ABSTRACT

Background:

Total energy expenditure (TEE) is estimated in clinical practice as a combined measure of resting energy expenditure and physical activity level. Commonly available questionnaires to estimate physical activity level have not been validated in patients with kidney disease using the doubly labelled water method.

Methods:

This prospective, cross-sectional study was conducted on 40 patients with Chronic Kidney Disease stages 1-5 with the objective of validating two physical activity questionnaires – Recent Physical Activity Questionnaire (RPAQ) and Stanford 7-day recall questionnaire. TEE was measured using doubly labelled water technique. TEE was also estimated using predicted resting energy expenditure and estimated physical activity measures from the questionnaires.

Results:

Measured TEE correlated better with TEE estimated from RPAQ compared to that from Stanford questionnaire. In Bland-Altman analysis, TEE estimated from RPAQ had the least bias and narrower limits of agreement compared to the measured TEE. A MET value of 1.3 for the unaccounted time in RPAQ provided the best approximation of estimated TEE to the measured TEE.

Conclusions:

RPAQ is an acceptable questionnaire tool to assess physical activity level in patients with chronic kidney disease.

INTRODUCTION

Individuals with chronic kidney disease (CKD) often have poor appetite, especially in advanced stages, which could potentially contribute to low energy intake and protein-energy wasting (1-3). Assessing total energy requirements of individuals is vital for appropriate nutritional management of these patients. In routine clinical practice, total energy requirements are estimated by a combined measure of estimated basal metabolic rate (i.e. resting energy expenditure) and estimated physical activity level. There are predictive equations for estimation of resting energy expenditure (REE) such as Harris-Benedict, Mifflin-St Jeor, Schofield and Henry equations which are commonly used in clinical practice. Recently, a novel disease-specific predictive equation for REE has also been published for use specifically in patients with renal disease (4).

The estimation of physical activity is usually carried out by means of self-report physical activity questionnaire although prospectively completed activity diaries are an alternate option. Most of the readily available questionnaires are derived from young healthy adults and as such, may not be applicable to specific groups of patients. CKD is predominantly a disease of the elderly and these activity questionnaires may not be valid in this patient population. A study examining the validity of ten physical activity questionnaires in elderly individuals in general population has found that only a few questionnaires were reliable for use in elderly (5). Moreover, the individual variability was high for all the questionnaires which limits their use in clinical practice.

None of the physical activity questionnaires used in studies involving patients with kidney disease have been validated against the doubly labelled water (DLW) method for estimation of Total Energy Expenditure (TEE). Some of the available questionnaires have been tested against energy expenditure obtained from accelerometers. However, this is not ideal as accelerometer measurements themselves may also have a degree of associated measurement error. This error in itself has not been quantified using the DLW method in patients with kidney disease. Whilst accelerometers serve as the next best tool to DLW, it is important to validate physical activity questionnaires against DLW in individuals with kidney disease.

Recent Physical Activity Questionnaire (RPAQ) enquires about the performance of various activities and the time spent on each of the reported activity over the preceding 4 weeks. The questionnaire has been validated in healthy individuals against DLW for categorising physical activity levels and estimation of Physical Activity-related Energy Expenditure (PAEE) (6). Each reported activity is assigned a Metabolic Equivalent of Task (MET) value as per the compendium of physical activities (7). However, the appropriate MET value for the unaccounted time is not clear. Stanford 7-day recall questionnaire was developed for the Stanford Five City Project (8) and has been validated in general population (9, 10). It has also been shown to have significant correlation with accelerometer-measured physical activity in patients with CKD (11). This questionnaire enquires about time spent on moderate, hard and very hard intensity activities and also sleep, over the preceding seven days. Any time not accounted for is considered to be spent performing light activities. These two questionnaires were chosen as the physical activity data from them could be easily converted to an energy expenditure measure.

Our aim in this study was to examine the validity of two physical activity questionnaires – RPAQ and Stanford 7-day recall questionnaire – for estimation of TEE in subjects with kidney disease. We also aimed to identify appropriate Metabolic Equivalent of Task (MET) value for unaccounted time in RPAQ that, when applied, will better reflect the measured TEE.

