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***Case Control Study***

**Resting energy expenditure in cirrhotic patients with and without hepatocellular carcinoma**

Henz AC *et al.* Resting energy expenditure in HCC

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**Abstract**

BACKGROUND

The diagnosis of malnutrition in patients with independent hepatocellular carcinoma (HCC) varies from 20% to 50%, is related to important complications and has a direct impact on the prognosis. Determination of the resting energy expenditure (REE) has become an important parameter in this population, as it allows therapeutic adjustments to recover their nutritional status. The REE in cirrhosis, with and without HCC, is not clearly defined, and requires the identification and definition of the best nutritional approach.

AIM

To evaluate the REE of patients with cirrhosis, with and without HCC.

METHODS

This is a prospective observational study evaluating the REE of 118 patients, 33 with cirrhosis and hepatocellular carcinoma and a control group of 85 patients with cirrhosis without HCC, using indirect calorimetry (IC), bioimpedance, and predictive formulas.

RESULTS

The REE determined by IC in cirrhotic patients with HCC was 1643 ± 364 and in those without HCC was 1526 ± 277 (*P* = 0.064). The REE value as assessed by bioimpedance was 1529 ± 501 for those with HCC and 1660 ± 385 for those without HCC (*P* = 0.136). When comparing the values of REE determined by IC and predictive formulas in cirrhotics with HCC, it was observed that only the formulas of the Food and Agriculture Organization (FAO)/World Health Organization (WHO) (1985) and Cunningham (1980) presented values similar to those determined by IC. When comparing the REE values determined by IC and predictive formulas in cirrhotics without HCC, it was observed that the formulas of Schofield (1985), FAO/WHO (1985), WHO (2000), Institute of Medicine (IOM) (2005) and Katch and McArdie (1996) presented values similar to those determined by IC.

CONCLUSION

The FAO/WHO formula (1985) could be used for cirrhotic patients with or without HCC; as it is the one with the values ​​closest to those obtained by IC in these cirrhotic patients.

**Key Words:** Carcinoma; Hepatocellular; Liver cirrhosis; Calorimetry; Indirect; Rest energy expenditure

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**Core Tip:** This prospective study was conducted to evaluate the resting energy expenditure in 118 patients with and without hepatocellular carcinoma. Indirect calorimetry is considered the golden standard for determining resting energy expenditure; however, when this is impossible, use of the FAO/WHO formula (1985) in this population is indicated.

**INTRODUCTION**

The main causes of liver cirrhosis worldwide are alcoholic liver disease and chronic hepatitis B virus and/or hepatitis C virus infections. Over a period of 15 to 30 years, chronic liver diseases can lead to liver cirrhosis and its complications. The prognosis is highly variable and influenced by several factors, such as etiology, severity of liver disease, presence of complications and comorbidities[1].

The prevalence of sarcopenia in patients with hepatocellular carcinoma (HCC) varies from 27.5%[2] to 78.2%[3] and malnutrition affects 20% to 50% of patients with cirrhosis, and both are related to important complications and have a direct impact on prognosis.

Early nutritional diagnosis has significant relevance in cirrhotics, as it reflects positively on their recovery, enables specific therapeutic interventions and prevents the appearance of complications[4-8].

Daily intake should be sufficient to meet the body's demands[9] and can be measured directly or indirectly[10]. Resting energy expenditure (REE) is the energy needed to maintain physiological processes; during indirect measurement, an interval of 4 h is necessary since the last meal, and a rest of 30 min before the examination[11].

Indirect calorimetry (IC) is the gold standard for measuring REE[11-13], it is non-invasive and safe, it uses the calorimeter to measure REE through gas exchange and, in a formula, using the Weir Equation (QR = 0.83) evaluates the volume of oxygen consumed, the volume of carbon dioxide produced and the nitrogen excreted, since each calorie consumed requires a certain amount of oxygen to be converted into energy, which are good predictors of REE changes[14].

Other methods, such as electrical bioimpedance (BIA) and predictive formulas, commonly used in clinical practice, can also be used to predict REE.

The aim of this study is to evaluate the REE of patients with cirrhosis, with and without HCC, measured by IC and to compare the results with those obtained by BIA and predictive formulas, in order to identify which is the best method of evaluation[15].

**MATERIALS AND METHODS**

The study included 118 patients, aged ≥ 18 years, of both sexes, divided into two groups. One group consisted of 33 patients with cirrhosis and HCC and a control group of 85 patients with cirrhosis but without HCC, who attended the Department of Gastroenterology and Liver Transplantation of Irmandade da Santa Casa de Misericórdia de Porto Alegre, RS, Brazil, from March 2017 to August 2018.

Hospitalized cirrhotics or those participating in dietary or physical activity programs for weight gain, and/or in a rehabilitation program were excluded; patients with neoplasms other than HCC and those who did not have physical and motor conditions for anthropometric and functional evaluation were also excluded.

All participants agreed to participate in the research by reading and signing the informed consent form. This research protocol was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre (number 2387800).

Data from the electronic medical records of the patients, related to the diagnosis, staging by the Child-Pugh score, age and sex of the participants were collected. The diagnosis of cirrhosis and/or HCC was made by clinical, laboratory, imaging and/or, eventually, liver biopsy. The classification of patients with HCC was carried out using the Barcelona Clinic Liver Cancer Group (BCLC) staging system[16].

