

Optimal Estimate for Energy Requirements in Adult Patients With the m.3243A>G Mutation in Mitochondrial DNA

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Abstract

Aim: We aimed to identify the optimal method to estimate total energy expenditure (TEE) in mitochondrial disease (MD) patients. **Methods:** Resting energy expenditure (REE) was measured in MD patients carrying the m3243A>G mutation using indirect calorimetry (IC) and compared with results of 21 predictive equations (PEs) for REE and with REE-IC measurements in healthy controls. Physical activity level (PAL) was measured using accelerometry (SenseWear) and compared with a fixed average PAL (1.4) as well as patients' self-estimated activity levels. TEE was calculated as REE-IC \times PAL SenseWear and compared with usual care and energy recommendations for healthy adults. **Results:** Thirty-eight MD patients (age: 48 ± 13 years; body mass index 24 ± 4 kg/m²; male 20%) and 25 matched controls were included. The accuracy of most PEs was between 63% and 76%. The difference in REE-IC in healthy controls (1532 ± 182 kcal) and MD patients (1430 ± 221) was borderline not significant ($P = .052$). Patients' estimations PAL were 18%–34% accurate at the individual level. The fixed activity factor was 53% accurate. Patients overestimated their PAL. Usual care predicted TEE accurately in only 32% of patients. **Conclusion:** TEE is lower in these MD patients than the recommendations for healthy adults because of their lower physical activity. In MD patients, 6 PEs for REE provide a reliable alternative for IC, with an accuracy of 71%–76%. As PAL is highly variable and not reliably estimated by patients, measurement of PAL using accelerometry is recommended in this population. (*JPEN J Parenter Enteral Nutr.* 2021;45:158–164)

Keywords

accelerometry; indirect calorimetry; m.3243A>G mutation; MELAS; MIDD; mitochondrial disease; physical activity level; resting energy expenditure; total energy expenditure

Clinical Relevancy Statement

This study provides innovative information on total energy expenditure, which can help guide individual dietary treatment of patients with mitochondrial disease. Energy requirements are very relevant for this patient population because the energy production in these patients is decreased.

Introduction

Mitochondria are responsible for the transformation of energy from nutrients into adenosine triphosphate, through oxidative phosphorylation (OXPHOS). Mitochondrial dysfunction can result from mutations in either nuclear DNA or mitochondrial DNA. The incidence of primary

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mitochondrial disorders is approximately 1:5000 of all live births.¹ The most frequently reported pathogenic mitochondrial mutation in adults is the m.3243A>G point mutation.^{1,2} The most frequently reported phenotype of the m.3243A>G mutation is maternally inherited diabetes and deafness (MIDD), but mitochondrial myopathy also is very common. Mitochondrial encephalomyopathy and lactate acidosis and stroke-like episodes (MELAS) is a more severe phenotype with a lower incidence. Frequently occurring symptoms are hearing loss, gastrointestinal symptoms, exercise intolerance, diabetes, and myopathy.² Because specific treatment options remain limited, treatment is based on symptoms' management, like exercise³ and nutrition care.⁴

Accurate prediction of total energy expenditure (TEE) is crucial to guide individual dietary treatment⁴ because mitochondrial disease (MD) patients are at risk for both malnutrition⁵⁻⁷ and overnutrition, with a higher risk for comorbidities and metabolic syndrome.^{4,8,9}

At this point, it is not clear if and how MD affects energy requirements. Defects in the OXPHOS system could theoretically lead to a lowered oxygen consumption rate at the cellular level,¹⁰ with lower resting energy expenditure (REE). A lower fat-free mass (FFM), as is frequently seen in MD,⁴⁻⁷ might also lower the REE.¹¹ Previously, Fiuza-Luces et al (2016) did not find a lower oxygen consumption rate or lower REE when assessing indirect calorimetry (IC) in 20 children with MD.¹² By contrast, the lactic acidosis that frequently occurs in MD may induce increases in the volume of CO₂ production based on exhaled CO₂. This could mean a higher REE. The latter could not be confirmed by Fiuza-Lucas et al (2016), although these authors reported a nearly significant ($P = .086$) increase in REE in children with MD as compared with healthy controls.