SUBJECTS AND METHODS

Ethical Review

The study was approved by the National Research Ethics service. All subjects gave written informed consent to take part.

Subjects

Patients older than 18 years with CKD stages 1-5 and not on renal replacement therapy were recruited. Categorisation of patients with CKD stages 1 and 2 were based both on estimated glomerular filtration rate (eGFR) and presence of renal disease. Exclusion criteria were patients with untreated thyroid disease, active malignancy, ongoing infection, active vasculitis or connective tissue disease, history of hospitalisation in the last month, current pregnancy, cardiac pacemakers or defibrillators, unexplained weight loss, limb amputations and those who are known to have had positive serology for Hepatitis B, C or HIV.

Study Protocol

Data collection

The following data were collected on all participants.

1. Demographic and anthropometric data including height and weight
2. Comorbidity data, which was used to calculate Charlson Comorbidity Index
3. REE
4. TEE
5. Physical activity assessment

Height was measured using a wall-mounted stadiometer and weight was measured using a standard calibrated scale.

Measurement of REE

REE was measured by indirect calorimetry using a Sensormedics VMax series 29n metabolic cart (SensorMedics Corp, Yorba Linda, California, USA) as previously described (4). This measurement was carried out at the beginning of the 14-day study period. REE was also estimated using a recently published validated predictive equation specific for patients with kidney disease. This equation was derived and validated in a cohort of patients with end-stage renal disease (4). The commonly used existing REE predictive equations – Harris-Benedict (12), Mifflin-St Jeor (13), Schofield (14) and Henry (15) equations – were also used to estimate TEE.

Measurement of TEE using DLW

Following a baseline urine sample collection, subjects were asked to drink a measured dose of DLW comprising 0.083 g/kg body mass of ^{2}H and 0.1375 g/kg of ^{18}O. A small sample (approximately 1ml) from this dose was removed prior to administering and this sample was used to precisely measure the enrichment of the dose delivered. Subjects were asked to collect daily urine samples in water-tight containers for the

next 14 days and precisely record sample collection time. Subjects stored the urine samples in a refrigerator. The dose sample, baseline pre-dose urine and post-dose urine samples from days 1, 8 and 14 were analysed for ^{2}H and ^{18}O isotope enrichment using mass spectrometry. Sample masses were measured using a calibrated Sartorius Cubis balance with 0.1mg readability. CO_2 production rate was calculated using a previously published revised equation (16). TEE was calculated from 14-day average daily CO_2 production rate (from DLW) and respiratory quotient (from indirect calorimetry) according to Weir equation.

Physical activity assessment

At the end of the 14-day study period, subjects completed two physical activity questionnaires – RPAQ and Stanford. RPAQ is a validated questionnaire which enquires about various activities performed at home, work and at leisure time and the time spent in each of those activities over the preceding 4 weeks (6). The questionnaire enquires about the time spent in watching television, use of computer, number of times of stairs climbing at home, type and intensity of employment and activity frequency of a list of specific recreational activities. We also instructed the subjects to add any activities they have performed in the preceding 4 weeks that were not listed. It also enquires about the usual mode of travel such as car, public transport, cycle etc.

Stanford questionnaire enquires about time spent in different intensities of activities at home and work in the preceding 7 days. It also enquires about the average daily duration of sleep in the same period. The specific activity intensities enquired were moderate, hard and very hard activities. Subjects were given a list of common

activities and their respective intensity categories along with the questionnaire to aid its completion.

Estimation of TEE from RPAQ

The metabolic cost of activity was expressed as MET value as per the Compendium of Physical Activities (7). The total reported activity duration was calculated by adding all the activity durations. If the total duration of reported activity exceeded 18 hours per day, then the total and individual activity duration was normalised to 18 hours. Assumption was made on the sleep duration. For those with reported activity duration of more than 16 hours, the sleep duration was assumed to be the remainder of the unreported activity time (6-8 hours). If the reported activity time was less than 16 hours per day, then sleep duration was assumed to be 8 hours. This meant that there was a portion of time unaccounted for by the questionnaire. We assigned different MET values from 1 to 1.3 (in 0.05 increments) for this unaccounted time to explore the most accurate value that will achieve the best approximation of TEE to that measured from DLW method. TEE was also estimated using the recommended MET value for this unaccounted time as per previous literature (6). The recommended MET value is 1.3 if the individual's common mode of travel is by walking or cycling and a value of 1 if any other mode of transport is specified.

