ISSN 2150-5349 (online)

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2021 January 5; 12(1): 1-31

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Pharmacology and Therapeutics

Contents

Continuous Publication Volume 12 Number 1 January 5, 2021

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

World Journal of Gastrointestinal Pharmacology and Therapeutics

Continuous Publication Volume 12 Number 1 January 5, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Dr. Tony Tham is a Consultant Gastroenterologist at Ulster Hospital, Dundonald, Belfast (Northern Ireland, United Kingdom). His publication record spans more than 80 articles and first-authorship of the "Gastrointestinal Emergencies" textbook. He has served as the Guidelines Editor for *Gut*, an International Editorial Board Member for *Gastrointestinal Endoscopy*, and Associate Editor for *Diagnostic and Therapeutic Endoscopy*. He has previously served as Chair of the British Society of Gastroenterology (BSG) Clinical Services and Standards Committee (as well as Deputy Chair and Secretary), BSG Quality Improvement lead, and Head of the School of Medicine, Northern Ireland (deanery). Currently, he is President of the Irish Society of Gastroenterology, Chair of Ireland's National Clinical Program for Gastroenterology and Hepatology, Clinical Advisory Group, and Vice Chair of the Specialist Advisory Committee for general internal medicine, Joint Royal Colleges of Physicians Training Board, United Kingdom. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pharmacology and Therapeutics* (*WJGPT*, *World J Gastrointest Pharmacol Ther*) is to provide scholars and readers from various fields of gastrointestinal pharmacology and therapeutics with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGPT mainly publishes articles reporting research results obtained in the field of gastrointestinal pharmacology and therapeutics and covering a wide range of topics including acid-related disorders, functional gastrointestinal disorders, fundamentals of gastrointestinal pharmacology, *etc.*

INDEXING/ABSTRACTING

The *WJGPT* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN
ISSN 2150-5349 (online)

LAUNCH DATE
May 6, 2010

FREQUENCY
Continuous Publication

EDITORS-IN-CHIEF
Emanuele Sinagra, Sin-Hyeog Im

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2150-5349/editorialboard.htm

PUBLICATION DATE
January 5, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Pharmacol Ther 2021 January 5; 12(1): 1-12

DOI: 10.4292/wjgpt.v12.i1.1

ISSN 2150-5349 (online)

ORIGINAL ARTICLE

Case Control Study

Resting energy expenditure in cirrhotic patients with and without hepatocellular carcinoma

Ana Cristhina Henz, Claudio Augusto Marroni, Daniella Miranda da Silva, Joise Munari Teixeira, Thiago Thomé Silveira, Shaiane Ferreira, Andresa Thomé Silveira, Natalia Perin Schmidt, Jessica Taina Stein, Roberta Goulart Rayn, Sabrina Alves Fernandes

ORCID number: Ana Cristhina Henz 0000-0002-4260-2881; Claudio Augusto Marroni 0000-0002-1718-6548; Daniella Miranda da Silva 0000-0001-9489-704; Joise Munari Teixeira 0000-0002-9267-5309; Thiago Thomé Silveira 0000-0001-7535-694X; Shaiane Ferreira 0000-0002-8131-6773; Andresa Thomé Silveira 0000-0002-9347-7531; Natalia Perin Schmidt 0000-0002-1084-7147; Jessica Taina Stein 0000-0001-9151-4303; Roberta Goulart Rayn 0000-0002-8492-8804; Sabrina Alves Fernandes 0000-0001-8504-603X.

Author contributions: Henz AC participated in the creation, elaboration, data collection, tabulation, statistical analysis and writing of the scientific article, Da Silva DM contributed to the creation, elaboration, tabulation, data collection and writing of the scientific article, Teixeira JM assisted in data collection, Silveira TT assisted in data collection, Ferreira S assisted in data collection, Silveira AT assisted in data collection, Schmidt NP assisted in data collection, Stein JT assisted in data collection, Rayn RG assisted in data collection, Marroni CA and Fernandes SA contributed to the creation, elaboration, data collection, tabulation, statistical analysis and

Ana Cristhina Henz, Sabrina Alves Fernandes, Department of Nutrition, Centro Universitário Metodista (IPA), Porto Alegre 90420-060, RS, Brazil

Claudio Augusto Marroni, Department of Gastroenterology and Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre 91760470, RS, Brazil

Daniella Miranda da Silva, Postgraduate Program in Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre 90050170, RS, Brazil

Joise Munari Teixeira, Postgraduate Program in Medicine, Hepatology, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre 90050170, RS, Brazil

Thiago Thomé Silveira, Shaiane Ferreira, Andresa Thomé Silveira, Natalia Perin Schmidt, Jessica Taina Stein, Roberta Goulart Rayn, Hepatology Graduate Program, Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre 90050170, RS, Brazil

Corresponding author: Sabrina Alves Fernandes, PhD, Professor, Department of Nutrition, Centro Universitário Metodista (IPA), Porto Alegre 90420-060, RS, Brazil. sabrinaafernandes@gmail.com

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

writing and revision of the scientific article.

Institutional review board statement: This project was approved by the Research Ethics Committee of Irmandade Santa Casa de Misericórdia de Porto Alegre (number 2.387.800).

Informed consent statement: Patients who agreed to participate in the study signed an informed consent form.

Conflict-of-interest statement: All authors declare that there are no conflicts of interest related to this article.

Data sharing statement: No additional data are available for sharing.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement checklist of items.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D, D

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

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.

Citation: Henz AC, Marroni CA, Silva DMD, Teixeira JM, Silveira TT, Ferreira S, Silveira AT, Schmidt NP, Stein JT, Rayn RG, Fernandes SA. Resting energy expenditure in cirrhotic patients with and without hepatocellular carcinoma. *World J Gastrointest Pharmacol Ther* 2021; 12(1): 1-12
URL: https://www.wjgnet.com/2150-5349/full/v12/i1/1.htm
DOI: https://dx.doi.org/10.4292/wjgpt.v12.i1.1

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-

Grade E (Poor): 0

Received: June 30, 2020
Peer-review started: June 30, 2020
First decision: September 12, 2020
Revised: September 26, 2020
Accepted: November 12, 2020
Article in press: November 12, 2020
Published online: January 5, 2021

P-Reviewer: Hu J, Mousa N
S-Editor: Zhang L
L-Editor: Webster JR
P-Editor: Wu YXJ

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 O^2 (VO^2), CO^2 production (VCO^2) and urinary urea nitrogen, using the formula REE = {[3.9 (VO2)] + [1.1 (VCO^2)]}, 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.