Current body weight was measured using a Filizola® anthropometric scale with 0.1 kg precision, previously calibrated. Height was measured with a stadiometer fixed to the wall, with the patient in an upright position and barefoot. Body mass index (BMI) was calculated by dividing the weight by height squared {BMI = Weight (kg)/[Height (cm)]2} and classification according to the Food and Agriculture Organization (FAO)/World Health Organization (WHO)[17].

The IC was measured by the Korr® MetaCheck calorimeter, with the patient fasting for 4 h and resting for 30 min before starting the assessment. The measurement was made under conditions of absolute rest for 10 to 30 min, with the patient sitting and using a rigid breathing mask, in a stable condition, and the calculation of energy expenditure was based on the consumption of O2 (VO2), CO2 production (VCO2) and urinary urea nitrogen, using the formula REE = {[3.9 (VO2)] + [1.1 (VCO2)]}, described by WEIR, 1949[18,19].

The BIA evaluation used the Biodynamics device model 450, with an electric current intensity of 800 µA, frequency of 50 kHz and disposable electrodes of the HeartBeat® brand. The patient was in the dorsal decubitus, comfortable and relaxed position, without shoes, socks, watch, bracelets and necklaces, with legs spread, hands open and supported on the stretcher. A distal electrode was placed at the base of the middle toe of the right foot and the proximal electrode just above the line of the right ankle joint, between the medial and lateral malleolus. Another set of electrodes were also placed, the distal electrode at the base of the middle finger of the right hand and the proximal electrode just above the line of the right wrist joint, coinciding with the styloid process[20].

The predictive formulas for calculating the energy expenditure used in this study are listed in Table 1[21-27].

***Sample size calculation***

The sample size for patients with HCC was by convenience sample, and the sample from the control group with cirrhosis was based on the study by Teramoto *et al*[28], comparing the measured and predicted energy expenditure in patients with liver cirrhosis, considering an 80% power and significance level of 5%, thus obtaining the sample number of 85 patients.

***Statistical analysis***

Quantitative variables were described by mean and standard deviation and categorical variables by absolute and relative frequencies.

To compare means between genders, the Student *t*-test for independent samples was applied. Population estimates were performed using the 95% confidence interval.

To compare groups, the Student *t*-test for independent samples (quantitative variables) and Pearson's Chi-square (categorical variables) were applied.

To compare means between the estimated energy expenditure formulas with indirect calorimetry, the Student *t*-test for paired samples was used.

To assess the association between anthropometric variables and indirect calorimetry, Pearson's correlation coefficient was used.

The level of significance adopted was 5% (*P* < 0.05) and the analyses were performed using the Statistical Package for Social Sciences 21.0 software for Windows.

**RESULTS**

The mean age of cirrhotic patients with HCC was 62.8 ± 8.1 years and in those without HCC was 56.7 ± 9.4 years (*P* = 0.001); 78.8% of those with HCC were male and 56.5% of those without HCC were female (*P* = 0.001). The clinical characterization of cirrhotic patients was performed using the Child-Pugh score, which identified similarities between the two groups (*P* = 0.224). According to the BCLC staging in our study, most patients with HCC were classified as 0, A and B, as shown on Table 2.

The REE determined by IC in cirrhotics with HCC was 1643 ± 364 and in those without HCC was 1526 ± 277 (*P* = 0.064), as shown on Table 3.

The REE value assessed by BIA was 1529 ± 501 for those with HCC and was 1660 ± 385 for those without HCC (*P* = 0.136). In the comparison between the REE determined by the IC, the group with HCC did not show a significant difference and the group without HCC did show a significant difference (*P* = 0.001), as shown on Table 4.

The estimated REE values of cirrhotics with and without HCC, using the predictive formulas of Harris and Benedict[21], Schofield[22], WHO[23], Mifflin *et al*[24], FAO/WHO[17], IOM[25], Cunningham[26] and McArdle *et al*[27] showed that only the Harris and Benedict[21] formula (*P* < 0.001) and the IOM formula[25] (*P* = 0.001) demonstrated a difference between the two groups, as shown on Table 5.

When comparing the REE values determined by the IC and the predictive formulas in cirrhotics with HCC, it was observed that only the formulas of the FAO/WHO[17] and Cunningham[26] presented values similar to those determined by the IC, the others underestimated these values, as shown on Table 6.

When comparing the REE values determined by the IC and the predictive formulas in cirrhotics without HCC, it was observed that the formulas of Schofield[22], WHO[23], FAO/WHO[17], IOM[25] and McArdle *et al*[27] presented similar but erratic values to those determined by the CI, as shown on Table 7.

**DISCUSSION**

Cirrhotic patients have an imbalance in energy metabolism, which contributes to protein-calorie malnutrition and a worse prognosis[5,27-32]. When HCC is associated with cirrhosis, clinical conditions and additional needs may worsen such as dietary restrictions. To date, there is no established standard and significant evidence to justify increased REE in these patients. Several studies, with different methodologies, such as IC, BIA and predictive formulas, have evaluated REE in cirrhotics with and without HCC[13,14,27,30,33-36].

In the present study, 118 cirrhotic patients were evaluated, 33 with HCC (62.8 ± 8.1 years and 78.8% male), and 85 without HCC (56.7 ± 9.4 years and 56.5% female) (*P* = 0.001) which is in accordance with the findings of the literature, where more older men present with HCC[30,32,37,38].