The MET value for each reported activity was multiplied by the duration of that activity. Similarly, assigned MET value for the unreported time and sleep was multiplied by the respective duration for the day. A total MET value, expressed as MET-hours/day, was calculated. This was then divided by 24 (hours) to give a mean daily MET. TEE_{rpaq} was calculated by multiplying the daily MET by REE. Two

separate estimates of TEE was calculated – one using the measured REE and the other with the REE estimated from the predictive equation.

$$Mean\ Daily\ MET = \frac{Total\ Daily\ MET}{24}$$

$$TEE_{rpaq}\ (kcal/day) = REE\ (kcal/day)\ \times\ Mean\ Daily\ MET$$

Estimate of TEE from Stanford Questionnaire

Stanford questionnaire collects data on time spent on sleep and on moderate, hard and very hard activities over the preceding 7 days. Any unreported time was assumed to be spent performing light activities. Average MET value was allocated for each intensity of activity – 1 for sleep, 1.5 for light, 4 for moderate, 6 for hard and 10 for very hard activities. Mean daily MET was calculated using the following formula.

$$Mean\ Daily\ MET = \frac{(S\ \times\ 1) + (L\ \times\ 1.5) + (M\ \times\ 4) + (H\ \times\ 6) + (VH\ \times\ 10)}{24\ (hours)}$$

where S, L, M, H and VH are the time spent in sleep, light, moderate, hard and very hard activities respectively. TEE_{Stan} was calculated similar to TEE_{rpaq} from the above equation.

The values of TEE_{rpaq} and TEE_{Stan} quoted in the remainder of the paper refer to those estimated using the novel predictive equation except where otherwise stated.

Physical activity related energy expenditure (PAEE) was calculated from each of the questionnaires as (0.9 x TEE) – REE (estimated using the novel predictive equation). PAEE from DLW was calculated similarly except that the measured REE was used in the equation.

Statistical Analysis

Statistical analysis was carried out using SPSS® version 19 (SPSS Software, IBM Corporation, Armonk, NY, USA). Normally distributed data are presented as mean ± standard deviation and non-normally distributed data as median (inter-quartile range). The significance of differences between means was determined using Student's t-test and of medians by Mann-Whitney U-test. Comparison between questionnaire-derived TEE and PAEE and that from DLW method was carried out using Bland-Altman analysis (17). A p-value of < 0.05 was considered significant.

RESULTS

A total of 40 patients were studied – 21 patients with CKD stages 1-3 and 19 patients with CKD stages 4 and 5. Their main demographic and biochemical characteristics are shown in Table 1. 22 subjects (55%) were males. The underlying aetiology for CKD in patients with CKD stages 1-3 were IgA nephropathy (3 patients), Adult polycystic kidney disease (2), membranous nephropathy (3), minimal change disease (3), ischaemic nephropathy (3), lupus nephritis (2), ANCA associated vasculitis (1) and unknown in 2 subjects. In those with CKD stages 4-5, the commonest aetiology were Diabetic nephropathy (3), IgA nephropathy (2), adult polycystic kidney disease (2) and unknown in 4 subjects. Ten subjects had diabetes mellitus of which 6 were treated with Insulin, 2 with oral hypoglycaemics and 2 were diet-controlled. All

patients were clinically euvolaemic. None of the patients were receiving diuretic therapy. There were no significant differences between the CKD groups with regards to demographic and body size parameters and comorbidity. As would be expected, eGFR and haemoglobin levels were lower in advanced CKD group. There was no significant difference in TEE (2384 vs 2485 kcal/day, $p = 0.535$) or physical-activity related energy expenditure (618 vs 640 kcal/day, $p = 0.832$) between the CKD groups 1-3 and 4-5.

The reported activity durations from RPAQ and Stanford questionnaires are shown in Table 2. The median reported activity time from RPAQ was 9.2 hours with sedentary activity being the major component of this time. The median unaccounted time from RPAQ was 6.8 hours. The median daily MET from Stanford questionnaire was 1.51 with light intensity activity being the principal component. Except for the light activity duration from Stanford questionnaire, which was higher in females, there were no other gender differences in any of the activity times in either of the questionnaires.