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.

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/m^2 (± 4.0) similar to that of the control group, and in cirrhotics without HCC, BMI was 28.7 kg/m^2 (± 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

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%)	0.001[2]
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/m^2)	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			0.224[2]
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%)	-	

[1]Student *t*-test for independent samples; [2]Pearson'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

[1]Student *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		

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

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

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

[1]Student *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

[1]Student *t*-test for paired samples.

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.

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

[1]Student *t*-test for paired samples.

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 [DOI: 10.1007/978-94-007-7675-3_43]
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 [PMID: 27706455 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 [DOI: 10.20960/nh.8]

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

World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Pharmacol Ther 2021 January 5; 12(1): 13-20

DOI: 10.4292/wjgpt.v12.i1.13

ISSN 2150-5349 (online)

ORIGINAL ARTICLE

Case Control Study

Increased colon transit time and faecal load in irritable bowel syndrome

Dennis Raahave, Andreas K Jensen

ORCID number: Dennis Raahave 0000-0003-3845-9047; Andreas K Jensen 0000-0002-8233-9176.

Author contributions: Raahave D and Jensen AK designed and performed the study and wrote and approved the manuscript.

Institutional review board statement: The study was reviewed and approved by the Scientific Committee, Department of Gastroenterology and Surgery, Copenhagen University North Sealand Hospital Institutional Review Board.

Informed consent statement: All patients and control persons provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Dennis Raahave, Department of Gastroenterology and Surgery, Copenhagen University North Sealand Hospital, Hilleroed 3400, Denmark

Andreas K Jensen, Faculty of Health Sciences, Section of Biostatistics, University of Copenhagen, Hilleroed 3400, Denmark

Corresponding author: Dennis Raahave, DSc, MD, PhD, Consultant Physician-Scientist, Senior Researcher, Department of Gastroenterology and Surgery, Copenhagen University North Sealand Hospital, Dyrehavevej 29, Hilleroed 3400, Denmark. dr.dr@dadlnet.dk

Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a bowel disorder involving abdominal pain or discomfort along with irregularity of stool form and passage frequency. The pathophysiology is poorly understood and seems to be multifactorial. Investigations of possible causes of IBS have included only a few colonic transit studies and no simultaneous determination of the colonic faecal content.

AIM

To compare colon transit time and faecal load between IBS-patients and healthy control subjects.

METHODS

The study included 140 patients with IBS, with a mean age of 50.0 years. The control group comprised 44 healthy persons with a mean age of 43.4 years, who were selected at random from the National Civil Register. Both the patient group and the control group underwent a marker study to measure colon transit time (CTT) and to calculate a faecal loading score. The patient group underwent treatment with a combined prokinetic regime, after which their CTT and faecal loading were reassessed. Analyses were performed to compare measurements between the control group and the patient group before and after treatment.

RESULTS

Compared to healthy controls, IBS-patients exhibited a significantly prolonged mean CTT (45.48 h *vs* 24.75 h, $P = 0.0002$) and significantly greater mean faecal loading scores in all colonic segments ($P < 0.001$). Among IBS patients, we found no significant differences between the 48 h and 96 h radiographs. Among patients exhibiting increased CTT and faecal loading, approximately half exhibited a

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Denmark

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 20, 2020
Peer-review started: October 20, 2020
First decision: October 27, 2020
Revised: November 26, 2020
Accepted: December 4, 2020
Article in press: December 4, 2020
Published online: January 5, 2021

P-Reviewer: Bouchoucha M
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Wu YXJ

palpable mass in the right iliac fossa. After intervention with a prokinetic treatment, the mean CTT among IBS patients was reduced from 45.48 h to 34.50 h (P = 0.091), with the post-treatment CTT not significantly differing from the CTT among control subjects (P = 0.095). The faecal loading score among IBS patients did not significantly differ before and after treatment (P = 0.442). The post-treatment faecal loading score in IBS patients remained significantly higher compared to that in controls (5.3 *vs* 4.3, P = 0.014). After treatment, half of the IBS-patients were relieved of bloating, while the majority no longer experienced abdominal pain and achieved a daily consistent stool.

CONCLUSION
IBS-patients exhibited prolonged CTT and heavier faecal loading. These assessments may aid in diagnosis. Faecal retention may contribute to IBS symptoms, which can be treated using a prokinetic regime.

Key Words: Irritable bowel syndrome; Functional bowel disease; Faecal retention; Colon transit time; Faecal load

Core Tip: Patients with irritable bowel syndrome (IBS) exhibit a significant prolonged colon transit time (CTT) and greater faecal loading compared to healthy people. This finding adds to our understanding of IBS since faecal retention may lead to major symptoms like abdominal bloating and pain and defaecation disturbances. The targeted therapy was a prokinetic regime. All the more, CTT/faecal load may serve as a diagnostic procedure.

Citation: Raahave D, Jensen AK. Increased colon transit time and faecal load in irritable bowel syndrome. *World J Gastrointest Pharmacol Ther* 2021; 12(1): 13-20
URL: https://www.wjgnet.com/2150-5349/full/v12/i1/13.htm
DOI: https://dx.doi.org/10.4292/wjgpt.v12.i1.13

INTRODUCTION

Irritable bowel syndrome (IBS) is a bowel disorder involving abdominal pain or discomfort along with irregularity of stool form and passage frequency[1]. Its prevalence ranges from 9%-23% of the world population[2]. IBS considerably affects quality of life and imposes a profound burden on patients, physicians, and the health-care system[3,4]. The pathophysiology is poorly understood and seems to be multifactorial. Investigations for possible causes of IBS have included only a few colonic transit studies[5,6], and none have included a simultaneous determination of the colonic faecal content. Therefore, in the present study we aimed to measure colon transit time and faecal load in patients with IBS and to compare these measures with those of a healthy control group.