MD patients are a heterogeneous group in whom nutrition intake tends to be inadequate.¹³ Measuring REE using IC is recommended,^{5,12} but this is a relatively expensive method that requires the presence of trained personnel. For this reason, REE is often estimated in an indirect manner by means of predictive equations (PEs).¹⁴ It is known that these PEs are not very accurate at an individual level,¹⁴ but how accurate they are in MD is not known.

Physical activity has a major influence on TEE,¹⁵ and it is known that patients with MD are less active than healthy controls in this respect.^{8,16} Physical activity can be reliably measured using noninvasive accelerometry.¹⁷ This, however, is not implemented in most clinical settings, and in usual care, physical activity level (PAL) is mostly estimated based on anamnestic data obtained from patients or by the use of standard PAL based on literature⁸ or protocols.^{11,18}

The aim of this study was to identify the optimal method to estimate TEE in MD patients. Also, we wanted to learn whether the energy requirements in adult MD patients differ from healthy adults.

Materials and Methods

Standard Protocol Approval, Registration, and Patient Consent

This study was conducted in accordance with good clinical practice and the Declaration of Helsinki. The Medical Ethics Committee of the Arnhem and Nijmegen region approved the study protocol (NL 39724.091.13/2013/146), and written informed consent was obtained from every patient.

Study Design/Patients

In this study, we used baseline data of the DINAMITE study, a randomized controlled trial with an individual dietary intervention in adult patients with MD due to the m.3243A>G mutation,⁴ as well as healthy control data from the DYNAMO study, a cross-sectional study on the association of body composition, physical functioning, and protein intake in adult patients with MDs.⁷

Thirty-nine patients with MD due to the m.3243A>G mutation, from the Radboudumc patient cohort, were included in the DINAMITE study. These could participate if they were at least 18 years of age, had no medical contraindication to undergo nutrition assessment after overnight fast, had no cardiac pacemaker, and did not suffer from claustrophobia. Patient measurements were performed between 2014 and 2017. Maternal lactation was another exclusion criterion for this study. Seventy-three healthy controls were included in the DYNAMO study: we used only the data of controls that on average matched for gender, age (± 2 years), and body mass index (BMI, ± 1 kg/m²).

Data on phenotype, the Newcastle Mitochondrial Disease Adult Scale,¹⁹ and heteroplasmy levels of the mutation measured in urinary epithelial cells²⁰ were collected from patient files.

Anthropometrics

Height (cm) and weight (kg) were measured. The FFM was estimated by single-frequency bioimpedance analysis (BIA) (Bodystat 1500 MDD) at 50 Hz; FFM (kg) was calculated according to the formula presented by Kyle et al.²¹

Resting Energy Expenditure

As the gold standard for REE (kcal), IC was measured as assessed for 20–30 minutes with the Cosmed Quark RMR, lying down with the canopy after an overnight fast, according to the Dutch national standard operating procedure. The REE-IC was compared with the results of 21 PEs, including 4 that incorporate FFM (see Table S1), and with the REE-IC of healthy controls.

Table 1. Activity Level Scored According to Criteria From the Dutch Health Council (Gezondheidsraad)²⁶ Translated Into Lower and Upper PAL Values as Described by Black (1996),¹⁵ Based on Double-Labeled Water Measurements.

Activity level according to Black (1996) ¹⁵	Answer in Dutch activity table ²⁶	Lower PAL	Upper PAL
Chair-bound or bed-bound	I use a wheelchair all the time	1.2	1.2
Seated work with no option of moving around and little or no strenuous leisure	I have limited activity, I alternate sitting with light housework and activities such as writing, washing	1.4	1.5
Seated work with discretion and requirement to move around but little or no strenuous leisure activity	I'm moderately active, I alternate sitting with light and heavier housework, gardening, walking, cycling, sports	1.6	1.7
Standing work (eg, housewife, shop assistant)	I'm normally active, I don't sit very often	1.8	1.9
Strenuous work or highly active leisure	I'm very active, I do heavy physical work and/or I exercise a lot	2.0	2.4

PAL, physical activity level.