Estimates of TEE from RPAQ (TEE_{rpaq}) were calculated using different MET values for the unreported time from the questionnaire. The difference in TEE measured by DLW method (TEE_{dlw}) and TEE_{rpaq} was calculated for each of these TEE estimates. Figure 1 shows the mean difference (bias) between TEE_{dlw} and TEE_{rpaq} for each assigned MET value using estimated REE from the predictive equation. The corresponding limits of agreement for the bias values for each of these estimates are shown in Table 3. It can be seen that MET value of 1.3 for the unaccounted time had the least bias (108 kcal/day) using the estimated REE or the measured REE (171

kcal/day). Bias with MET values over 1.3 were similar but limits of agreement were very wide and unacceptable for clinical use. The same MET value also had the narrowest range of limits of agreement indicating better approximation of TEE estimate to that measured from DLW method (Table 3).

Using MET value of 1.3 for the unaccounted time in RPAQ, TEE estimates were calculated using different REE predictive equations. Five predictive equations – the novel kidney disease-specific equation, Harris-Benedict, Mifflin-St Jeor, Schofield and Henry equations – were used. The bias and limits of agreement associated with each of the TEE estimates and TEE_{dlw} are shown in Table 4. The novel equation had the least bias (108 kcal/day) and Mifflin-St Jeor the highest (285 kcal/day). The limits of agreement were comparable between TEE estimates from different equations. TEE was also estimated using measured REE and the above MET value. The bias for TEE estimate with measured REE was 171 kcal/day (limits of agreement: 1105 kcal/day, -764 kcal/day). The bias estimates were similar using the PAEE from the Stanford questionnaire (ranging from -182 [novel equation] to +18 kcal [Mifflin-St Jeor]), the limits of agreement associated with the use of all the equations were very large.

The mean TEE_{dlw} was 2481 (± 476) kcal/day, TEE_{rpaq} was 2324 (± 538) kcal/day and TEE_{Stan} was 2615 (± 687) kcal/day. TEE_{dlw} had a moderately strong correlation with TEE_{rpaq} (R^2=0.576) and weaker correlation with TEE_{Stan} (R^2=0.235). Bland-Altman plots comparing TEE_{dlw} with TEE_{rpaq} and TEE_{Stan} are shown in Figures 2 and 3. The bias was less with TEE_{rpaq} (108 kcal/day) compared to that with TEE_{Stan} (-183 kcal/day). Similarly, the limits of agreement were also narrower with TEE_{rpaq}.

The mean PAEE estimated from DLW was 628 kcal/day, from RPAQ was 473 kcal/day and that from Stanford questionnaire was 734 kcal/day. There was significant correlation between PAEE from DLW and that from RPAQ with a Spearman correlation coefficient (rho) of 0.408 ($p = 0.009$). The correlation between PAEE from DLW and Stanford questionnaire was not statistically significant (rho = 0.302, $p = 0.06$).

DISCUSSION

The primary aim of this study was to examine the validity of the two physical activity questionnaires as tools to estimate TEE in clinical practice. The study showed the RPAQ questionnaire performs better for estimating energy requirements compared to Stanford 7-day recall questionnaire and has a higher correlation to TEE measured using the gold-standard doubly labelled water method. A MET value of 1.3 for the unreported time in RPAQ provides the best approximation of TEE from the questionnaire to the measured TEE.

Assessing physical activity in patients with kidney disease can be beneficial in many ways. Firstly, it can help to identify patients with poor physical function. Secondly, it can be used to monitor the level of physical activity with disease progression and aid early detection of declining physical functioning. Finally, it can also be used to monitor the response to any clinical and psychological interventions related to physical activity levels.

The DLW method does not offer a practical solution for measurement of TEE in clinical practice due to the time-consuming nature and its cost. Furthermore, the method cannot be easily used in patients being treated with dialysis due to alterations to body water turnover. Physical activity questionnaires are useful tools to assess activity levels on a routine basis. Questionnaires developed in younger people are inaccurate when used in elderly population (18, 19). Patients with kidney disease are likely to be older adults and to have higher comorbidity and hence, the activity questionnaires need to be validated in this patient group.