Anthropometry showed that the BMI in those with HCC was 27 kg/m2 (± 4.0) similar to that of the control group, and in cirrhotics without HCC, BMI was 28.7 kg/m2 (± 5.7). We identified a low prevalence of malnutrition, with overweight, but we must consider that the BMI underestimates the prevalence of malnutrition in cirrhotic patients, as body weight can represent significant changes due to frequent hydroelectrolytic disorders (edema and ascites), and these findings are concordant with previous studies carried out in cirrhotic[23,39-41] and cancer patients[42,43]. These results are also in line with studies carried out in cirrhotic patients, with and without HCC[14,30,31,34,37]. A publication by Fernandes *et al*[31], did not identify BMI as a safe method of assessing nutritional status in this population, due to inherent changes in body weight.

Considered as the gold standard for measuring REE, IC is a safe and non-invasive method, capable of determining nutritional needs through gas exchange[11,44,45].

In our study, the average REE calculated by IC in cirrhotic patients with HCC was 1643 ± 364 calories and that of cirrhotics without HCC was 1526 ± 277 calories (*P* = 0.064). These results are similar to those found by Segadilha *et al*[45], where REE was 1568 ± 374 calories in a population of 97 elderly cirrhotic patients hospitalized in Rio de Janeiro, and similar to those found by Pinto *et al*[44], of 1534 ± 300 calories, who studied a population of 45 cirrhotic patients listed for liver transplantation, which corroborates the expectation of correct caloric prediction by the method used[44].

Our REE findings, determined by BIA, in cirrhotics with HCC were 1529 ± 501 calories and 1660 ± 385 calories in those without HCC (*P* = 0.136). These values differ from those of Pinto *et al*[44], in their study with 53 cirrhotic patients with HCC in the liver pre-transplant, who found the average REE calculated by the BIA was 1817 calories, while that calculated by IC was 1651 calories, similar to our findings.

When comparing the REE determined by BIA with the IC value, we found that the group with HCC did not show a significant difference (*P* = 0.136), and the group without HCC did show a significant difference (*P* = 0.001).

Table 1 shows the predictive formulas used to calculate the REE, with their peculiarities.

Table 6 shows the estimated REE values in cirrhotics with and without HCC, and it can be seen that, with the exception of the Harris Benedict (1919)[22] and IOM (2005)[25] formulas, which show significant differences between the two groups (*P* < 0.001), the others show similar values.

A comparison of the REE data from the IC with those estimated by the predictive formulas, in relation to cirrhotics with HCC, shows that only the FAO/WHO[17] (*P* = 0.054) and Cunningham[26] (*P* = 0.806) formulas have similarity, and the other six were different (*P* < 0.05); in cirrhotics without HCC the inverse was noted, where five values were similar (*P* > 0.05) and three were different (*P* < 0.05). These findings prevent the determination of a uniform rule. The disparities in our data are consistent with numerous findings in the literature that demonstrate different values for the various methods[14,28,34-36,46].

The applicability of predictive formulas, even with their practicality and low cost, is controversial because they are very erratic, and underestimate or overestimate the REE[35,23], and are thus unreliable.

Our results suggest that the predictive formulas do not provide precise REE values because when using the body weight of cirrhotics, they may incur an intrinsic error, due to water retention (ascites and edema) that directly affects the calculation of REE[38,39].

Studies on other diseases, such as that by Zanella *et al*[11], who compared the calculation of REE by IC with predictive formulas and BIA, in patients with pulmonary hypertension, showed that IC obtained values were different to all the other methods, which underestimated the predicted REE by more than 200 kcal, except that of the Cunningham's formula[26], and the formula by McArdle *et al*[27] showed the greatest difference in the REE estimate in the studied population[15].

The use of IC for determining the REE in routine clinical practice has some difficulties, related to difficulty in buying the device, which has a high cost, the time needed to perform the test and the possible lack of cooperation in patients[35].

Thus, based on the data from our study, we suggest the use of BIA values for cases with HCC or those of the FAO/WHO formula[17] for those with or without HCC; the Cunningham formula[26] could be used in cases without HCC and the formula by McArdle *et al*[27] for those with HCC, as they are the ones closest to those obtained by IC in these cirrhotic patients[23].

The choice of these formulas in the present study is not in line with the recommendation by Plauth *et al*[47] in the guidelines of the European Society for Parenteral and Enteral Nutrition of 1997 for nutrition in liver diseases and transplants, where it was suggested that the Harris and Benedict predictive formula[21] should be applied to estimate REE in patients with cirrhosis when IC is not available in a clinical setting[47].

Our results demonstrate that the formulas of Harris and Benedict[21] and IOM[25] were the ones that showed the greatest differences when compared to the determination of REE by IC, which is why we do not recommend these predictive formulas.

The determination of REE by IC, BIA or by any recommended predictive formula, in cirrhotics with or without HCC, is essential for the nutritional diagnosis. Individualized treatment and specific nutritional interventions can delay the emergence of malnutrition and poor clinical evolution[48].

Thus, we emphasize that the same method of evaluation in different populations can present different correlations with the available predictive formulas.

**CONCLUSION**

The REE by IC in cirrhotic patients with and without HCC was similar. When comparing the IC values with those of the BIA, we found that in patients with HCC, the values were similar. The values estimated by the predictive formulas are very erratic and disparate, when compared to IC. The FAO/WHO formula[17] could be used for those with or without HCC; Cunningham formula[26] in those without HCC and the McArdle *et al*[27] in those with HCC, as they are the ones with the closest values to those obtained by IC in these cirrhotic patients[23,49]. Apparently, the presence of HCC in cirrhotics does not appear to significantly alter the REE.