Physical Activity Level

Physical activity was measured using a validated multisensor actometer²²⁻²⁵ (SenseWear, Bodymedia with SenseWear Pro algorithm version 5.2), which was worn over a 7-day period. Patients wore the device day and night; they only were allowed to take it off for showering.

Physical activity data are presented as average metabolic equivalents (METs) per day, in which 1 MET = resting metabolic rate. PAL is defined as the TEE/REE. Therefore, average METS were interpreted as PAL and used as the gold standard.

The gold standard was compared with the following:

1. Patients' estimated activity level scored by the Dutch activity table (see Table 1).
2. Usual care using a fixed PAL of 1.4. This was chosen for 2 reasons:
 - a Apabhai et al (2011) found in 100 genetically proved adult MD patients with SenseWear accelerometry an average PAL of 1.4⁸; this result is consistent with the average PAL in the DINAMITE study.⁴
 - b Literature on PAL in patients with various diseases advises to consider a PAL of 1.3–1.5. This value is therefore commonly used in dietary practice, including in our center.¹⁸
3. Average PAL in healthy Dutch adults is considered to be 1.7 in persons up to 50 years of age and 1.6 from 50 years and older.²⁶ The recommended PAL is higher: 1.9–1.8.²⁶

Total Energy Expenditure

We compared our gold standard for TEE (REE-IC × PAL SenseWear) to usual care and energy recommendations for healthy adults. The usual care at our center involves using the World Health Organization (WHO) formula with weight

and height¹⁴ as the PE for REE for patients with a BMI of <30 kg/m² and Harris-Benedict (1918)²⁷ for patients with BMI of ≥30 kg/m², based on the study by Kruijenga et al (2016). This estimated REE is multiplied with the usual-care fixed PAL of 1.4 to calculate the usual-care TEE. The energy recommendations are based on the WHO REE PE + weight multiplied with a PAL of 1.7 for patients <50 years old and 1.6 for patients aged 50 years and older.²⁶

Statistics

Data were reported as means ± SD or frequencies and percentage of the group or total population, if applicable. Normal distribution of the variables was assessed by Shapiro-Wilk tests. Differences between MD patients and controls were tested using the independent *t*-test. Differences between estimated PAL and measured PAL and between gold-standard TEE with energy recommendations were tested using the paired *t*-test. Accuracy of predictions for REE/PAL/TEE was evaluated as the percentage of participants who predicted within ±10% of measured REE/PAL/TEE, root-mean-square error (bias), and mean absolute percentage difference between predicted and measured REE/PAL/TEE. Statistical analyses were performed using SPSS statistics (IBM Statistics 23). Two-sided testing was used in all cases, and the significance level was set at *P* < .05.

Results

Thirty-eight MD patients (age: 48 ± 13 years; BMI 24 ± 4 kg/m²; male 20%; patient characteristics are shown in Table 2) and 25 matched controls (age: 46 ± 11 years; BMI 24 ± 3 kg/m²; male 20%) were included. One patient from the DINAMITE study was excluded because she was lactating. Twelve controls from the DYNAMO were excluded because they did not match for gender, age, and/or BMI.

Table a. Patients Characteristics.

Variable	MD patients (n = 38)
Age (years)	48 ± 13
Female gender	31 (82)
BMI, kg/m ²	24 (±4.2)
Underweight (BMI ≤ 18.5 kg/m ²)	2 (5)
Normal (BMI 18.5–25 kg/m ²)	21 (55)
Overweight (BMI 25–30 kg/m ²)	12 (32)
Obesity (BMI ≥ 30 kg/m ²)	3 (8)
NMDAS score	18 ± 10
Heteroplasmy UECs	48 ± 22
Phenotypes	
MIDD	20 (53)
Myopathy	15 (42)
MELAS	2 (5)
METS SenseWear = PAL	1.4 ± 0.25
FFMI, kg/m ² ^a	15.7 ± 2.3
Low n (%)	18 (47)
Normal n (%)	20 (53)
Self-estimated activity, n (%)	
Limited activity	11 (30)
Moderately active	17 (46)
Normally active	7 (19)
Very active	2 (5)
Wheelchair use, n (%)	
I don't use a wheelchair	34 (92)
I only use a wheelchair outside with long distances	3 (8)
Activity-stimulating factors	
No activity-stimulating factors	16 (43)
Rehabilitation program	3 (8)
Physiotherapy	8 (22)
Sports	12 (32)

Data are shown as mean ± SD, n (%).

