et al* (1995*a*). Differences between measured and predicted values of TBW and ECW within groups were evaluated by paired t-tests. The same differences were evaluated by one-way ANOVA when the equations generated on controls were applied to JRA patients. These differences were also correlated to the ECW : TBW ratio in order to assess their degree of dependence from body water distribution of JRA patients (Deurenberg *et al*, 1995*a*). ANCOVA was used to compare regression equations

generated on controls to those generated on JRA patients (Norgan, 1995). Results are expressed as mean ± s.d.

Results

The main characteristics of controls and JRA patients are given in Table 1.

Children affected by JRA are female for the most part, reflecting the higher incidence of JRA in female subjects (Cassidy, 1990). Body weight is similar in control and JRA subjects while body height is higher in controls ($P < 0.05$). However, BMI, AFA, AMC and AMA do not differ between controls and patients. TBW% and ECW% are higher ($P < 0.005$ and $P < 0.0001$ respectively) and ICW% lower ($P < 0.0001$) in JRA patients as compared to controls. It follows that the ECW : ICW ratio is higher in JRA patients than in controls ($P < 0.0001$). Z is not significantly different in JRA and control subjects at 5, 50 and 100 kHz.

As determined by ANOVA, differences in TBW%, ECW% and ICW% between control and JRA groups were not influenced by their different sex distribution (P = ns).

Of the 39 children with JRA, 18 had oligo- and 21 poly-arthritis. A further distinction was performed among the latter between those having active ($n = 10$) and remitting ($n = 11$) poly-arthritis (Cassidy, 1990).

Patients with oligo- and poly-arthritis had a similar TBW% and ECW% (p = ns; data not shown). Moreover, no difference in TBW% and ECW% was seen in patients with active and remitting poly-arthritis (p = ns; data not shown) and no significant correlation was found between the clinical duration of JRA and TBW% or ECW% after correcting for the subject's age (data not shown).

Patients treated with NSAIDs ($n = 22$) had a TBW% and an ECW% comparable to those of untreated patients (p = ns; data not shown). However, ECW% was significantly lower in patients treated with MTX ($n = 4$) as compared to the remaining patients ($n = 35$; 39.6 ± 3.7 *vs* 44.9 ± 4.5, with $P < 0.05$). This value was similar to that of control subjects (P = ns; Table 1). Since only one of the enrolled patients was taking CS, it was not possible to assess any effect of these drugs on water distribution.

Table 1 Characteristics of control and JRA subjects. Abbreviations: BMI = body mass index, AFA = arm fat area, AMC = arm muscle circumference, TBW% = total body water (TBW) standardized per kg of body weight, ECW% = extracellular water standardized per l of TBW, ICW% = intracellular water standardized per l of TBW, ECW : ICW = extra- to intra-cellular water ratio, Z_x = bioelectric impedance at frequency x (5, 50 and 100 kHz)

	Controls ($n = 23$)	*JRA patients* ($n = 39$)
Age (y)	10.1 ± 4.4	11.8 ± 3.0
Sex (m : f)	9 : 14	9 : 30
Weight (kg)	38.0 ± 16.5	40.9 ± 12.2
Height (cm)	144.8 ± 15.4	137.0 ± 19.8*
BMI (kg/m^2)	18.2 ± 2.7	21.7 ± 3.8
AFA (mm^2)	13.4 ± 7.8	12.0 ± 6.0
AMC (cm)	18.6 ± 3.7	18.4 ± 2.9
AMA (mm^2)	28.5 ± 11.2	27.7 ± 9.3
TBW%	57.7 ± 2.7	59.7 ± 2.4**
ECW%	38.1 ± 7.9	44.5 ± 4.6***
ICW%	62.5 ± 8.1	55.5 ± 4.6***
ECW : ICW	0.64 ± 0.21	0.81 ± 0.16***
Z_5 (Ω)	767 ± 82	781 ± 88
Z_{50} (Ω)	682 ± 66	692 ± 87
Z_{100} (Ω)	650 ± 62	658 ± 77

*$P < 0.05$, ** $P < 0.005$ and *** $P < 0.0001$ *vs* controls.