**ARTICLE HIGHLIGHTS**

***Research background***

The diagnosis of malnutrition in patients with hepatocellular carcinoma (HCC) varies from 20% to 50%, as it is related to important complications and has a direct impact on prognosis. Determination of the resting energy expenditure (REE) has become an important parameter in this population, as it allows therapeutic adjustments to recover their nutritional status. The REE in HCC is not clearly defined, and requires the identification and definition of the best nutritional approach.

***Research motivation***

The diagnosis of malnutrition in patients with HCC varies from 20% to 50%, is related to important complications and has a direct impact on prognosis. Determination of the REE has become an important parameter in this population, as it allows therapeutic adjustments to recover their nutritional status. The REE in HCC is not clearly defined, and the identification and definition of the best nutritional approach is necessary.

***Research objectives***

The aim of this study is to evaluate the REE of patients with cirrhosis, with and without HCC, measured by IC and to compare these values with those obtained by bioimpedance (BIA) and predictive formulas, in order to identify which is the best method of evaluation.

***Research methods***

This prospective observational study included 118 patients, aged ≥ 18 years, of both sexes, divided into two groups. One group consisted of 33 cirrhotic patients with HCC and a control group of 85 cirrhotics without HCC, attending the Department of Gastroenterology and Liver Transplantation of Irmandade da Santa Casa de Misericórdia de Porto Alegre, RS, Brazil, from March 2017 to August 2018. Quantitative variables were described by mean and standard deviation and categorical variables by absolute and relative frequencies.

***Research results***

The REE determined by indirect calorimetry (IC) in cirrhotic patients with HCC was 1643 ± 364 and in those without HCC was 1526 ± 277 (*P* = 0.064). The REE value as assessed by BIA was 1529 ± 501 for those with HCC and was 1660 ± 385 for those without HCC (*P* = 0.136). When comparing the values of REE determined by IC and predictive formulas in cirrhotics with HCC, it was observed that only the formulas of FAO/WHO (1985) and Cunningham (1980) presented values similar to those determined by IC. When comparing the REE values determined by the IC and predictive formulas in cirrhotics without HCC, it was observed that the formulas of Schofield (1985), FAO/WHO (1985), WHO (2000), IOM (2005) and Katch and McArdie (1996) presented values similar to those determined by IC.

***Research conclusions***

The REE determined by IC in cirrhotic patients with HCC was 1643 ± 364 and in those without HCC was 1526 ± 277 (*P* = 0.064). The REE value assessed by BIA was 1529 ± 501 for those with HCC and 1660 ± 385 for those without HCC (*P* = 0.136). When comparing the values of REE determined by IC and predictive formulas in cirrhotics with HCC, it was observed that only the formulas of FAO/WHO (1985) and Cunningham (1980) presented values similar to those determined by IC. When comparing the REE values determined by the IC and predictive formulas in cirrhotics without HCC, it was observed that the formulas of Schofield (1985), FAO/WHO (1985), WHO (2000), IOM (2005) and Katch and McArdie (1996) presented values similar to those determined by IC.

***Research perspectives***

The REE as assessed by IC in cirrhotics with and without HCC was similar. When comparing the IC values with those of the BIA, we found that in patients with HCC, the values were similar. The values estimated by the predictive formulas were very erratic and disparate, when compared to IC. The FAO/WHO formula could be used for those with or without HCC; the Cunningham formula in those without HCC and the McArdle in those with HCC, as they are the ones with the closest values to those obtained by IC in these cirrhotic patients. Apparently, the presence of HCC in cirrhotics does not appear to significantly alter the REE.

**REFERENCES**

1 **Romanelli RG**, Stasi C. Recent Advancements in Diagnosis and Therapy of Liver Cirrhosis. *Curr Drug Targets* 2016; **17**: 1804-1817 [PMID: 27296314 DOI: 10.2174/1389450117666160613101413]

2 **Nader LA**, de Mattos AA, Bastos GA. Burden of liver disease in Brazil. *Liver Int* 2014; **34**: 844-849 [PMID: 24422599 DOI: 10.1111/liv.12470]

3 **Desmet VJ**, Roskams T. Cirrhosis reversal: a duel between dogma and myth. *J Hepatol* 2004; **40**: 860-867 [PMID: 15094237 DOI: 10.1016/j.jhep.2004.03.007]

4 **Periyalwar P**, Dasarathy S. Malnutrition in cirrhosis: contribution and consequences of sarcopenia on metabolic and clinical responses. *Clin Liver Dis* 2012; **16**: 95-131 [PMID: 22321468 DOI: 10.1016/j.cld.2011.12.009]

5 **Alberino F**, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis. *Nutrition* 2001; **17**: 445-450 [PMID: 11399401 DOI: 10.1016/s0899-9007(01)00521-4]

6 **Møller S**, Bendtsen F, Christensen E, Henriksen JH. Prognostic variables in patients with cirrhosis and oesophageal varices without prior bleeding. *J Hepatol* 1994; **21**: 940-946 [PMID: 7699257 DOI: 10.1016/s0168-8278(05)80599-9]

7 **Mendenhall C**, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. *Alcohol Clin Exp Res* 1995; **19**: 635-641 [PMID: 7573786 DOI: 10.1111/j.1530-0277.1995.tb01560.x]

8 **Jackson AA**. Nutrition and Liver Health. *Dig Dis* 2017; **35**: 411-417 [PMID: 28468010 DOI: 10.1159/000456596]