Two questionnaires – RPAQ and Stanford 7-day recall questionnaire – were examined for their validity in patients with kidney disease in this study. TEE derived from RPAQ correlated well with that measured from DLW method. The strong correlation of RPAQ derived TEE with TEE_{dlw} implies the questionnaire is an acceptable tool for use in patients with kidney disease. On the other hand, Stanford questionnaire had a weaker correlation with TEE_{dlw} with the R^2 being 0.24. This is comparable to other questionnaires that have been examined in patients with kidney disease (11). Johansen et al compared 4 activity questionnaires against accelerometer derived energy expenditure data and found wide variations in the validity of these questionnaires (11). Human Activity Profile was the best performing questionnaire in that study with a R^2 of 0.53 for the Adjusted Activity Score from the questionnaire and the Stanford questionnaire had a R^2 of 0.35. In a review by Neilson et al, it was shown that the TEE derived from various questionnaires across many studies had only moderate correlation with TEE measured from DLW method (20). This highlights the limited capability of questionnaires for TEE estimation. However, the correlation

between RPAQ-derived TEE and that from DLW is better than many of the other currently available questionnaires for energy expenditure estimation.

The superior performance of RPAQ over Stanford questionnaire may be due to the design of the questionnaire itself. RPAQ categorises activities into those at home, work and in leisure time. Also, it enquires about specific activities that are commonly performed everyday. Such a questionnaire design possibly aids in better recall of activities. In contrast, Stanford questionnaire enquires about overall time spent in every activity intensity level. Subjects may find it difficult to categorise their activities into appropriate intensity levels resulting in poor reporting of activity level. It is worth noting that this study involves only those with CKD and Stanford questionnaire may be a reliable tool in other disease conditions.

There is a considerable amount of unreported time from RPAQ (median 6.8 hours per day) which does not include the sleep time. Excluding this time from TEE calculation will grossly underestimate the energy expenditure. The questionnaire captures higher intensity activities well with specific activities listed in detail. However, activities that are routinely carried out at home and low intensity activities are not specifically enquired for in the questionnaire. This may lead to these activities not being reported by patients. It is reasonable to assume that individuals are performing some activity – likely sedentary or low intensity activities – in this unreported time and hence, assigning an average MET value above 1 for this unreported time seems prudent. It is essential to identify an appropriate MET value to assign for this period which will enable better approximation of estimated TEE to the directly measured TEE from DLW method.

A range of MET values (1 to 1.3) for the unreported time in RPAQ was explored. Our study shows that TEE estimated by assigning a MET value of 1.3 for the unreported time was the closest to the measured TEE compared to other MET values. Not only did the MET value of 1.3 showed the least bias but the limits of agreement with TEE_{dlw} were also narrower when compared to other MET values. Intuitively, this would seem the appropriate MET for the unreported time. A MET value of 1.3 is generally considered the threshold between sedentary and light activities. Patients are more likely to under-report sedentary activities especially when not specifically enquired about it and hence, it is possible that patients with kidney disease are performing sedentary activities during this time. However, it is worth noting that this value may not be applicable to certain subset of CKD patients performing at the extremes of physical activity levels.

The novel predictive equation for REE has been shown to be at least as accurate as the existing ones and was associated with less bias in predicting REE (4). In keeping with these findings, TEE estimates using this equation also performed better compared to the existing general equations. Moreover, TEE estimate derived using this equation was comparable to those derived using measured REE values. Our findings highlight the importance of using disease-specific predictive equation for TEE estimation.

Validity of activity questionnaires should not be assessed solely on correlations alone (21, 17, 22). We used the Bland-Altman technique to compare TEE estimated from questionnaires to a gold standard DLW method. A limitation of our comparison is that the questionnaire measures activity for a time period that differed somewhat from the

14-day DLW study. If the questionnaire measures activity for a different time point than that measured by DLW, this may result in unreliable results from the questionnaire data (20). To mitigate this, we administered questionnaires at the end of the 14-day study period to reflect recalled physical activity during the latter part of the DLW measurement.