In control subjects, ZI was highly correlated with TBW and ECW at all frequencies ($r \geq 0.93$ and $r \geq 0.85$ respectively, with $P < 0.0001$). After partial correlation analysis, however, ZI appeared to be significantly correlated with TBW only at frequencies of 50 and 100 kHz ($r = 0.64$ and $r = 0.63$, respectively with $p < 0.05$). Following the same procedure, it was shown that ZI was significantly correlated with ECW only at 5 kHZ ($r = 0.34$, $P < 0.05$). The same s.e.e. was associated to the prediction of TBW from ZI_{50} and ZI_{100} (2.2 l).

A regression model was developed to predict TBW and ECW from ZI_{100} and ZI_5, respectively in control subjects:

$$\text{TBW (l)} = 0.716 \times ZI_{100} - 1.504,$$

$$r = 0.934,\ P < 0.0001,\ \text{s.e.e.} = 2.2\ \text{l}$$

$$\text{ECW (l)} = 0.430 \times ZI_5 - 3.652,$$

$$r = 0.869,\ P < 0.0001,\ \text{s.e.e.} = 1.7\ \text{l}.$$

Values of TBW measured by dilution and predicted by the control-generated formula were not significantly different in JRA patients (P = ns). However, the difference between measured and predicted values (bias) was high (−2.7 ± 3.2 l) for the equation to be safely employed in a clinical context. Values of ECW measured by dilution and predicted from the formula generated on controls were significantly different ($P < 0.005$) in JRA patients, with a bias of −3.1 ± 1.7 l. The bias associated to the prediction of TBW was not correlated with ECW : TBW ratio (P = ns) on the contrary of that associated to the prediction of ECW ($r = 0.604$, $P < 0.0001$).

Population-specific equations were therefore developed in order to assess the accuracy of the BIA method for predicting water compartments in JRA patients.

In patients, ZI was highly correlated with TBW and ECW at all frequencies ($r \geq 0.90$ and $r \geq 0.87$, respectively, with $P < 0.0001$). However, partial correlation coefficients were significant for TBW only at frequencies of 50 and 100 kHz ($r = 0.61$ and $r = 0.62$, respectively with $P < 0.05$) and for ECW only at 5 kHz ($r = 0.32$ with $P = < 0.05$). Similar SEEs were associated to the prediction of TBW from ZI_{50} and ZI_{100} (2.9 and 2.8 l, respectively).

Therefore, also for JRA patients, a regression model was developed to predict TBW and ECW from ZI_{100} and ZI_5, respectively:

$$\text{TBW (l)} = 0.766 \times ZI_{100} - 0.053,$$

$$r = 0.939,\ P < 0.0001,\ \text{s.e.e.} = 2.8\ \text{l}$$

$$\text{ECW (l)} = 0.399 \times ZI_5 - 0.283,$$

$$r = 0.886,\ P < 0.0001,\ \text{s.e.e.} = 1.71\ \text{l}.$$

Using these equations, measured and predicted values of TBW and ECW were not significantly different in JRA patients (P = ns). A bias of 0.0 ± 2.7 and 0.0 ± 1.7 l was associated to the prediction of TBW and ECW, respectively from these formulae. In both cases, the bias was not correlated with the ECW : TBW ratio (P = ns).