MATERIALS AND METHODS

This study included 140 patients diagnosed with IBS based on recurrent abdominal pain and abdominal discomfort during the last 3 mo, which was associated with two or more of the following: Improvement with defecation, change in frequency of stool, and change in form (appearance) of stool[7]. The patients were recruited from a database of 281 patients who were referred for abdominal and ano-rectal symptoms[8]. A control group was recruited from a random selection of 372 people over 18 years of age, from the National Civil Register. Screening excluded individuals with gastrointestinal symptoms who took laxatives or strong analgesics and who had previous abdominal surgery. A total of 44 people fulfilled these criteria and were included in the control group. This study was approved by a local ethical and research

committee and was conducted in accordance with the Declaration of Helsinki.

Included patients underwent a physical examination with special attention to abdominal signs, as well as a colonic marker study. The patients were on their own diet, and each patient swallowed a capsule containing 24 radiopaque markers (Sitzmark, Konsyl, Pharmaceutical Inc., Fort Worth, TX, United States), and then abdominal X-rays were taken after 48 h and 96 h[9]. Abdominal X-rays were divided into three segments, in a reverse Y-design, formed by the vertical column and two imaginary lines extending from the fifth lumbar vertebra to the right and left pelvic brim, pointing towards the femoral head, which was a modification from earlier studies[10,11]. The three segments include the right, transverse, and left colon and the rectum (Figure 1). The number of markers was counted in each segment and colonic transit time (CTT) was calculated using the following equation: CTT (in hours) = (48/n) × (n48 + n96), where n48 and n96 are the total number of markers observed at 48 h and 96 h after ingestion of n = 24 markers[12]. The control subjects also ingested 24 markers at the same time for 6 d, followed by an abdominal X-ray on day 7. In the control subjects, the number of markers visible on X-ray was then equal to the CTT in hours[12] (Figure 2).

The estimated faecal load in the colon from each segment on the X-ray was scored from 0-3, where 0 indicated no faeces visible, 1 indicated slight, 2 moderate, and 3 severe faecal loading. We then obtained a segmental score of 0-3 and a total score of 0-9 for each radiograph. Similarly, faecal loading scores were estimated for the controls. The presently used score is a modification of the Leech-score, which details faecal loading from 0-5[13]. The X-ray images were examined by observers who were unaware of the patients' clinical course.

Intervention

The present study was designed to investigate the pathogenic mechanisms of IBS rather than a therapeutic trial. Thus, the patients received an established bowel stimulatory treatment, which included a low fat and fibre-rich diet and dietician-guided meal planning, in accordance with guidelines of the Danish Nutritional Council. The diet was supplemented with 10-20 g of ispaghula husk per day, and the prokinetic drug, domperidone, 10 mg × 3 a day. Patients were also encouraged to perform 30 min of physical activity on a daily basis. This treatment continued until patients reported relief of symptoms. At this time, CTT and faecal loading were reassessed.

Statistical analysis

The data were entered into a database, and analyses were performed using R 4.0.1 (R Core Team). Patients' characteristics were expressed using frequency, percentage, mean, range, and standard deviation (SD). Differences (*e.g.*, between the sexes) were calculated using a t-test and a permutations test for independence. The permutation test was also used to calculate differences between CTT values and between faecal loading scores. This test was selected because the variables did not show a normal distribution. Finally, we investigated possible associations of CTT and faecal load with specific symptoms and physical signs. A P of < 0.05 was considered to indicate statistical significance.

RESULTS

Among 140 patients, the mean age was 50.0 years (range 17.0-81.2 years), and 118 patients were female and 22 were male. Mean age did not significantly differ between sexes, 49.6 years *vs* 52.3 years, P = 0.448. The control group included 44 randomly selected healthy persons with mean age of 43.4 years (range 21.0-67.0 years) and included equal numbers of males and females.

The marker study revealed a mean CTT of 45.48 h among the 140 patients, compared to 24.75 h in the 44 controls, (P = 0.0002). CTT did not significantly differ between male and female patients (41.22 h *vs* 38.63 h, P = 0.741) or between male and female controls (19.73 h *vs* 29.77 h, P = 0.111). Patients and controls exhibited significant differences in mean faecal loading scores in all colonic segments at 48 h (right: 2.25 *vs* 1.80, left: 1.95 *vs* 1.25, distal: 1.95 *vs* 1.27; all $P < 0.001$) and at 96 h (right:2.41 *vs* 1.80, left: 2.05 *vs* 1.25, distal: 2.05 *vs* 1.27; all $P < 0.001$). Mean loading scores did not significantly differ between the 48 h and 96 h radiographs. Total mean faecal loading scores significantly differed between women and men among patients (5.77 *vs* 6.40, P = 0.025) but not among controls (4.55 *vs* 4.09, P = 0.179).

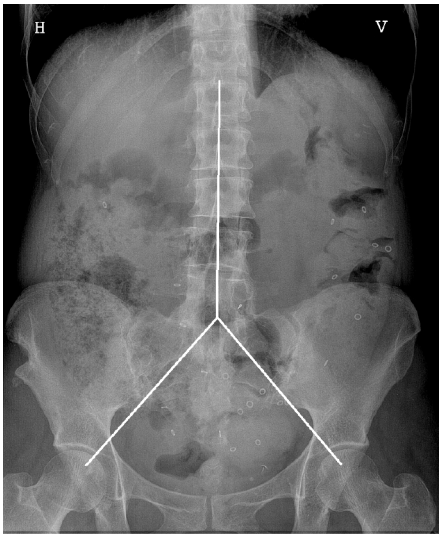

Figure 1 Colon transit study in an irritable bowel syndrome patient. Patient ingested 24 markers, and an X-ray was acquired at 48 h. From the X-ray, we counted the number of markers in each segment: 2 + 8 + 10 = 20; faecal load score: 2 + 2 + 1 = 5 (see text).