BMI, body mass index; FFMI, fat-free mass index; MELAS, mitochondrial encephalomyopathy and lactate acidosis and stroke-like episodes; METS, metabolic equivalents; MIDD, maternally inherited diabetes and deafness; NMDAS, Newcastle Mitochondrial Disease Adult Scale; UEC, urinary epithelial cell.

^aLow or normal FFMI as compared with reference values by Pichard et al (2004).³¹

Resting Energy Expenditure

Table 3 shows statistics of the 21 REE PEs for the MD patients. The accuracy of most (n = 15) PEs was between 63% and 76%. Three out of 4 PEs that use FFM as a variable were all <50% accurate. The 3 best-scoring REE formulas were Henry based on weight and height,²⁸ Muller using FFM,²⁹ and Harris-Benedict (1984).²⁷ The difference in REE-IC in healthy controls (1532 ± 182 kcal) and MD patients (1430 ± 221) almost reached statistical significance ($P = .052$); see Figure 1.

Physical Activity Level

The patients' estimations for PAL were 18%–34% accurate at the individual level. The fixed activity factor (1.4) was 53%

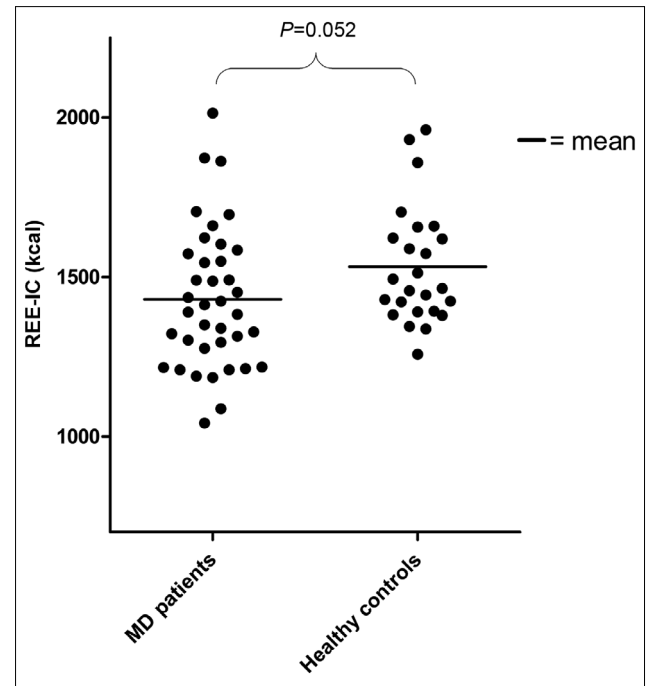


Figure 1. Resting energy expenditure measured by indirect calorimetry (REE-IC) in mitochondrial disease (MD) patients and healthy controls.

accurate (see Table 4). Patients overestimated their PAL. The difference between measured and estimated PAL was significant ($P = .001$ for the lower estimated PAL and $P < .001$ for the higher estimated PAL).

Total Energy Expenditure

Usual care accurately predicted TEE in only 32% of patients (see Table 5). Total energy requirements of MD patients were significantly lower than Dutch energy recommendations ($P < .0001$).

Discussion

The main finding of the present study is that the method in usual care of estimating TEE in adult MD patients seems adequate in only 32% of all patients, whereas 6 available PEs for REE showed an accuracy of 71%–76% and seem a relatively reliable alternative to IC. The patients' own estimations for PAL proved not to be a suitable alternative to accelerometry.

The REE-IC seemed slightly (±100 kcal) lower in MD patients as compared with healthy controls (1430 ± 221 kcal in MD patients vs 1532 ± 182 in controls), but this difference was not statistically significant ($P = .052$). Fiuza-Luces et al (2016) found an opposite but nonsignificant difference ($P = .085$) in REE-IC in children with MD vs controls.¹² Based

Table f. Comparison of 21 REE Predictive Equations With Gold Standard.