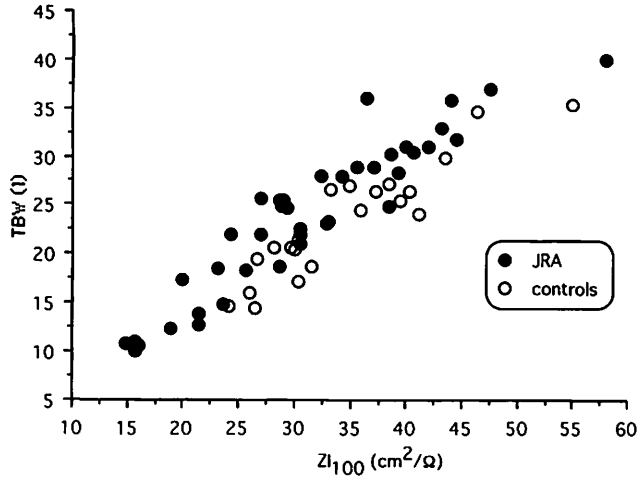

Figure 1 Relationship between TBW and ZI_{100} in control and JRA subjects.

Plots of TBW and ECW *vs* ZI_{100} and ZI_5, respectively are given in Figures 1 and 2, for patients and controls.

From these graphs it can be seen that JRA patients have higher values of TBW and ECW for the same values of ZI_{100} and ZI_5 of control subjects. Regression coefficients were significantly different in JRA as compared to control subjects ($P < 0.01$ for both TBW and ECW), thus enforcing the need of using population-specific equations.

Discussion

In the present study we investigated the possibility that BIA may be employed to assess the hydration status of JRA patients. The accuracy of BIA relies largely on the ECW : ICW ratio which is frequently modified by disease (Bedogni *et al*, 1996). There are a number of reasons for which the ECW : ICW ratio could be altered in JRA patients. Among these, the effects of chronic inflammation and pharmacological therapy should be accurately evaluated (Chrousos, 1995; Rose, 1994).

Our study shows an increase in TBW% and in the ECW : ICW ratio of JRA patients in comparison to control subjects. There is both clinical and experimental evidence that body composition may be altered by chronic inflammation. In subjects with rheumatoid arthritis, Roubenoff and colleagues have observed an inverse relationship between the amount of FFM and the circulating levels of some cytokines (Roubenoff *et al*, 1992, 1993). This finding suggests that body composition may be directly affected by inflammation in patients with rheumatic disorders. Moreover, there is increasing evidence that some cytokines (interleukins), which are commonly elevated in the plasma of patients with rheumatic disorders, may interfere with the renal (and possibly cellular) handling of water (Chrousos, 1995). These factors should be adequately considered when trying to explain the altered water distribution of our JRA patients. In the present study, the immuno-inflammatory indexes commonly employed for the evaluation of JRA patients (erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, etc.) were not correlated with the increase in TBW% or in the ECW : ICW ratio (data not shown). However, this may partly reflect the limits of these indexes in evaluating the degree of chronic rather than acute inflammation (Cassidy, 1990). Although the hypothesis of a direct effect of inflammation on body water distribution is intriguing, further studies are needed in order to ascertain its pathophysiological significance.

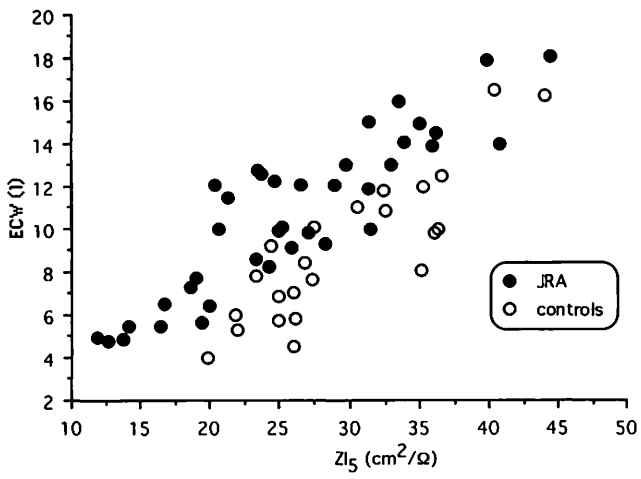

Figure 2 Relationship between ECW and ZI_5 in control and JRA subjects.