In addition to the assumptions of the DLW method (23), the main limitations of the study are related to the use of questionnaires. Recall bias may have been a confounding factor in the accuracy of the data. This has been negated to some extent by enquiring about specific activities in the preceding weeks which facilitates recall of the activities by the subjects. Moreover, the strength of relationship between questionnaire data and DLW method is also in line with previously published literature. Finally, the study is limited by its relatively small sample size but the costs associated with DLW method restrict the use of this technique in large-scale studies.

In conclusion, this is the first study to have validated activity questionnaires against doubly labelled water method in patients with kidney disease. This study has shown that RPAQ is an acceptable tool for assessment of activity level and TEE in CKD patients in conjunction with the disease-specific REE predictive equation or measurement of REE. The Stanford questionnaire, though showing some relationship to the measured TEE, does not perform as well as RPAQ in estimating TEE in this patient group. A MET value of 1.3 has been shown to be the best estimate of the activity level for the unreported time in RPAQ and use of this value is recommended when using RPAQ for patients with kidney disease.

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CONFLICT OF INTEREST

None for all authors

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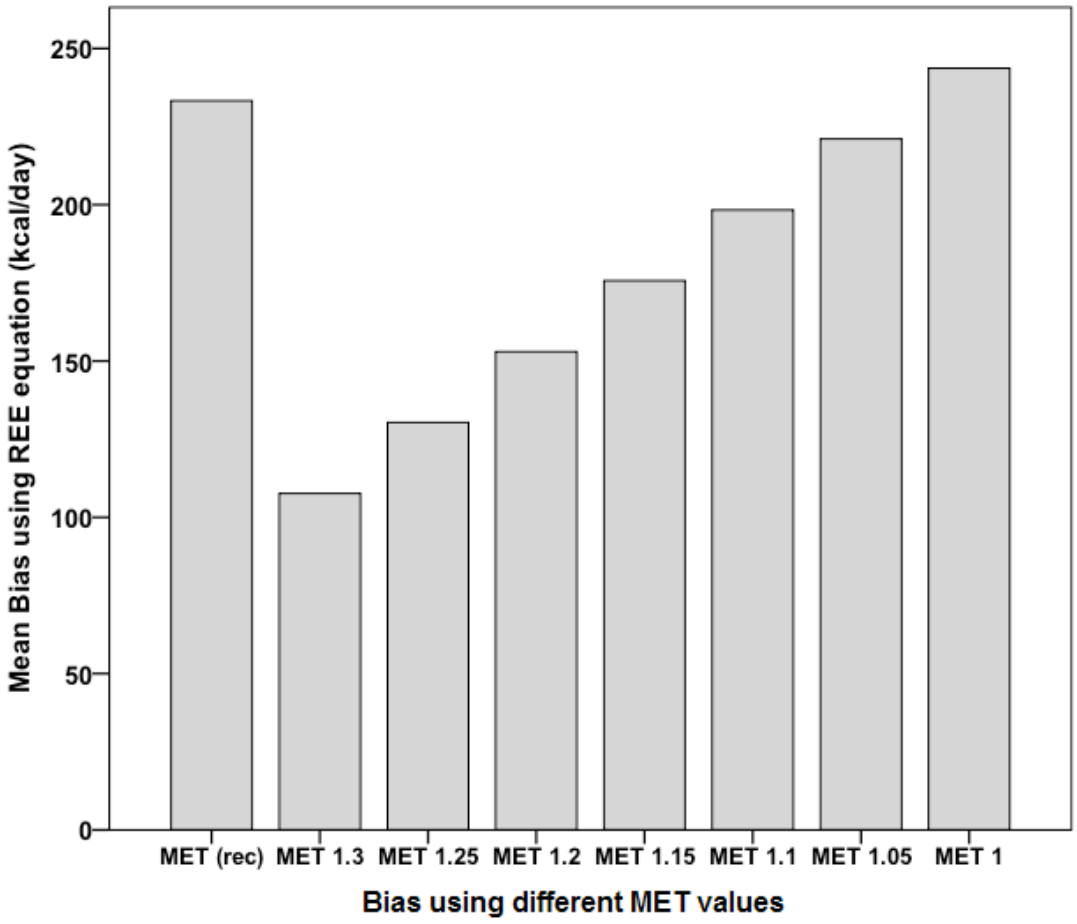
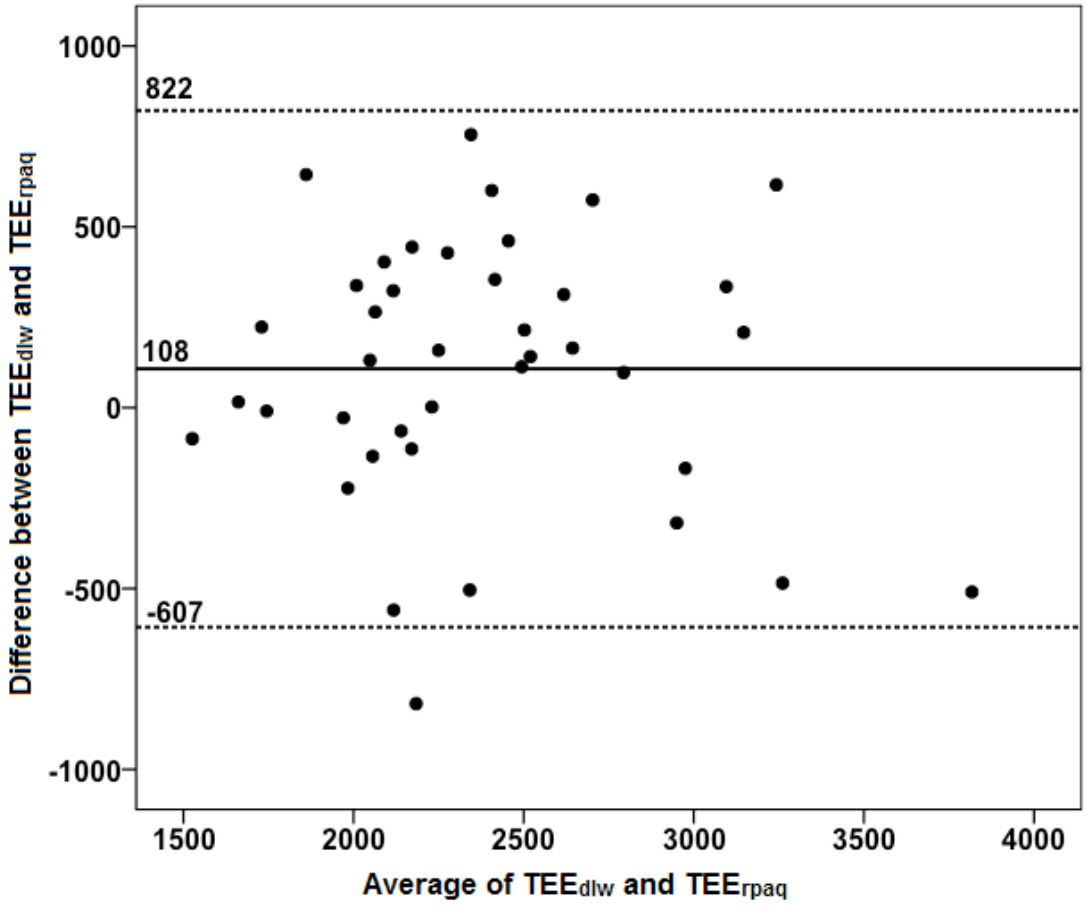
<u>Figure 1</u>: Mean difference (bias) between TEE_{dlw} and TEE_{rpaq} using estimated REE and various MET values for the unreported time



<u>Figure 2</u>: Bland-Altman plot showing bias and limits of agreement between TEE_{dlw} and TEE_{rpaq}

Difference between TEE measured by DLW and RPAQ plotted against the mean of the two measurements. A negative sign indicates an overestimation and a positive sign indicates an underestimation by the questionnaire.



<u>Figure 3</u>: Bland-Altman plot showing bias and limits of agreement between TEE_{dlw} and TEE_{Stan}

Difference between TEE measured by DLW and Stanford questionnaire plotted against the mean of the two measurements. A negative sign indicates an overestimation and a positive sign indicates an underestimation by the questionnaire.