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DOCTORAL THESIS

THE EVALUATION OF ACCURACY AND PRECISION IN BODY COMPOSITION EVALUATION THROUGH ULTRASONOGRAPHIC ANTHROPOMETRY

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T i m i ş o a r a

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1. INTRODUCTION

The body composition is very much linked to the health and has a great influence on the self-esteem and the way someone is accepted in society. Therefore, study of body composition is very much needed, especially because there is reported an increase in overweight and obesity in all the countries of the world. The WHO stated that the problem of obesity is about to become more important than infectious disease and malnutrition. It will become the most significant cause of morbidity (1) and therefore it is already formally considered being epidemic (2).

To evaluate the health risk and to create a better classification of obesity it is mandatory to have a parameter that evaluates the amount of excess fat in the body. The most used measure of obesity is the body mass index (BMI) which is expressed as the ratio of body mass to body height squared. It easy to collect but body mass index does not reflect any variations in body composition. For example, using just body mass index, you cannot tell how much fat mass the patient has. Differentiation between muscle mass and fat mass is impossible just by this method. Therefore, a better way to evaluate obesity is to use the body fat percentage (%BF). This parameter is a good measure of body composition and it is a great way for tracking the progress of a person who struggles with losing weight.

Many different measuring techniques evolved, based on different principles. There are very accurate devices on the market for quite some time, but they are too big and very expensive. These are not portable, therefore mostly not suitable for the everyday use, especially when large populations should be evaluated in a short period of time. On the other hand, the small, portable devices often do not have a proper accuracy and precision.

Apart from the complex laboratory methods that were previously described, there are also field methods, which are far easier to use and are suitable for bed-side measurements.

A relatively new and interesting principle to assess body composition is based on ultrasonography. Ultrasounds are produced by a transducer, the sound waves travel into the body and hit the boundaries between tissues, some of the waves reflect, some others travel further depending on the difference between the acoustic impedance of different tissues. The A (amplitude modulation) mode generates spikes, by plotting the amplitude of the reflected ultrasound beam vs the position of the interface that caused the reflection. The high of the spike is correlated to the amplitude of the echo. This very promising tool, derived from anthropometry it is a small, handheld device, commercially available.

The purpose of our original research is to evaluate this instrument in terms of reliability and validity against the method of air displacement plethysmography.

The evaluation of this instrument involves more steps. The first step was to determine the intratester reliability of the ultrasound device. This provides information to which degree an operator does reproduce his/her own results in a set of measurements.

In the next step was to compare the results obtained by the same operator with the ones obtained when the measurement was repeated and by two different operators on the same subjects. It would be great if results were close to each other, condition which is a required for a good intratester and intertester agreement.

The final step is the validation analysis of the ultrasound method. When a new instruments is validated, this validation is done by using another instrument as gold standard. Air displacement plethysmography serves as a reference method in our validation study.

The idea of validity or accuracy refers to the possibility of a technique to determine the true value of the measured quantity. Since the true value is most of the times unknown (with the exceptions of geometric quantities), the accuracy evaluation relies on comparisons between the results obtained using a reference technique and the instrument we do want to evaluate.

We did want to find the anthropometric formula that realizes a correspondence between ultrasonographic anthropometry and plethysmography, so that more accurate results can be obtained for the ultrasound evaluation.

We were also interested in identifying subjects with high body fat percent, despite a normal body mass index. This condition is called normal weight obesity. It was also an important objective to evaluate to which extent is ultrasound able to identify patients with normal weight obesity.

2. MATERIALS AND METHODS

Participants in our study were recruited via social networks and flyers posted in the local community. Clinically healthy adults, aged 18-70 years, were included in the study upon providing written informed consent. Before coming to our laboratory, someone from our team talked which each of them, explained the study that will be done. They were asked not to eat or drink for at least for four hours before arriving to our laboratory and to bring the right equipment with them (tight swimming suit). For the beginning, the participants were asked to change their clothes, to take the swimming suit on, to put the swimming cap on, and to remove all their jewellery. The swimming cap was put very carefully, so that no amount of hair will be out. Their height was measured by someone of our team, they were weighted on a standard scale. Our measurements were done in the framework of the two-compartment model of body composition. This model differentiates between fat mass (FM) and fat-free body mass (FFM); their sum is the body mass BM = FM + FFM. We estimated these quantities, as well as percent body fat (%BF = 100%×FM/BM) employing two techniques: air displacement plethysmography (ADP) and ultrasound anthropometry.