9 **Frade RE,** Viebig RF, Pereira MS, Ruza NB, Valente TR. Uses of equations and methods to estimatethe basal energetic cost and the total energetic cost of adults that practice physical activities: a case study. *Rev Bras Nutr Esportiva* 2016; **10:** 43-49

10 **Kamimura MA,** Avesani CM, Draibe SA, Cuppari L. Resting energy expenditure in patients with chronic kidney disease. *Rev Nutr* 2008; **21:** 75-84 [DOI: 10.1590/S1415-52732008000100008]

11 **Zanella PB**, Ávila CC, de Souza CG. Estimating Resting Energy Expenditure by Different Methods as Compared With Indirect Calorimetry for Patients With Pulmonary Hypertension. *Nutr Clin Pract* 2018; **33**: 217-223 [PMID: 29596719 DOI: 10.1177/0884533617727731]

12 **Becker Veronese CB**, Guerra LT, Souza Grigolleti S, Vargas J, Pereira da Rosa AR, Pinto Kruel CD. Basal energy expenditure measured by indirect calorimetry in patients with squamous cell carcinoma of the esophagus. *Nutr Hosp* 2013; **28**: 142-147 [PMID: 23808442 DOI: 10.3305/nh.2013.28.1.6152]

13 **Belarmino G**, Singer P, Gonzalez MC, Machado NM, Cardinelli CS, Barcelos S, Andraus W, D'Albuquerque LAC, Damiani L, Costa AC, Pereira RMR, Heymsfield SB, Sala P, Torrinhas RSM, Waitzberg DL. Prognostic value of energy expenditure and respiratory quotient measuring in patients with liver cirrhosis. *Clin Nutr* 2019; **38**: 1899-1904 [PMID: 30007480 DOI: 10.1016/j.clnu.2018.07.001]

14 **Gottschall CB**, Alvares-da-Silva MR, Camargo AC, Burtett RM, da Silveira TR. [Nutritional assessment in patients with cirrhosis: the use of indirect calorimetry]. *Arq Gastroenterol* 2004; **41**: 220-224 [PMID: 15806264 DOI: 10.1590/s0004-28032004000400004]

15 **Marroni CA,** Miranda D, Boemeke L, Fernandes SA Phase Angle Bioelectrical Impedance Analysis (BIA) as a biomarker tool for liver disease. In: Patel V, Preedy V. Biomarkers in liver disease. Biomarkers in Disease: Methods, Discoveries and Applications. Dordrecht: Springer, 2017: 735-751

16 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]

17 **Food and Agriculture Organization (FAO).** World Health Organization (WHO). Energy and protein requiriments. (WHO Technical Report Series 724) 1985 [cited 2019 Oct 12]. Available from: <http://www.fao.org/3/aa040e/aa040e00.htm>

18 **WEIR JB**. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol* 1949; **109**: 1-9 [PMID: 15394301 DOI: 10.1113/jphysiol.1949.sp004363]

19 **TBW Importadora.** Calorímetro MetaCheck. Available from: <https://www.tbw.com.br/metacheck>

20 **TBW Importadora.** Bioimpedância Biodynamics 450. Available from: <https://www.tbw.com.br/bioimpedancia-450>

21 **Harris JA**, Benedict FG. A Biometric Study of Human Basal Metabolism. *Proc Natl Acad Sci* 1918; **4**: 370-373 [PMID: 16576330 DOI: 10.1073/pnas.4.12.370]

22 **Schofield WN**. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985; **39 Suppl 1**: 5-41 [PMID: 4044297]

23 **World Health Organization (WHO).** Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation (WHO Technical Report Series 894) 2000 [cited 2019 Oct 14]. Available from: <https://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/>

24 **Mifflin MD**, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. *Am J Clin Nutr* 1990; **51**: 241-247 [PMID: 2305711 DOI: 10.1093/ajcn/51.2.241]

25 **Institute of Medicine (IOM).** Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. 2005. [cited 2019 Oct 12]. Available from: <https://www.nal.usda.gov/sites/default/files/fnic_uploads/energy_full_report.pdf>

26 **Cunningham JJ**. A reanalysis of the factors influencing basal metabolic rate in normal adults. *Am J Clin Nutr* 1980; **33**: 2372-2374 [PMID: 7435418 DOI: 10.1093/ajcn/33.11.2372]

27 **McArdle W,** Katch FI, Katch VL. Exercise physiology energy, nutrition, and human performance. 4th ed. Baltimore: Williams and Wilkins, 1996 [DOI: 10.1016/S0031-9406(10)61985-2]

28 **Teramoto A**, Yamanaka-Okumura H, Urano E, Nakamura-Kutsuzawa T, Sugihara K, Katayama T, Miyake H, Imura S, Utsunomiya T, Shimada M, Takeda E. Comparison of measured and predicted energy expenditure in patients with liver cirrhosis. *Asia Pac J Clin Nutr* 2014; **23**: 197-204 [PMID: 24901087 DOI: 10.6133/apjcn.2014.23.2.12]

29 **Gomes MA**, Priolli DG, Tralhão JG, Botelho MF. Hepatocellular carcinoma: epidemiology, biology, diagnosis, and therapies. *Rev Assoc Med Bras (1992)* 2013; **59**: 514-524 [PMID: 24041910 DOI: 10.1016/j.ramb.2013.03.005]

30 **Silva DMD**, Henz AC, Fernandes SA, Marroni CA. Nutritional diagnosis of patients with hepatocellular carcinoma: what is the best method? *Nutr Hosp* 2019; **36**: 884-889 [PMID: 31192693 DOI: 10.20960/nh.02542]