It should be pointed out that JRA patients treated with NSAIDs had a TBW% and an ECW% comparable to those of untreated patients. This is of interest because NSAIDs have sodium- and water-retaining effects which can lead to an expansion of ECW (Rose, 1994). It should nonetheless be noted that these effects are more common in subjects with cardiac, hepatic or renal disease while in our patients there was no evidence of such disorders.

Interestingly, patients treated with methotrexate (MTX) had a decreased ECW% as compared to the rest of JRA patients. MTX is used to treat severe forms of arthritis which are unresponsive to conventional therapy (Cassidy, 1990). MTX has immuno-suppressive and anti-inflammatory effects so that the decrease in ECW% of these patients could possibly be explained by the anti-inflammatory action of this drug (Cassidy, 1990). However, it cannot be completely excluded that a different degree of disease activity may be associated to a different distribution of body water in JRA patients. In every case, this finding has important implications for the prediction of TBW and ECW from BIA. In fact, the applicability of BIA-based formulae relies heavily on the ECW : ICW ratio (Deurenberg *et al*, 1989). In the present study, however, exclusion of the patients treated with MTX from the set generating the equations, was not associated to any improvement in the prediction of TBW and ECW (data not shown).

In the search for an explanation of the altered body water distribution of our JRA patients it should be kept in mind that a state of subclinical malnutrition may produce an expansion of TBW% and ECW% similar to that observed in the present study (Shetty, 1995). Although our patients had a stable weight and an apparently normal food intake (as detected by consecutive 24-h dietary recalls), the possibility of subclinical malnutrition should always be considered in children with JRA (Strano *et al*, in press).

In view of their altered water distribution, it is not surprising that formulae developed on controls gave a biased prediction of TBW and ECW in JRA subjects. However, population-specific formulae, which took into account their altered body water distribution, offered a reliable prediction of water compartments in JRA patients. The fact that, after correction for TBW, ECW was significantly correlated with *ZI* only at a frequency of 5 kHz confirms that bioelectric impedance is a measure of ECW at low frequencies (Segal *et al*, 1991; Deurenberg *et al*, 1993, 1995*a*,*b*). However, we did not find any significant advantage of using a frequency of 100 kHz over one of 50 kHz for predicting TBW from *ZI*. This is in agreement with the results of recent studies performed on healthy subjects (Deurenberg *et al*, 1993, 1995*a*,*b*). It should not be excluded, however, that frequencies higher than 100 kHz may be useful for predicting TBW from BIA. Unfortunately, technical limitations intrinsic to currently available tetrapolar plethysmographs do not allow very accurate measurements of *Z* at frequencies under 1 or over 100 kHz (Deurenberg, 1994).

Finally, it is noteworthy that TBW% and the ECW : ICW ratio were altered in JRA patients despite an anthropometric status comparable to that of controls. This finding, which has already been described in both physiological and clinical conditions (Battistini *et al*, 1994; Bedogni *et al*, 1996) should alert against the use of anthropometric indexes alone for evaluating body composition in patients affected by oligo- or poly-articular JRA.

The altered body hydration of JRA patients also suggests that standard methods for the assessment of body composition may require adjustments for use in subjects with JRA. For example, the assessment of FFM from BIA in these patients would probably require population-specific formulae owing to their altered body hydration (Heymsfield & Wang, 1994).

In summary, our study shows that body hydration and water distribution may be altered in children affected by JRA. This impedes the use of formulae generated on healthy subjects for predicting body water compartments from bioelectric impedance in these patients. Population-specific formulae, which take into account the effects of their altered ECW : ICW ratio, appear to be sufficiently reliable for predicting TBW and ECW in JRA patients. These formulae may be applied to patients with oligo- and poly-articular JRA even if they are undergoing treatment with NSAIDs. However, the clinical use of these formulae should be preceded by their cross-validation on external populations.

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