The full ADP evaluation was done before de ultrasound measurement. For air displacement plethysmography (ADP) we used the BOD POD® Gold Standard Body Composition Tracking System (Cosmed, USA), with BOD POD® software version 5.3.2, DLL version 3.70. It is a commercially available ADP system that consists of the plethysmograph, a high precision electronic scale and a computer. The plethysmograph measures the volume of air displaced by the body, while the patient is enclosed in a hermetically closed chamber and the scale measures the body mass to the nearest gram. For this study the entire test procedure was repeated 3 times so that 3 values were obtained for the %BF.

For the A mode ultrasound study, the participants completed 6 consecutive measurements of the subcutaneous fat layer thickness at 8 anatomical sites. The measurements were done, alternatively, by two testers, using a BodyMetrix™ instrument. To compute %BF, 4 formulas from the BodyView™ software were applied: 7-sites Jackson and Pollock, 3-sites Jackson and Pollock, 3-sites Pollock, and 1-point biceps. Two testers, with about 1 year of experience, took all measurements in triplicate.

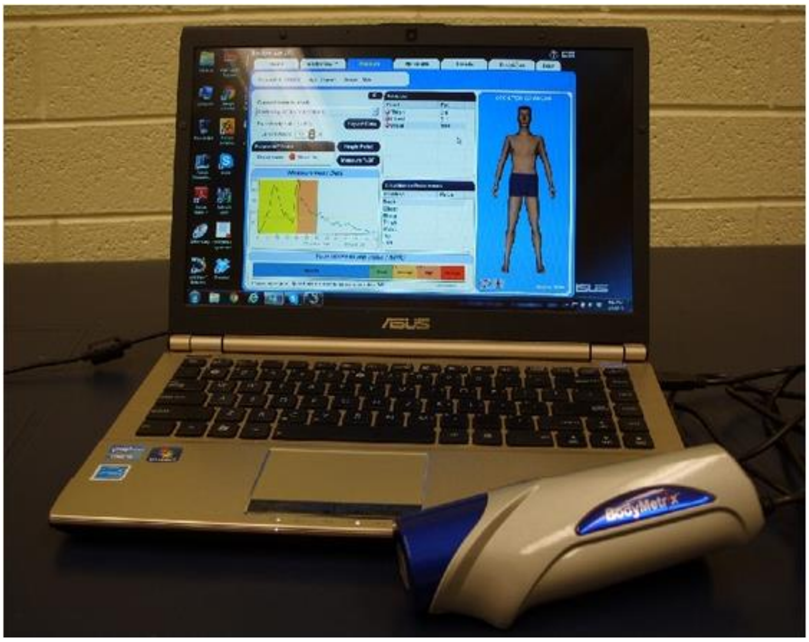

Figure 1 - BodyMetrix ultrasound

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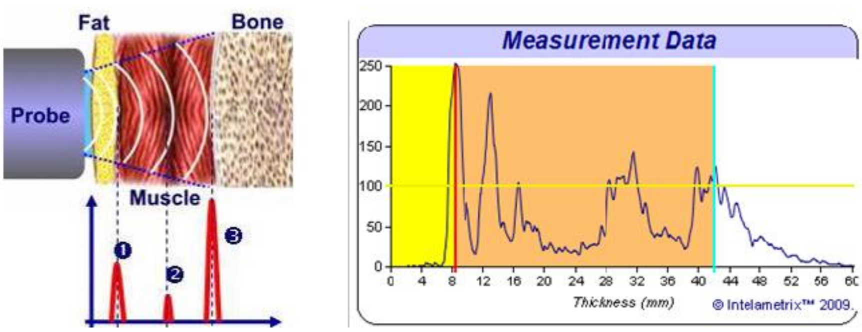

Figure 2 - Visualization of the ultrasound principle on a human tissue cross section with 1 being the fat-muscle interface (left). The graph plotted by the BodyView™ software in a normal measurement with detected tissue interfaces (right). (3)