31 **Fernandes SA**, de Mattos AA, Tovo CV, Marroni CA. Nutritional evaluation in cirrhosis: Emphasis on the phase angle. *World J Hepatol* 2016; **8**: 1205-1211 [PMID: 27803765 DOI: 10.4254/wjh.v8.i29.1205]

32 **Tajika M**, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, Moriwaki H. Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition* 2002; **18**: 229-234 [PMID: 11882395 DOI: 10.1016/s0899-9007(01)00754-7]

33 **Riggio O**, Angeloni S, Ciuffa L, Nicolini G, Attili AF, Albanese C, Merli M. Malnutrition is not related to alterations in energy balance in patients with stable liver cirrhosis. *Clin Nutr* 2003; **22**: 553-559 [PMID: 14613758 DOI: 10.1016/s0261-5614(03)00058-x]

34 **Meng QH**, Wang JH, Yu HW, Li J, Feng YM, Hou W, Zhang J, Zhang Q, Wang X, Wang X, Liu Y. Resting energy expenditure and substrate metabolism in Chinese patients with acute or chronic hepatitis B or liver cirrhosis. *Intern Med* 2010; **49**: 2085-2091 [PMID: 20930434 DOI: 10.2169/internalmedicine.49.3967]

35 **Eslamparast T**, Vandermeer B, Raman M, Gramlich L, Den Heyer V, Belland D, Ma M, Tandon P. Are Predictive Energy Expenditure Equations Accurate in Cirrhosis? *Nutrients* 2019; **11**: [PMID: 30720726 DOI: 10.3390/nu11020334]

36 **Schlein KM**, Coulter SP. Best practices for determining resting energy expenditure in critically ill adults. *Nutr Clin Pract* 2014; **29**: 44-55 [PMID: 24336442 DOI: 10.1177/0884533613515002]

37 **Santos E**, Rodríguez A, Prieto C, Gil MJ, Frühbeck G, Quiroga J, Herrero JI, Salvador J. [Factors modulating food intake and energy expenditure prior to liver transplantation]. *An Sist Sanit Navar* 2016; **39**: 105-114 [PMID: 27125612 DOI: 10.4321/1137-6627/2016000100012]

38 **Knudsen AW**, Krag A, Nordgaard-Lassen I, Frandsen E, Tofteng F, Mortensen C, Becker U. Effect of paracentesis on metabolic activity in patients with advanced cirrhosis and ascites. *Scand J Gastroenterol* 2016; **51**: 601-609 [PMID: 26673350 DOI: 10.3109/00365521.2015.1124282]

39 **Fernandes SA**, Bassani L, Nunes FF, Aydos ME, Alves AV, Marroni CA. Nutritional assessment in patients with cirrhosis. *Arq Gastroenterol* 2012; **49**: 19-27 [PMID: 22481682 DOI: 10.1590/s0004-28032012000100005]

40 **Nunes FF,** Fernandes A, Bertolini CM, Rabito EI, Gottschall CBA. Nutritional evaluation of cirrhotic patients: comparison between several methods. *Arq Gastroenterol* 2016; **53:** 4 [DOI: 10.1590/S0004-28032016000400008]

41 **Aydos MED,** Fernandes SA, Nunes FF, Bassani L, Leonhardt LR, Harter DL, Pivato B, Miranda D, Marroni CA. One-year follow-up of the nutritional status of patients undergoing liver transplantation. Nutrición hospitalaria: Organo oficial de la Sociedad española de nutrición parenteral y enteral 2016; **33:** 8-13. Available from: https://dialnet.unirioja.es/servlet/articulo?codigo=6202181

42 **Souza Thompson Motta R**, Alves Castanho I, Guillermo Coca Velarde L. CUTOFF POINT OF THE PHASE ANGLE IN PRE-RADIOTHERAPY CANCER PATIENTS. *Nutr Hosp* 2015; **32**: 2253-2260 [PMID: 26545685 DOI: 10.3305/nh.2015.32.5.9626]

43 **Sharma D**, Kannan R, Tapkire R, Nath S. Evaluation of Nutritional Status of Cancer Patients during Treatment by Patient-Generated Subjective Global Assessment: a Hospital-Based Study. *Asian Pac J Cancer Prev* 2015; **16**: 8173-8176 [PMID: 26745056 DOI: 10.7314/apjcp.2015.16.18.8173]

44 **Pinto AS**, Chedid MF, Guerra LT, Álvares-DA-Silva MR, Araújo A, Guimarães LS, Leipnitz I, Chedid AD, Kruel CR, Grezzana-Filho TJ, Kruel CD. Estimating basal energy expenditure in liver transplant recipients: the value of the harris-benedict equation. *Arq Bras Cir Dig* 2016; **29**: 185-188 [PMID: 27759783 DOI: 10.1590/0102-6720201600030013]

45 **Segadilha NLAL**, Rocha EEM, Tanaka LMS, Gomes KLP, Espinoza REA, Peres WAF. Energy Expenditure in Critically Ill Elderly Patients: Indirect Calorimetry vs Predictive Equations. *JPEN J Parenter Enteral Nutr* 2017; **41**: 776-784 [PMID: 26826262 DOI: 10.1177/0148607115625609]

46 **Anderegg BA**, Worrall C, Barbour E, Simpson KN, Delegge M. Comparison of resting energy expenditure prediction methods with measured resting energy expenditure in obese, hospitalized adults. *JPEN J Parenter Enteral Nutr* 2009; **33**: 168-175 [PMID: 19251910 DOI: 10.1177/0148607108327192]