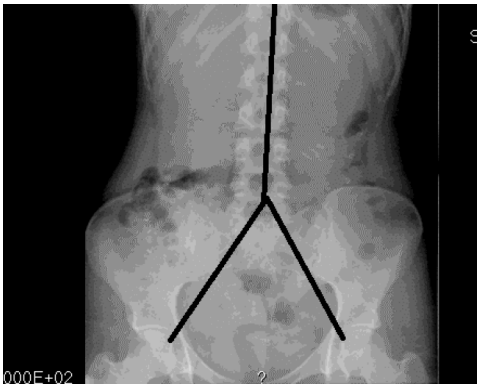

Figure 2 Colon transit study in a healthy control. Subjects ingested the 24 markers for 6 d, and an X-ray was acquired on day 7. From the X-ray we counted the number of markers in each segment: 11 + 6 + 1 = 18; faecal load score: 2 + 1 + 1 = 4 (see text).

We used linear regression model to examine associations between markers and faecal load. Data from patients´ radiographs at 48 h and 96 h revealed significant associations between markers and faecal load ($P < 0.001$). These parameters showed the same relationship patterns among controls.

The mean intervention treatment period was 690 d. The mean CTT among patients was reduced from 45.48 h pre-intervention to 34.50 h post-intervention ($P = 0.091$). The mean CTT did not significantly differ between treated patients and healthy controls ($P = 0.095$). On the other hand, we found no significant difference between pre-treatment and post-treatment values of total faecal loading score 48 h ($P = 0.442$) or at 96 h ($P = 0.127$). Compared to healthy controls, post-treatment patients showed significantly heavier total faecal loading at both 48 h (5.3 *vs* 4.3, $P = 0.014$) and 96 h.

Of the 140 patients, 58 (41.4%) exhibited a palpable faecal mass in the right fossa. Among the 57 patients with an elevated CTT of > 24.75 h (mean among healthy controls), 28 patients (49.1%) had a palpable mass. Similarly, of the 102 patients with a 48 h faecal loading score of > 1.80 (mean among healthy controls), 47 (46.1%) exhibited a palpable mass. Additionally, among 56 patients with an increase in CTT of > 24.75 h, 37 (66.1%) exhibited meteorism ($P < 0.001$).

After the intervention, 43.9% of the patients were relieved from bloating ($P = 0.1083$), and 60.9% of patients no longer experienced abdominal pain ($P = 0.0193$). With regards to defaecation after the intervention, 88.6% of patients achieved normal daily defaecation ($P < 0.001$), and 74.3% had a formed stool ($P < 0.001$).

DISCUSSION

To our knowledge, our present study was the first to report the CTT and faecal load in IBS-patients. Our results showed that IBS patients had a prolonged CTT and heavier faecal load in all parts of the colon compared to healthy controls. Prior measurements of the degree of faecal loading have been exclusively described in children, and several systems have been developed to score both the amount of faeces and its localization in different colon segments[14,15]. The Leech-score is a reproducible tool for assessing faecal loading, with high intra-observer and interobserver agreement[13,16-18]. The plain abdominal radiograph has seldom been used in adults[18,19].

In contrast, CTT is widely used as a reproducible method[9]. In particular, CTT is utilized to assess for the presence of slow transit constipation. In our present study of IBS-patients, we utilized a single ingestion of markers to ensure better compliance, and the markers were counted on radiographs acquired at 48 h and 96 h after ingestion. We counted the localized markers in the right, left, and distal parts of the colon, including the rectum. This method was used regardless of bowel outlines that may suggest some other placement of a part of the colon. In the control subjects, we utilized multiple marker ingestion at the same time for 6 consecutive days followed by an abdominal X-ray on day 7, to circumvent the difficulty and unnecessary radiation exposure involved in obtaining two radiographs. With this technique, we measured the mean value of the mean transit times of different boluses of ingested markers, and the numbers of markers visible on the radiograph was equal to the segmental total transit time in hours[12]. This method is analogous to a bolus ingestion of markers visible on successive daily abdominal X-rays, and the two techniques were significantly correlated[9].

CTT has seldom been measured in IBS patients. After eliminating many patients with IBS constipation, Bouchoucha *et al*[20] found that CTT values in IBS patients significantly differed between male patients (25.7 h; n = 194) and female patients (31.1 h; n = 558). Other reports have also shown sex-based differences in CTT among both IBS-patients and control subjects[21]. However, in our study CTT of patients and controls was not associated with gender. Among healthy adults, CTT reportedly varies between 24.5 h and 45.6 h[20,22-24], and thus it is rather difficult to define a normal CTT. Variations in CTT can be attributed to the population investigated, dietary and fluid intake, physical activity, and study methodology. Notably, the CTT measurements obtained in sitz- or plastic marker studies of patients and controls have decreased over many years. Thus, our present CTT measurements for both IBS-patients and controls are at the lower end compared to prior studies.

Radiopaque markers are not absorbed, do not alter gut metabolism, and have the same specific gravity as gut content and can thus be assumed to travel at the same rate as faeces. Markers are proven to be significantly associated with faecal load. Despite this, we observed great variation. Thus, patients with a heavy load may have few markers, and patients with a high load may have many markers. Additionally, the faecal load determined at 96 h was the same as at 48 h, indicating a stationary condition. A significant difference in faecal load was found between female and male IBS-patients, which was not the case for controls.

The pathophysiology of IBS is poorly understood and appears to be multifactorial, involving the combined impact of food intake, physical activity, mental status, previous infections, and genetics[25]. Recent years have brought emerging insights into the nervous system, and nervous system dysfunction may play a role in IBS[26]. Our increasing understanding of the gut microbiome has also highlighted its potential role in IBS symptoms[27]. In this context, faeces in the colon, and thereby the faecal load, may be viewed as the end result of all of these factors. Here, we found that faecal load was heavier in IBS patients than in healthy persons, and thus appears to be important in IBS. All the more, a palpable faecal mass in the right iliac fossa was found in many patients. The retention was observed irrespective of defaecation patterns (*i.e.*, diarrhoea or constipation) and represents a hidden constipation.