3. PRECISION OF BODY COMPOSITION ASSESSMENTS VIA A-MODE ULTRASOUND

This work evaluated the intra- and intertester reliability of %BF assessments via A-mode US. To our knowledge, this is the first study of learning effects in the context of this technique and the first to evaluate its reliability in a heterogeneous sample of more than 50 subjects of each gender. To check for learning effects on the measurement error, we analyzed consecutive pairs of trials (4) - first and second (1-2), first and third (1-3), second and third (2-3). The indices of precision derived from different pairs displayed no clear trend. Tester 1 (T1) had the best precision for pair 2-3 (as expected in the presence of learning effects), but only for the JP7, JP3 and P3 formulas. T2 was most precise for pair 1-2 with JP7 and for pair 1-3 otherwise. It seems safe to conclude that learning effects are absent in %BF estimates via A-mode US. For JP7, the intratester TEM was similar to that of ADP (5), which suggests that the BodyMetrix is as reliable as the BOD POD.

Figure 3 illustrates the agreement between two sets of ultrasound measurements performed by Tester 1. Similar plots were obtained for Tester 2.

In Figure 3 experimental points are evenly distributed around the solid line that represents the bias - i.e. the intratester agreement is unaffected by the subject's adiposity. In each panel, zero belongs to the 95% confidence interval (CI) of the bias. The width of the 95% interval of agreement, ULA - LLA, is smallest in panel (a), indicating that the JP7 formula assures the best intratester reliability, being followed by JP3 and P3 on the same footing (panels (b) and (c)), and by BIC (panel (d)). Similar results were obtained, for both testers, when the first reading was compared with the third (1-3) and when the second reading was compared with the third (2-3).

We also applied the BA method to characterize the intertester reliability of %BF measurements via US . The width of the 95% interval of agreement was slightly larger than those corresponding to intratester agreement. Our study points out examiner performance as a possible cause of the difference in reliability between Wagner et al. (6) and other works. The reliability of T2 was higher than that of T1, suggesting that, unlike in the case of the BOD POD (7), US assessments of body composition do depend on the technician's performance.

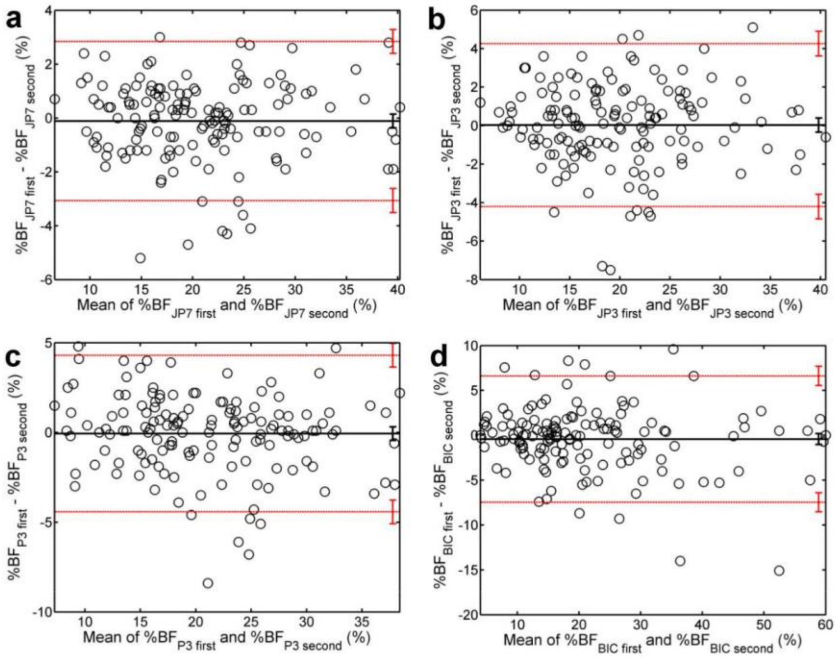

Figure 3 - Bland-Altman plots of differences vs. means of the first and second assessment of %BF by Tester 1 using A-mode ultrasound and four different formulas: (a) 7-sites Jackson and Pollock (JP7), (b) 3-sites Jackson and Pollock (JP3), (c) 3-sites Pollock (P3), and (d) 1-point biceps (BIC). The thick horizontal line depicts the bias, whereas the thin dotted lines depict the 95% limits of agreement. The vertical segments on the right represent the 95% confidence intervals (CI) of the corresponding quantities

A-mode US is highly reliable for %BF assessments, but it is more precise for men than for women. Examiner performance is a source of variability that needs to be mitigated to further improve the precision of this technique