47 **Plauth M**, Merli M, Kondrup J, Weimann A, Ferenci P, Müller MJ; ESPEN Consensus Group. ESPEN guidelines for nutrition in liver disease and transplantation. *Clin Nutr* 1997; **16**: 43-55 [PMID: 16844569 DOI: 10.1016/s0261-5614(97)80022-2]

48 **Ribeiro HS**, Coury NC, de Vasconcelos Generoso S, Lima AS, Correia MITD. Energy Balance and Nutrition Status: A Prospective Assessment of Patients Undergoing Liver Transplantation. *Nutr Clin Pract* 2020; **35**: 126-132 [PMID: 31190346 DOI: 10.1002/ncp.10323]

49 **World Health Organization (WHO).** International Agency for Research on Cancer (IARC). GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. Available from: https://publications.iarc.fr/Databases/Iarc-Cancerbases/GLOBOCAN-2012-Estimated-Cancer-Incidence-Mortality-And-Prevalence-Worldwide-In-2012-V1.0-2012

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**Table 1** **Predictive formulas for calculating energy expenditure[8]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Age range** | **Gender** | **Equation** |
| Harris and Benedict[21] | Non-specifed | Male | 66.437 + [5.0033 × H (cm)] + [13.7516 × W (kg)] – [6.755 × Y (yr)] |
| Non-specifed | Female | 655.0955 + [1.8496 × H (cm)] + [9.5634 × W (kg)] – [4.6756 × Y (yr)] |
| Schofield[22] in kcal/day | 10-17 | Male | [0.074 × W (kg) + 2.754] × 239 |
| Female | [0.056 × W (kg) + 2.898] × 239 |
| 18-29 | Male | [0.063 × W (kg) + 2.896] × 239 |
| Female | [0.062 × W (kg) + 2.036] × 239 |
| 30-59 | Male | [0.048 × W (kg) + 3.653] × 239 |
| Female | [0.034 × W (kg) + 3.538] × 239 |
| From 60 yr | Male | [0.049 × W (kg) + 2.459] × 239 |
| Female | [0.038 × W (kg) + 2.755] × 239 |
| WHO[23] in kcal/day | 10-17 | Male | 17.5 × W + 651 |
| Female | 12.2 × W + 746 |
| 18-29 | Male | 15.3 × W + 679 |
| Female | 14.7 × W + 496 |
| 30-59 | Male | 11.6 × W + 879 |
| Female | 8.7 × W + 829 |
| From 60 yr | Male | 13.5 × W + 487 |
| Female | 10.5 × W + 596 |
| Mifflin *et al*[24] in kcal/day | 19-78 | Male | 10 × W (kg) + 6.25 × H (cm) – 5 × Y (yr) + 5 |
| 19-78 | Female | 10 × W (kg) + 6.25 × H (cm) – 5 × Y(yr) – 161 |
| FAO/WHO[17] | 10-17 | Male | (16.6 × W) + [77 × H(m)] + 572 |
| Female | (7.4 × W) + [482 × H (m)] + 217 |
| 18-30 | Male | (15.4 × W) – [27 × H (m)] + 717 |
| Female | (13.3 × W) + [334 × H (m)] + 35 |
| 31-60 | Male | (11.3 × W) + [16 × H (m)] + 901 |
| Female | (8.7 × W) – [25 × H (m)] + 865 |
| From 60 yr | Male | (8.8 × W) + [1128 × H (m)] – 1071 |
| Female | (9.2 × W) + [637 × H (m)] – 302 |
| IOM[25] | Non-specifed | Male | 293 – (3.8 × age) + (401.5 × height) + (8.6 × weight) |
| Non-specifed | Female | 247 – (2.67 × age) + (456.4 × height) + (10.12 × weight) |
| Cunningham[26] | Non-specifed | Male, Female | 500 kcal + (lean mass in kg × 22) |
| McArdle *et al*[27] | Non-specifed | Male, Female | (lean mass in kg × 21.6) + 370 |

W: Weight; H: Height; Y: Years.

**Table 2** **Sample characterization - cirrhotics with and without hepatocellular carcinoma (*n* = 118)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **HCC (*n* = 33)** | **Without HCC (*n* = 85)** | **1*P* value** |
|  | **Mean ± SD** | **Mean ± SD** |  |
| Age (yr) | 62.8 ± 8.1 | 56.7 ± 9.4 | 0.001 |
| Male gender | 26 (78.8%) | 37 (43.5%) | 0.0012 |
| Weight (kg) | 73.9 ± 12.9 | 78.2 ± 17.2 | 0.206 |
| Height (m) | 1.65 ± 0.09 | 1.65 ± 0.09 | 0.810 |
| BMI (kg/m2) | 27.0 ± 4.0 | 28.7 ± 5.7 | 0.115 |
| Lean mass (kg) | 51.3 ± 10.6 | 53.4 ± 12.3 | 0.396 |
| Child Pugh |  |  | 0.2242 |
| A | 13 (39.4%) | 32 (37.6%) |  |
| B | 17 (51.5%) | 34 (40.0%) |  |
| C | 3 (9.1%) | 19 (22.4%) |  |
| BCLC |  |  | - |
| 0 | 4 (12.1%) | - |  |
| A | 12 (36.4%) | - |  |
| B | 10 (30.3%) | - |  |
| C | 4 (12.1%) | - |  |
| D | 3 (9.1%) | - |  |

1Student *t*-test for independent samples; 2Pearson's chi-square test. HCC: Hepatocellular carcinoma; SD: Standard deviation; BCLC: Barcelona Clinic Liver Cancer Group.