Nearly half of the IBS patients in our study exhibited a palpable faecal mass in the right fossa, which was associated with both increased CTT and heavier faecal load. Moreover, a high proportion of IBS patients with an increased CTT suffered from meteorism. The endogenous source of intestinal gas is the fermentation processes of yeast and bacteria, which produces hydrogen, carbon dioxide, methane, butyric acid, and odoriferous sulphur compounds[28]. In particular, colonic hydrogen production is greater in patients with IBS than controls[29]. Thus, patients' symptoms of bloating and abdominal pain may be caused by gas distending the colonic wall. This is in agreement with a study showing greater abdominal distension in IBS patients with delayed transit than in those with normal transit[30]. Our present results are consistent

with that finding.

The simultaneous determination of CTT and faecal loading may serve as a diagnostic tool for IBS, rather than diagnosing this condition based on a constellation of symptoms alone.

The present study was not a therapeutic trial but rather an investigative study of the mechanisms of IBS. Various IBS treatment concepts have been suggested[31]. Our patients exhibited faecal retention, and the administered treatment was targeted to relieve faecal retention with a dietary and prokinetic regime, including physical activity. Domperidone blocks the inhibitory effect of dopamine in the proximal colon in dogs[32] and thereby facilitates movements. In a placebo-controlled study, domperidone resulted in significantly reduced abdominal pain, flatulence, and abnormal bowel habits[33]. After the intervention, the patients exhibited reduced CTT values that were very close to the CTT values of healthy controls. However, the patients did not exhibit a corresponding reduction of faecal loading, which remained heavier than in the controls. These findings are in good agreement with the fact that only half of our patients experienced relief from bloating after the intervention. Fortunately, the majority of the patients no longer experienced abdominal pain and achieved daily and formed defaecation. It is possible that a treatment including prucalopride may constitute a more effective prokinetic regime for accelerating transit[34].

CONCLUSION

Our present results showed a significantly prolonged CTT and significantly heavier faecal loading in IBS-patients compared to healthy controls. This suggests that faecal retention may contribute to the symptoms in IBS, which could thus be relieved by treatment with a prokinetic regime. Our findings also indicate that the simultaneous determination of CTT and faecal loading may serve as a diagnostic procedure for IBS.

ARTICLE HIGHLIGHTS

Research background

Patients with irritable bowel syndrome (IBS) experience abdominal pain and irregularities of stool form and passage frequency. The prevalence ranges from 9%-23%, and IBS imposes profound burdens on patients, physicians, and the healthcare system. The pathophysiology is poorly understood.

Research motivation

Faecal retention is suspected to play a role in IBS symptoms. However, few colonic transit studies exist, and none have included simultaneous determination of colonic faecal content. Such information would likely have implications for choice of therapeutic decisions.

Research objectives

The present case-control study was performed to compare colonic transit time (CTT) and faecal load between IBS-patients and healthy controls. We further aimed to compare these parameters in patients before and after treatment with a prokinetic regime.

Research methods

CTT and faecal load were measured by performing a marker study. IBS-patients swallowed a capsule containing 24 radiopaque markers, and abdominal X-rays were taken after 48 h and 96 h. Control subjects ingested 24 markers at the same time for 6 d, followed by an X-ray on day 7. For both groups, CTT was calculated in hours, and a faecal load score was estimated.

Research results

Compared to 44 healthy controls, 140 IBS-patients exhibited a significantly prolonged mean CTT (45.48 h *vs* 24.75 h, $P < 0.001$) and a significantly greater mean faecal loading scores in each colonic segment ($P < 0.001$). After the intervention, the mean CTT in IBS-patients was reduced from 45.48 h to 34.50 h ($P > 0.05$), with the post-

treatment CTT not significantly differing from the CTT among control subjects (P > 0.05). Moreover, following treatment, half of the patients were relieved from bloating, and the majority no longer experienced abdominal pain and had achieved a consistent daily stool.

Research conclusions

IBS-patients were examined by using a new method comprising the simultaneous determination of CTT and faecal load. Our results showed a significantly prolonged CTT and significantly heavier faecal loading in IBS-patients compared to healthy control persons. These findings may contribute to the IBS symptoms, which were relieved to some degree following treatment with a prokinetic regime. Studies are needed to examine further the association between faecal retention and symptoms.

Research perspectives

Simultaneous measurement of CTT and faecal load may serve as a diagnostic tool for investigating IBS-patients and could also be extended for use in patients with other bowel disorders. This method may also be useful for monitoring the effects of different treatment regimens.

REFERENCES

1 **Thompson WG**, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; **45** Suppl 2: II43-II47 [PMID: 10457044 DOI: 10.1136/gut.45.2008.ii43]

2 **Oświęcimska J**, Szymlak A, Roczniak W, Girczys-Połedniok K, Kwiecień J. New insights into the pathogenesis and treatment of irritable bowel syndrome. *Adv Med Sci* 2017; **62**: 17-30 [PMID: 28135659 DOI: 10.1016/j.advms.2016.11.001]

3 **American College of Gastroenterology Task Force on Irritable Bowel Syndrome**, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; **104** Suppl 1: S1-35 [PMID: 19521341 DOI: 10.1038/ajg.2008.122]

4 **Enck P**, Aziz Q, Barbara G, Farmer AD, Fukudo S, Mayer EA, Niesler B, Quigley EM, Rajilić-Stojanović M, Schemann M, Schwille-Kiuntke J, Simren M, Zipfel S, Spiller RC. Irritable bowel syndrome. *Nat Rev Dis Primers* 2016; **2**: 16014 [PMID: 27159638 DOI: 10.1038/nrdp.2016.14]

5 **Ansari R**, Sohrabi S, Ghanaie O, Amjadi H, Merat S, Vahedi H, Khatibian M. Comparison of colonic transit time between patients with constipation-predominant irritable bowel syndrome and functional constipation. *Indian J Gastroenterol* 2010; **29**: 66-68 [PMID: 20443103 DOI: 10.1007/s12664-010-0015-2]

6 **Sadik R**, Björnsson E, Simrén M. The relationship between symptoms, body mass index, gastrointestinal transit and stool frequency in patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol* 2010; **22**: 102-108 [PMID: 19701093 DOI: 10.1097/MEG.0b013e32832ffd9b]

7 **Longstreth GF**, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]