REE prediction equations	REE (kcal/d)	SD (\pm)	Mean absolute percent error (%)	Bias (kcal/d)	Percentage of MD patients with accurate estimation ^a	Percentage of MD patients with underestimation ^b	Percentage of MD patients with overestimation ^c
Gold standard = REE-IC	1430	221	-	-	-	-	-
Henry H + W ²⁵	1378	189	7.6 ^e	164	76 ^d	21	3
Muller A ²⁶	1376	184	7.8 ^f	163	74 ^e	24	3
H&B1984 ²³	1393	178	7.8 ^f	159 ^e	71 ^f	18	11
Henry H ²⁵	1356	176	7.9	174	71 ^f	26	3
Cole ³⁴	1345	154	7.6 ^e	174	71 ^f	29	0
Muller FFM ²⁶	1369	166	7.5 ^d	160 ^f	71 ^f	24	5
H&B1919 ²⁷	1398	171	7.9	158 ^d	68	21	11
Muller B ²⁶	1367	210	8.9	182	68	26	5
WHO W ¹¹	1422	176	8.4	162	66	16	19
Mifflin1 ³⁰	1324	199	8.7	192	66	34	0
Mifflin2 ³⁰	1320	200	8.6	195	66	34	0
Schofield H + W ³¹	1401	175	8	167	66	21	13
Schofield W ³¹	1418	172	8.2	162	66	16	18
WHO H + W ¹¹	1423	175	8.4	158 ^d	63	16	21
Owen ^{28,29}	1317	172	9.1	200	63	37	0
Luis ³²	1474	200	10.6	197	53	13	34
Mifflin FFM ³⁰	1255	168	11.7	214	45	55	0
Weijs ¹⁴	1560	204	13.5	215	37	5	58
Owen FFM ^{28,29}	1194	194	16.2	273	21	79	0
Bernstein ³³	1148	130	18.9	325	16	84	0
Bernstein FFM ³³	1068	171	25.1	383	0	100	0

Bias, root-mean-square error; FFM, fat-free mass; H, height; IC, indirect calorimetry; MD, mitochondrial disease; PE, predictive equation; REE, resting energy expenditure; SD, standard deviation; W, weight; WHO, World Health Organization.

^aAccurate estimation = REE PE between 90% and 110% of REE-IC.

^bUnderestimation = REE PE <90% of REE-IC.

^cOverestimation = REE PE >110% of REE-IC.

^dBest outcome.

^eSecond-best outcome.

^fThird-best outcome.

on these limited data, it seems fair to assume that REE of these MD patients does not substantially differ from healthy individuals and does not have clinical implications.

The accuracy of 6 PEs was between 71% and 76% (see Table 2). This is significantly better compared with the maximally 49% accurate predictions of Kruijenga et al¹⁴ in a large hospital patient cohort (n = 513). This suggests that for most MD patients, the use of 1 of these 6 PEs provides a relatively reliable alternative to IC. Yet dietitians should be aware that PEs remain estimations. The PEs can be used as an aid to the initial energy estimation, which then should be corrected according to changes in the patient's nutrition status.

Patients' estimations of PAL did not prove reliable alternatives for accelerometry, given their accuracy of only 18%–34%, with patients overestimating their PAL. It should be mentioned here that the activity table that we used and which has been validated for healthy individuals does not seem suitable for patients with exercise intolerance. For example, patients perform even light household tasks at

a slower pace and with lower intensity. Because of our results, we recommend using accelerometry in all adult MD patients as part of their nutrition assessment. This technique is not expensive and is doable for patients, whereas the alternatives seem inaccurate. In case this is not possible, the use of a fixed PAL of 1.4 provides a more reliable alternative (53%) compared with the patients' self-estimated PAL.