4. EVALUATION OF THE VALIDITY (ACCURACY) OF ULTRASOUND ANTHROPOMETRY IN BODY COMPOSITION ASSESSMENT

The term validity or accuracy refers to the capacity of a technique to determine the true value of the measured quantity. Since the true value is most of the times unknown (notable exceptions being geometric quantities that result from theorems), the accuracy evaluation relies on comparisons between the results obtained using a reference technique and the instrument we do want to evaluate. We choose air displacement plethysmography as reference technique in our study. To investigate the differences between ultrasound anthropometry and ADP, we conducted a Bland-Altman analysis, representing the differences versus mean values for the validation samples of men and women. Currently, the available technology for air displacement plethysmography is referred to as the Bod Pod. In this system a measuring chamber and a reference chamber are linked together by a flexible airtight diaphragm which is perturbed to induce small pressure changes between both chambers. The pressure-volume relationship at a fixed temperature is used to calculate the volume of the participant in the measuring chamber (Poisson"s Law). After the system is calibrated with a known volume, the participant is weighed wearing swimwear and cap, then occupies the measuring chamber for two for two minutes for the volumetric measurement (8).

We performed also a linear regression of the Bland-Altman data, starting from this observation. We fitted a regression line $y = px + q$ where $y = \%\mathrm{BF}_{\mathrm{US}} - \%\mathrm{BF}_{\mathrm{ADP}}$ and$x = \frac{(\%\mathrm{BF}_{\mathrm{US}} + \%\mathrm{BF}_{\mathrm{ADP}})}{2}$, and calculated the slope, p, and intercept, q, of this line. The regression line is the one depicted as a black dashed line in Fig 4. We also computed the coefficient of determination R^2. The coefficient of determination is equal to the fraction of the variation in the data that is described by the linear relationship $y = px + q$.

The agreement between the two methods is affected by the subject's adiposity, the larger the body fat percent, the larger the difference between methods. Moreover, zero does not belong to the 95% percent confidence interval of the bias, showing that the bias would be nonzero for any sample chosen from the entire population of healthy adults. The best agreement between the two methods was obtained for the JP7 formula, especially in subjects with relatively low adiposities, both for men and women. On the opposite side, the widest interval of agreement was obtained for the 1-site biceps formula, indicating a low accuracy with the exception of certain ranges of %BF.

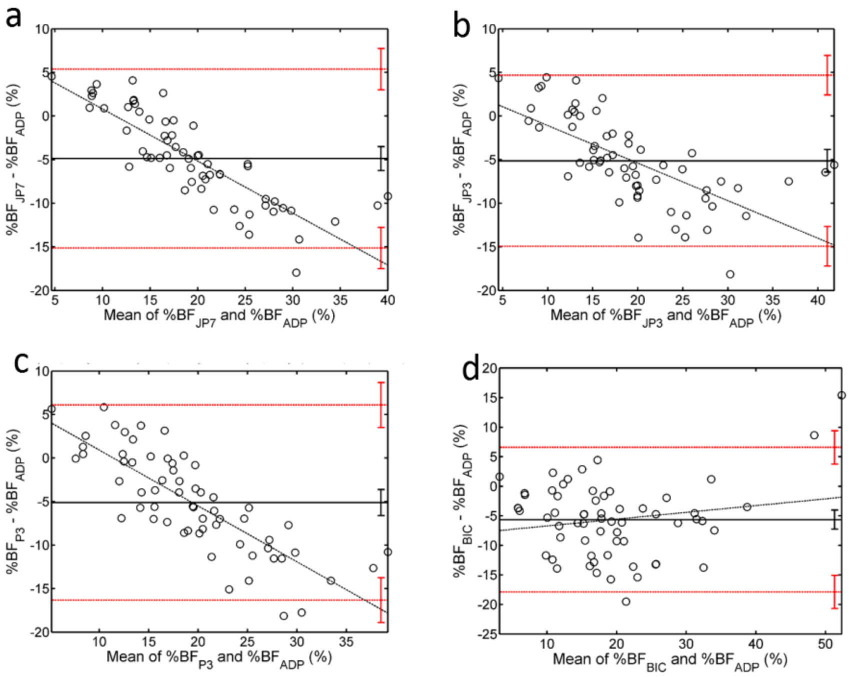

Figure 4 - Bland-Altman plots of differences vs. means of %BF values obtained by ultrasound anthropometry (US) and air displacement plethysmography (ADP) in men; for US, we employed four different anthropometric models: (a) the 7-site Jackson-Pollock model, (b) the 3-site Jackson-Pollock model, (c) the 3-site Pollock model, and (d) the 1-site biceps model.