8 **Raahave D**. Faecal retention: A common cause in functional bowel disorders, appendicitis and haemorrhoids – with medical and surgical therapy (PhD thesis). Faculty of health and medical sciences: University of Copenhagen, 2014

9 **Bouchoucha M**, Devroede G, Arhan P, Strom B, Weber J, Cugnenc PH, Denis P, Barbier JP. What is the meaning of colorectal transit time measurement? *Dis Colon Rectum* 1992; **35**: 773-782 [PMID: 1644002 DOI: 10.1007/BF02050328]

10 **Martelli H**, Devroede G, Arhan P, Duguay C, Dornic C, Faverdin C. Some parameters of large bowel motility in normal man. *Gastroenterology* 1978; **75**: 612-618 [PMID: 710830 DOI: 10.1016/S0016-5085(19)31666-X]

11 **Zaslavsky C**, da Silveira TR, Maguilnik I. Total and segmental colonic transit time with radio-opaque markers in adolescents with functional constipation. *J Pediatr Gastroenterol Nutr* 1998; **27**: 138-142 [PMID: 9702642 DOI: 10.1097/00005176-199808000-00002]

12 **Devroede G**, Bouchoucha M, Steiber W. A simplified way to assess colorectal transit time. *Tech Coloproctol* 1999; **3**: 71-73 [DOI: 10.1007/s101510050018]

13 **Leech SC**, McHugh K, Sullivan PB. Evaluation of a method of assessing faecal loading on plain abdominal radiographs in children. *Pediatr Radiol* 1999; **29**: 255-258 [PMID: 10199902 DOI: 10.1007/s002470050583]

14 **Barr RG**, Levine MD, Wilkinson RH, Mulvihill D. Chronic and occult stool retention: a clinical tool for its evaluation in school-aged children. *Clin Pediatr (Phila)* 1979; **18**: 674, 676, 677-679, passim [PMID: 498690 DOI: 10.1177/000992287901801103]

15 **Blethyn AJ**, Verrier Jones K, Newcombe R, Roberts GM, Jenkins HR. Radiological assessment of constipation. *Arch Dis Child* 1995; **73**: 532-533 [PMID: 8546512 DOI: 10.1136/adc.73.6.532]

16 **van den Bosch M**, Graafmans D, Nievelstein R, Beek E. Systematic assessment of constipation on plain abdominal radiographs in children. *Pediatr Radiol* 2006; **36**: 224-226 [PMID: 16418835 DOI: 10.1007/s00247-005-0065-2]

17 **Koh H**, Lee MJ, Kim MJ, Shin JI, Chung KS. Simple diagnostic approach to childhood fecal retention using the Leech score and Bristol stool form scale in medical practice. *J Gastroenterol Hepatol* 2010; **25**: 334-338 [PMID: 19817956 DOI: 10.1111/j.1440-1746.2009.06015.x]

18 **Park HJ**, Noh SE, Kim GD, Joo MC. Plain abdominal radiograph as an evaluation method of bowel dysfunction in patients with spinal cord injury. *Ann Rehabil Med* 2013; **37**: 547-555 [PMID: 24020036 DOI: 10.5535/arm.2013.37.4.547]

19 **Starreveld JS**, Pols MA, Van Wijk HJ, Bogaard JW, Poen H, Smout AJ. The plain abdominal radiograph in the assessment of constipation. *Z Gastroenterol* 1990; **28**: 335-338 [PMID: 2238762]

20 **Bouchoucha M**, Devroede G, Dorval E, Faye A, Arhan P, Arsac M. Different segmental transit times in patients with irritable bowel syndrome and "normal" colonic transit time: is there a correlation with symptoms? *Tech Coloproctol* 2006; **10**: 287-296 [PMID: 17115321 DOI: 10.1007/s10151-006-0295-9]

21 **Sadik R**, Abrahamsson H, Stotzer PO. Gender differences in gut transit shown with a newly developed radiological procedure. *Scand J Gastroenterol* 2003; **38**: 36-42 [PMID: 12608462 DOI: 10.1080/00365520310000410]

22 **Metcalf AM**, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. *Gastroenterology* 1987; **92**: 40-47 [PMID: 3023168 DOI: 10.1016/0016-5085(87)90837-7]

23 **Abrahamsson H**, Antov S, Bosaeus I. Gastrointestinal and colonic segmental transit time evaluated by a single abdominal x-ray in healthy subjects and constipated patients. *Scand J Gastroenterol Suppl* 1988; **152**: 72-80 [PMID: 3254616 DOI: 10.3109/00365528809095938]

24 **Chan YK**, Kwan AC, Yuen H, Yeung YW, Lai KC, Wu J, Wong GS, Leung CM, Cheung WC, Wong CK. Normal colon transit time in healthy Chinese adults in Hong Kong. *J Gastroenterol Hepatol* 2004; **19**: 1270-1275 [PMID: 15482534 DOI: 10.1111/j.1440-1746.2004.03492.x]

25 **Holtmann GJ**, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol* 2016; **1**: 133-146 [PMID: 28404070 DOI: 10.1016/S2468-1253(16)30023-1]

26 **Stasi C**, Rosselli M, Bellini M, Laffi G, Milani S. Altered neuro-endocrine-immune pathways in the irritable bowel syndrome: the top-down and the bottom-up model. *J Gastroenterol* 2012; **47**: 1177-1185 [PMID: 22766747 DOI: 10.1007/s00535-012-0627-7]

27 **Simrén M**, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S, Verdu EF, Whorwell PJ, Zoetendal EG; Rome Foundation Committee. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut* 2013; **62**: 159-176 [PMID: 22730468 DOI: 10.1136/gutjnl-2012-302167]

28 **Suarez F**, Furne J, Springfield J, Levitt M. Insights into human colonic physiology obtained from the study of flatus composition. *Am J Physiol* 1997; **272**: G1028-G1033 [PMID: 9176210 DOI: 10.1152/ajpgi.1997.272.5.G1028]

29 **King TS**, Elia M, Hunter JO. Abnormal colonic fermentation in irritable bowel syndrome. *Lancet* 1998; **352**: 1187-1189 [PMID: 9777836 DOI: 10.1016/s0140-6736(98)02146-1]