The TEE of MD patients is lower than that of recommendations for healthy individuals, and because there was no difference in REE, this difference is mainly explained by their lower PAL. This finding is in line with previous research in MD patients by Apabhaj et al (2011).⁸ Because interindividual differences in TEE may be substantial in this very heterogeneous patient group, nutrition assessment is recommended for accurate estimates at the individual level.⁴⁻⁶

The SenseWear accelerometer has been reported to overestimate energy expenditure in healthy adults, especially at high intensities.²⁵ Although patients with

Table 4. Comparison of Estimated PAL With Gold Standard.

	PAL	SD ^b (±)	Mean absolute percent error (%)	Bias (kcal/d)	Percentage of MD patients with accurate estimation ^a	Percentage of MD patients with underestimation ^b	Percentage of MD patients with overestimation ^c
Gold standard = PAL (SenseWear)	1.4	0.24	-	-	-	-	-
Patient-estimated lower PAL	1.6	0.17	18	0.29	34	13	53
Patient-estimated upper PAL	1.7	0.21	24	0.38	18	11	71
Usual care = fixed average PAL	1.4	-	13 ^d	0.24 ^d	53 ^d	29	18

Bias, root-mean-square error; MD, mitochondrial disease; PAL, physical activity level; SD, standard deviation; SW, Sensewear.

^aAccurate estimation = predictive equation PAL 90%–110% of PAL (SW).

^bUnder estimation = predictive equation PAL < 90% of PAL (SW).

^cOverestimation = predictive equation PAL > 110% of PAL (SW).

^dBest outcome.

Table 5. Comparison of the Gold Standard of TEE in MD Patients With Usual Care and the Dutch Energy Recommendations.

	TEE (kcal/d)	SD (±)	Mean absolute percent error (%)	Bias (kcal/d)	Percentage of MD patients with accurate estimation ^a	Percentage of MD patients with underestimation ^b	Percentage of MD patients with overestimation ^c
Gold standard = REE (IC) × PAL (SenseWear)	2058	414	-	-	-	-	-
Usual care = WHO ¹¹ (if BMI < 30 kg/m ²) or HB (1918) (if BMI ≥ 30 kg/m ²) × 1.4	1985	243	18	422	32	37	32
Energy recommendations WHO + W ¹¹ × 1.7 (if age < 50 years) or × 1.6 (if age > 50 years)	2348	281	23	498	32	11	58

Bias, root-mean square error; BMI, body mass index; H, height; HB, Harris Benedict; IC, indirect calorimetry; MD, mitochondrial disease; PAL, physical activity level; REE, resting energy expenditure; SD, standard deviation; TEE, total energy expenditure; W, weight; WHO, World Health Organization.

^aAccurate estimation = Estimated TEE 90%–110% of gold standard TEE.

^bUnderestimation = Estimated TEE < 90% of gold standard TEE.

^cOverestimation = Estimated TEE > 110% of gold standard TEE.

a mitochondrial disorder do not perform much intense activities³⁰ and the 5.2 version of the SenseWear Pro algorithm that was used shows better validity for measuring energy expenditure than the older 2.2 version,²⁴ this presents a methodological limitation. Another shortcoming is the use of BIA to evaluate body composition. This is a double indirect method, and BIA is known to overestimate FFM compared with dual-energy x-ray absorptiometry in MD patients.⁷ Finally, the use of the healthy energy recommendations as a control for total energy requirements, instead of using a healthy control group that had the same accelerometry + IC measurements, is a limitation. The energy recommendations for healthy adults²⁶ are not very recent (2006) and are based on local Dutch recommendations stemming from the international WHO recommendations, which are even older (2001).¹¹

Conclusion

TEE in MD patients is lower than suggested by recommendations for healthy adults because of MD patients' lower amount of physical activity. In MD patients, 6 PEs for REE present a relatively reliable alternative for IC measurements. As PAL is highly variable and not reliably estimated by patients themselves, measurement of PAL using accelerometry is recommended in this population. If measuring activity is not feasible, the use of a fixed PAL of 1.4 is a more reliable method than using patient-estimated activity levels.

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Statement of Authorship

H. E. E. Zweers contributed to conception/design of the research and drafted the manuscript; H. E. E. Zweers, M. C. H. Janssen, and G. J. A. Wanten contributed to acquisition, analysis, or interpretation of the data. All authors critically revised the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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