For both men and women, the coefficient of determination, R^2, shows that a large part of the variance of the dependent variable (%BF determined by ultrasound) is predictable from the independent variable (%BF determined by BOD POD) by using the regression equation.

To improve the accuracy of ultrasound assessments in the overweight and obese, we proposed a linear correction formula for the body fat percentage determined using the BodyMetrix ultrasound instrument. The correction formula is based on the slope and intercept obtained, for each anthropometric formula, from measurements performed on the validation sample,

As shown in Figure 5 the linear correction performed by Eq 1 removes both the progressive loss of accuracy with increasing body fat percentage and the bias.

$$\%BF_{\mathrm{UScorr}} = \%BF_{\mathrm{US}}\frac{2-p}{2+p} - \frac{2q}{2+p}$$

Equation 1

As a result of the correction that was made (linear correction), the %BF values obtained for obese subjects are no longer underestimated by ultrasound anthropometry. Differences (deviations) from the BOD POD® results are still present, but they are much smaller compared to deviations present before correction, especially for the JP7 models. Zero belongs to the 95% percent limits of agreement of the bias.

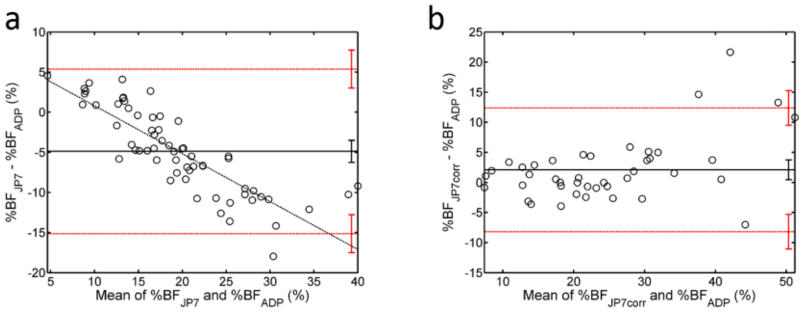

Figure 5 - Bland-Altman plots that compare %BF values obtained for men before and after the linear correction of %BF given by ultrasound anthropometry (US) – the JP7 formula with %BF assessed by air displacement plethysmography (ADP) The results of panel (a) were obtained for the validation sample (n = 62), whereas those of panel (b) correspond to the cross-validation sample (n = 42).

After correction, the points are evenly distributed around the line of identity and the agreement between the two methods was significantly improved for men having body fat percent between 10-35% BF. This is an important progress, since there are many patients in the general population with this body fat percent. Nevertheless, but for people with a high degree of obesity, the linear correction was unable to attenuate the large differences between the two techniques. The marked scatter might stem from insufficient precision of the measurements performed in morbidly obese subjects, or from a less adequate prediction formula. Further investigations, performed on at least 50 morbidly obese subjects might elucidate this problem.

The results presented in this chapter indicate that, for both genders, the commonly used formulas from the software of the BodyMetrix instrument lead to an underestimation of the amount of body fat present in the body of an overweight or obese person. Therefore, there is a need for prediction formulas specifically designed for these categories of subjects. Alternatively, one can rely on mathematical tools devised to improve the predictions of the proprietary formulas implemented in the BodyView software. The latter was the objective of the present study.

The investigation focused on four prediction formulas, the 7-site Jackson-Pollock (JP7) formula, the 3-site Jackson-Pollock (JP3) formula, the 3-site Pollock (P3) formula, and the 1-site biceps (BIC) formula. Based on Bland-Altman plots, we concluded that, except for the BIC formula, overweight and obese persons appeared to be leaner when tested with A-mode ultrasound than they were when they were evaluated using the reference technique, air displacement plethysmography.

Relying on linear regression analysis of the Bland-Altman plots, we devised a method to compute corrected values of %BF obtained from ultrasound measurements, and applied them for all 4 formulas. Significant improvements were observed, especially in the case of the JP7 and JP3 formulas, which are among the most popular in the literature (6). Most importantly, the overall bias was reduced and the progressively larger error was eliminated, thereby obtaining more accurate assessments of %BF for people with increased adiposity.