30 **Agrawal A**, Houghton LA, Reilly B, Morris J, Whorwell PJ. Bloating and distension in irritable bowel syndrome: the role of gastrointestinal transit. *Am J Gastroenterol* 2009; **104**: 1998-2004 [PMID: 19491831 DOI: 10.1038/ajg.2009.251]

31 **Wall GC**, Bryant GA, Bottenberg MM, Maki ED, Miesner AR. Irritable bowel syndrome: a concise review of current treatment concepts. *World J Gastroenterol* 2014; **20**: 8796-8806 [PMID: 25083054 DOI: 10.3748/wjg.v20.i27.8796]

32 **Bueno L**, Fargeas MJ, Fioramonti J, Honde C. Effects of dopamine and bromocriptine on colonic motility in dog. *Br J Pharmacol* 1984; **82**: 35-42 [PMID: 6145468 DOI: 10.1111/j.1476-5381.1984.tb16439.x]

33 **Milo R**. Use of the peripheral dopamine antagonist, domperidone, in the management of gastro-intestinal symptoms in patients with irritable bowel syndrome. *Curr Med Res Opin* 1980; **6**: 577-584 [PMID: 6996928 DOI: 10.1185/03007998009109491]

34 **Dai L**, Zhong LL, Ji G. Irritable bowel syndrome and functional constipation management with integrative medicine: A systematic review. *World J Clin Cases* 2019; **7**: 3486-3504 [PMID: 31750331 DOI: 10.12998/wjcc.v7.i21.3486]

World Journal of Gastrointestinal Pharmacology and Therapeutics

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Pharmacol Ther 2021 January 5; 12(1): 21-31

DOI: 10.4292/wjgpt.v12.i1.21

ISSN 2150-5349 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical features and relative factors of constipation in a cohort of Chinese patients with Parkinson's disease

Bai-Hua Sun, Tao Wang, Nian-Ying Li, Qiong Wu, Jin Qiao

ORCID number: Bai-Hua Sun 0000-0002-6514-3702; Tao Wang 0000-0002-8292-5300; Nian-Ying Li 0000-0002-9844-5336; Qiong Wu 0000-0003-1803-579X; Jin Qiao 0000-0002-7344-9461.

Author contributions: Qiao J and Wu Q designed, organized, and supervised the study and revised the manuscript; Sun BH, Wang T, and Li NY completed the data collection; Sun BH performed the statistical analysis and article writing.

Supported by Key Research and Development Program of Shaanxi Province, China, No. 2018SF-016 and No. 2020SF-153.

Institutional review board statement: The study was reviewed and approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2019LSK-037 and No. XJTU1AF2020LSK-182).

Conflict-of-interest statement: The authors has no potential conflicts of interest to disclose.

Bai-Hua Sun, Nian-Ying Li, Department ofNeurology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Bai-Hua Sun, Department of Neurology, Xi'an Third Hospital, Xi'an 710021, Shaanxi Province, China

Tao Wang, Department ofNeurology, the Shaanxi Sengong Hospital, Xi'an 710300, Shaanxi Province, China

Qiong Wu, Jin Qiao, Department of Rehabilitation Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Corresponding author: Jin Qiao, MD, Professor, Department of Rehabilitation Medicine, the First Affiliated Hospital of Xi'an Jiaotong University, No. 277 West Yanta Road, Xi'an 710061, Shaanxi Province, China. qiaojn123@163.com

Abstract

BACKGROUND

Constipation as a most common non-motor symptom of Parkinson's disease (PD), has a higher prevalence compared to the general population. The etiologies of constipation in PD are diverse. In addition to physical weakness and other factors of disease, the lifestyles and eating habits are also important factors. Therefore, the prevalence and influencing factors of constipation may vary among different populations.

AIM

To determine the prevalence of constipation and analyze relative factors in a cohort of Chinese patients with PD.

METHODS

All the patients diagnosed with PD according to the movement disorders society criteria were consecutively collected by a self-developed questionnaire. Rome III diagnostic criteria were used to assess functional constipation and Wexner score was used to estimate the severity of constipation. Non-motor symptoms (NMS) were assessed with the non-motor symptoms assessment scale (NMSS). Unified Parkinson's disease Rating Scale III (UPDRS III) was used to evaluate the severity of motor symptoms. The modified Hoehn-Yahr stage was used to evaluate the severity of PD. Cognitive function was assessed using Montreal cognitive

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: July 23, 2020
Peer-review started: July 23, 2020
First decision: September 24, 2020
Revised: September 28, 2020
Accepted: November 5, 2020
Article in press: November 5, 2020
Published online: January 5, 2021

P-Reviewer: Byeon H
S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Wu YXJ

assessment (MoCA). Depression and anxiety were rated with the Hamilton depression scale (HAMD) and the Hamilton anxiety scale (HAMA). Quality of life was assessed using the Parkinson's disease Questionnaire-39 items (PDQ-39).

RESULTS

Of 166 patients enrolled, 87 (52.41%) were accompanied with constipation, and 30 (34.48%) experienced constipation for 6.30 ± 5.06 years before motor symptoms occurred. Age, Hoehn-Yahr stage, disease duration, levodopa medication times, incidence of motor complications, the scores of UPDRS total, UPDRS III, NMSS, HAMD, HAMA, and PDQ-39 in the constipation group were higher than those in the non-constipation group ($P < 0.05$), but there was no difference in the scores of MoCA, clinical types, or medications between the two groups ($P > 0.05$). There was a higher incidence of depression in patients with constipation ($P < 0.05$), but there were no difference in the incidence of anxiety and cognitive impairment between the two groups ($P > 0.05$). As Hoehn-Yahr stages increased, the severity of constipation increased ($P < 0.05$), but not the incidence of constipation ($P > 0.05$). Pearson correlation analysis showed that constipation was moderately positively correlated with age, Hoehn-Yahr stage, and scores of NMSS, UPDRS III, UPDRS total, PDQ-39, HAMD, and HAMA ($r = 0.255$, 0.172, 0.361, 0.194, 0.221, 0.237, 0.238, and 0.207, $P < 0.05$). Logistic regression analysis showed that only NMSS score was an independent risk factor for constipation ($P < 0.001$).