**Table 3 Energy expenditure at rest by indirect calorimetry in cirrhotics with and without hepatocellular carcinoma (*n* = 118)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **HCC (*n* = 33)** | **Without HCC (*n* = 85)** | **1*P* value** |
|  | **Mean ± SD** | **IC 95%** | **Mean ± SD** | **IC 95%** |  |
| Calorimetry | 1643 ± 364 | 1514–1772 | 1526 ± 277 | 1466–1586 | 0.064 |

1Student *t*-test for independent samples. HCC: Hepatocellular carcinoma; SD: Standard deviation; IC: Indirect calorimetry.

**Table 4** **Resting energy expenditure by electrical bioimpedance in cirrhotics with and without hepatocellular carcinoma, compared with indirect calorimetry (*n* = 118)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **HCC (*n* = 33)** | **Without HCC (*n* = 85)** |  |
|  | **Mean ± SD** | **IC 95%** | **Mean ± SD** | **IC 95%** | **1*P* value** |
| BIA | 1529 ± 501 | 1352–1707 | 1660 ± 385 | 1577–1743 | 0.133 |
| Calorimetry | 1643 ± 364 | 1606–1907 | 1526 ± 277 | 1356-1623 | 0.064 |
| *P* value | 0.136 |  | 0.001 |  |  |

1Student *t*-test for independent samples. HCC: Hepatocellular carcinoma; BIA: Electrical bioimpedance; SD: Standard deviation; IC: Indirect calorimetry.

**Table 5** **Resting energy expenditure calculated using predictive formulas in cirrhotics with and without hepatocellular carcinoma (*n* = 118)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **HCC (*n* = 33)** |  **Without HCC (*n* = 85)** | **1*P* value** |
|  | **Mean ± SD** | **IC 95%** | **Mean ± SD** | **IC 95%** |  |
| Harris and Benedict[20] formula | 1466 ± 224 | 1387–1546 | 2138 ± 499 | 2030-2246 | < 0.001 |
| Schofield[22] formula | 1489 ± 203 | 1417–1561 | 1539 ± 218 | 1491-1586 | 0.265 |
| WHO[23] formula | 1518 ± 208 | 1444–1592 | 1536 ± 282 | 1475-1597 | 0.744 |
| Mifflin *et al*[24] | 1433 ± 196 | 1363–1503 | 1439 ± 212 | 1393-1485 | 0.883 |
| FAO/WHO formula[17] | 1522 ± 208 | 1449–1596 | 1566 ± 223 | 1518-1614 | 0.333 |
| IOM[25] formula | 1402 ± 168 | 1342–1462 | 1544 ± 242 | 1491-1596 | 0.001 |
| Cunningham[26] formula | 1629 ± 233 | 1546–1712 | 1674 ± 271 | 1616-1733 | 0.396 |
| McArdle *et al*[27] formula, 1996 | 1478 ± 229 | 1397–1559 | 1523 ± 266 | 1466-1581 | 0.396 |

1Student *t*-test for independent samples. HCC: Hepatocellular carcinoma; SD: Standard deviation.

**Table 6** **Differences between resting energy expenditure calculated using predictive formulas in cirrhotic patients with hepatocellular carcinoma, compared with indirect calorimetry (*n* = 118)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Mean difference** | **IC 95%** | **1*P* value** |
| Calorimetry X Harris Benedict formula[21] | 177 | 59.8 a 293 | 0.004 |
| Calorimetry X Schofield formula[22] | 154 | 36.9 a 270 | 0.011 |
| Calorimetry X WHO formula[23] | 125 | 9.1 a 240 | 0.035 |
| Calorimetry X Mifflin *et al*[24] formula | 210 | 98.5 a 321 | 0.001 |
| Calorimetry X FAO/WHO formula[17] | 120 | -2.3 a 243 | 0.054 |
| Calorimetry x IOM formula[25] | 241 | 116 a 366 | < 0.001 |
| Calorimetry x Cunningham formula[26] | 14 | -101 a 129 | 0.806 |
| Calorimetry x McArdle *et al*[27] formula | 165 | 49.5 a 279 | 0.006 |

1Student *t*-test for paired samples.

**Table 7** **Differences between resting energy expenditure calculated using predictive formulas in cirrhotics without hepatocellular carcinoma, compared with indirect calorimetry (*n* = 118)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Mean difference** | **IC 95%** | **1*P* value** |
|  |
| Calorimetry X Harris Benedict formula[21] | -611 | -691 a -531 | < 0.001 |
| Calorimetry X Schofield formula[22] | -12.3 | -67.2 a 42.6 | 0.658 |
| Calorimetry X WHO formula[23] | -9.5 | -73.1 a 54.2 | 0.768 |
| Calorimetry X Mifflin-St Jeo formula[24] | 87.2 | 49.5 a 125 | < 0.001 |
| Calorimetry X FAO/WHO formula[17] | -39.8 | -93.2 a 13.6 | 0.142 |
| Calorimetry x IOM formula[25] | -17.5 | -41.5 a 6.6 | 0.153 |
| Calorimetry x Cunningham formula[26] | -148 | -172 a -123 | < 0.001 |
| Calorimetry x McArdle *et al*[27] formula | 3.2 | -20.9 a 27.3 | 0.792 |

1Student *t*-test for paired samples.