The work presented in this chapter, however, has certain limitations. The most important one is related to the sample size. Although the validation sample exceeded 50 subjects of each gender, the cross validation sample was smaller. Moreover, the proportion of overweight and obese people was small in both samples. Further investigations will be needed to firmly establish the value of the proposed mathematical approach. Another limitation of the present study concerns the applied statistical methodology: it relies exclusively on Bland-Altman analysis (the most commonly used technique for this purpose). Other tools, such as linear regression will be presented in the next chapter.

If future studies, involving larger samples, will reinforce the conclusion that linear correction of the standard formulas implemented in the BodyView software leads to accurate assessments of body fat percentage in women, the mathematical approach proposed in this work has the potential to bring ultrasound anthropometry into the clinic for routine monitoring of body mass management.

5. NORMAL WEIGHT OBESITY INVESTIGATED USING A-MODE ULTRASOUND

Obesity has been classified recently by distinguishing four phenotypes: normal weight obese, metabolically obese normal weight, metabolically healthy obese, and metabolically unhealthy obese. Prevalence of normal weight obesity is considered to be low in general population, but it is definitely higher in women that man. (9).

The most used definition is the one established by Romerro-Coral in 2010: Normal weight obesity (NWO) is a condition of subjects with normal BMI (18.5–24.99 kg/m^2) but excess body fat, defined by the highest sex-specific tertile of %BF. Based on this definition, a study of over 6000 normal weight subjects established the lower limits of body fat percentage of people that suffer from NWO as 23.1% BF in men and 33.3% BF in women (10).

NWO is associated with significant cardiometabolic dysregulation, including metabolic syndrome and cardiovascular risk factors. It also increases cardiovascular mortality (11) (12). Furthermore, NWO appears to be associated independently with increased cardiovascular mortality in women (10), it is highly prevalent among them, suggesting that maybe sex hormones do play an important role in this condition (13).

NWO patients have higher degree of vascular inflammation, compared to normal weight lean people. Inflammation influences atherosclerotic progression, being major determinant of plaque rupture. The degree of subclinical vascular inflammation was evaluated using the mean and maximum target-to-background ratios of the carotid artery, which were measured by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) - PET/CT (a noninvasive tool for assessing vascular inflammation). (14).

As described earlier, people with normal weight obesity are those which have an increased percent of bod, although they could not be classified as obese using the body mass index. We asked the question whether A-mode US is an accurate technique for evaluating human body composition.

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A-mode ultrasound was found accurate in the present study in the case of lean subjects, whose body fat percentage (%BF) was similar to elite athletes. At larger levels of %BF, the higher was the subject's adiposity, the larger was the difference between the %BF given by air displacement plethysmography and %BF given by ultrasound. The discrepancy between the two techniques was larger for men than for women. Our work suggests that body composition assessments using A-mode ultrasound are affected by a systematic underestimation of percent body fat in subjects with average to high adiposity. Therefore, ultrasound was incapable of identifying subjects with normal weight obesity in our sample. By contrast, ultrasound was effective in the investigation of expanded normal weight obesity, which is based on classifying subjects into low body fat and high body fat categories within standard intervals of body mass index.

The accuracy of A-mode ultrasound needs to be improved for certain categories of subjects. Nevertheless, the reliability, portability, and affordability of this technique are likely to motivate further progress in the field of ultrasound-based body composition assessment, turning it into a promising tool of clinical relevance.

6. CONCLUSIONS AND PERSONAL CONTRIBUTIONS

The evaluation of human body composition is of great interest in both clinical medicine and sports medicine. Many times people that are doing specific sports where weight is crucially important need to be evaluated before they participate specific sports and body composition can change many aspects regarding their performance. On the other hand, obese patients need to be regularly evaluated when a specific diet is prescribed, a specific treatment needs to be followed or even when bariatric surgery is recommended or if they are in the course of recovery from such a procedure. Although laboratory methods are of high performance, they are not always affordable. Moreover, laboratory methods cannot be applied in a standard clinical setting – they need adequate space and conditions.

Ultrasound as a method of body composition assessment has elicited increasing interest in recent years, but it has to be carefully evaluated. If we wish to bring this instrument closer to the day to day practice, the first thing that needs to be evaluated is the reliability, taking into consideration the fact that there will be many people that will use it, and often the change in a body composition variable is more important than the actual value of that parameter. Therefore, even if the accuracy of a technique is not satisfactory, it can be useful in practice if its precision is good.

Studies published so far addressed the validity of this technique or evaluated both validity and reliability, but involved relatively small, homogeneous samples. Therefore, the present study was conducted to determine the reliability of percent body fat measurements using A-mode US in a heterogeneous sample of 144 healthy adults (81 men and 63 women) between 19 and 66 years of age 30.4(10.1) years (mean(SD)), and BMI = 24.6(4.7) kg/m^2, ranging from 16.6 to 45 kg/m^2.

Unlike previous works, our study is based on triplicate trials performed by two examiners. The analysis of consecutive pairs of trials demonstrated the absence of learning effects. Four prediction formulas were compared in what concerns intra- and intertester reliability: 7-sites Jackson and Pollock, 3-sites Jackson and Pollock, 3-sites Pollock, and 1-point biceps. We found that reliability for this is instrument was good, both for intratester and intertester reliability. The best results were obtained for the Jackson-Pollock 7 formula. The next important thing is to find out if there were any significant differences between men and women. Based on over 50 subjects of each gender, our study revealed that body composition assessments via A-mode US are more precise for men than for women.

After we got encouraging answer regarding the reliability, we went to the next step, the validity of this instrument. Validity or accuracy refers to the capacity of a certain technique to determine the true value of the measured quantity. The true value is most of the times unknown (with the exception of the theorems), so the accuracy evaluation relies on comparisons between the results obtained using a reference technique and the instrument we do want to evaluate.

In our study, the reference technique was air displacement plethysmography, via the BOD POD®. We compared the results obtained by ultrasound with the ones obtained with BOD POD. The results presented indicate that, for both genders, the commonly used formulas from the software of the BodyMetrix instrument lead to an underestimation of body fat present in the body of an overweight or obese person. Ultrasound was found accurate in the present study for lean subjects, where body fat percentage was similar to athletes. The larger adiposity of an individual, the larger the discrepancy between the two ways methods. Therefore, prediction formulas specifically designed for these categories of subjects are very much needed. Alternatively, mathematical tools can be used to improve the predictions of the proprietary formulas implemented in the BodyView software.

This was one the objectives of the present study. We performed a linear regression of the Bland-Altman data. As a result of the correction that was made (the linear correction), the %BF values obtained for obese subjects are no longer underestimated by ultrasound anthropometry. Differences (deviations) from the BOD POD® results are still present, but they are much smaller compared to deviations that were present before correction.

The work presented has certain limitations, he most important one being related to the sample size. Although the validation sample exceeded 50 subjects of each gender, the cross validation sample was smaller. Another limitation was that the proportion of overweight and obese people was small in both samples. Further investigations will be needed to firmly establish the value of the proposed mathematical approach. Another limitation of the present study concerns the applied statistical methodology: it relies exclusively on Bland-Altman analysis (the most commonly used technique for this purpose).

If future studies, involving larger samples, will reinforce the conclusion that linear correction of the standard formulas implemented in the BodyView software leads to accurate assessments of body fat percentage in women, the mathematical approach proposed in this work has the potential to bring ultrasound anthropometry into the clinic for routine monitoring of body mass management.

Another subject that was studied in our team was the evaluation of the patients with normal weight obesity. People with normal weight obesity are those which have an increased percent of bod, although they could not be classified as obese using the body mass index. Ultrasound was not capable of identifying subjects with normal weight obesity in our sample. By contrast, ultrasound was useful in the investigation of expanded normal weight obesity, which is based on classifying subjects into low body fat and high body fat categories within standard intervals of body mass index.

The accuracy of A-mode ultrasound needs to be improved. We believe that we succesfully made the first steps, by using the linear correction. This leads to an important step forward for the results obtained for ultrasound, especially for patients with high body fat percent. We would like to continue our study, with a larger sample of overweight subjects. We hope to find a better prediction forumula, which will produce results comparable to those obtained using air displacement plethysmography. We believe that this will make the ultrasound more appropiate for identifying patients with normal weight obesity, so that they can get medical advice on time, before complications occur.

Nevertheless, the reliability, portability, and affordability of this technique are likely to motivate further progress in the field of ultrasound-based body composition assessment, turning it into a promising tool of clinical relevance.

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