CONCLUSION

Our findings confirm that constipation has a relatively high frequency in patients with PD. PD patients with constipation have a higher incidence of depression, which leads to worse quality of life.

Key Words: Parkinson's disease; Non-motor symptoms; Constipation; Clinical characteristics; Quality of life; Depression

Core Tip: This study aimed to determine the prevalence of constipation and analyze its clinical characteristics and relative risk factors in a cohort of Chinese patients with Parkinson's disease (PD). Our findings confirmed that constipation had a relatively high frequency in patients with PD. The patients with constipation had a higher incidence of depression, which led to worse quality of life.

Citation: Sun BH, Wang T, Li NY, Wu Q, Qiao J. Clinical features and relative factors of constipation in a cohort of Chinese patients with Parkinson's disease. *World J Gastrointest Pharmacol Ther* 2021; 12(1): 21-31
URL: https://www.wjgnet.com/2150-5349/full/v12/i1/21.htm
DOI: https://dx.doi.org/10.4292/wjgpt.v12.i1.21

INTRODUCTION

Parkinson's disease (PD) is a degenerative disease of the central nervous system. In addition to motor symptoms such as resting tremor, bradykinesia, myotonia, and posture imbalance, non-motor symptoms (NMS) are also very common: Olfactory dysfunction, autonomic dysfunction, mood disorders, sleep disorders, gastrointestinal symptoms, cognitive impairment, *etc*[1,2]. NMS can occur at any stage of the disease, and some even appear before the onset of motor symptoms and seriously affect quality of life, especially in later stages. In recent years, it has been considered that the brain-intestinal-microbial axis plays a significant role in pathogenesis or progression of PD. The intestinal nervous system may be the onset site of PD. Gastrointestinal symptoms may be correlated to the occurrence and deterioration of PD[3,4]. The factors causing constipation are complex. It is not only physical weakness but also lifestyle risks such as less fluid intake[5]. Additionally, side effects of medications are responsible for many patients[3,6]. More and more evidence showed that delayed colonic transit and

peripheral parasympathetic system dysregulation are very important mechanisms[7]. The lifestyles and eating habits are also important factors. Different races and regions have different lifestyles and eating habits. In addition, studying on the gastrointestinal symptoms in PD can be conducive to understanding the pathogenesis and heterogeneity of clinical manifestations of PD. In the present study, we comprehensively screened NMS, especially constipation, in patients with PD in northwestern China and analyzed the clinical characteristics and relative factors of constipation.

MATERIALS AND METHODS

Patients

Based on a cross-sectional survey, consecutive patients who met the movement disorders society criteria for PD[8] were recruited at the First Affiliated Hospital of Xi'an Jiaotong University (Shaanxi Province, China) from March to November 2018. The secondary Parkinson's syndrome such as post-traumatic, drug-induced, and vascular parkinsonism were excluded. Patients who could not complete rating scales due to severe cognitive dysfunction and those with acute and chronic gastrointestinal diseases in the past 6 mo were excluded. The research was approved by the local ethics committee. All patients gave their consent to participate and were assessed by experienced neurologists by face-to-face interviews.

Clinical assessments

Demographic variables, such as gender, age, side of onset, education level, disease duration, medical history, motor complications, and equivalent daily dose of levodopa were recorded for all patients using a self-designed questionnaire.

Constipation was assessed based on Roman III criteria for functional constipation. The constipation severity was evaluated by Wexner score (The lowest score is 0, and the highest score is 30. The higher the score, the more severity of constipation).

The modified Hoehn-Yahr stage was used to assess severity and Unified Parkinson's disease Rating Scale (UPDRS) III was used to assess motor symptoms.

NMS were evaluated with the non-motor symptoms assessment scales (NMSS), a self-administered 30-item instrument for screening the presence NMS and incidence of each non-motor symptom. The higher the scores, the more severe the NMS.

Depression was assessed using the Hamilton depression scale (HAMD)-24 items. A score of HAMD scale-24 items ≥ 8 points suggested depression.

Anxiety was assessed using the Hamilton anxiety scale (HAMA)-14 items. A score of HAMD scale-14 items ≥ 7 points indicated anxiety.

Quality of life was assessed using the Parkinson's disease Questionnaire-39 (PDQ-39). The higher the score, the worse the quality of life.

Cognitive impairment was evaluated using the Montreal cognitive assessment (MoCA) (if educational years < 12 years, 1 point was added to the test results to correct the test bias, and < 26 points suggested cognitive dysfunction).

The tremor score was composed of item 16 in UPDRS II and items 20 and 21 in UPDRS III, and non-tremor scores included items 5, 7, and 12 to 15 in UPDRS II and items 18 to 19 and 22 to 31 in UPDRS III. The motor symptoms have two clinical subtypes: Tremor type (tremor score/non-tremor score > 1) and non-tremor type (straight-type, tremor score/non-tremor score ≤ 1).

Data analysis

Data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, IL, United States). The Normally distributed continuous data are represented by the mean ± standard deviation (SD), and non-normally distributed data are presented by medians (quartile) and were analyzed by the Kruskal-Wallis test. Discrete variables were compared by the Chi square test. The *t*-test was used to compare the age, age of onset, UPDRS III, levodopa equivalent dose, NMSS, HAMA, HAMD, MoCA, PDQ-39, and Wexner scores between the constipation and non-constipation groups. The Kruskal-Wallis test was used to compare the incidence of constipation and one-way ANOVA was used to compare Wexner scores among different Hoehn-Yahr stages.

Pearson correlation analysis was performed to examine the correlation of constipation with sex, age, age of onset, scores of NMS, UPDRS total, UPDRS, PDQ-39, MoCA, HAMD, and HAMA, and Hoehn-Yahr stage. The unconditional logistic regression model was conducted to identify the risk factors for constipation in PD patients. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 166 subjects with PD were enrolled, including 76 women and 90 men, with a mean age of 65.92 ± 9.02 years, mean disease duration of 4.89 ± 3.93 years, and mean age at onset of 61.01 ± 9.97 years. Table 1 shows their characteristics and scores of rating scales. According to modified Hoehn-Yahr stage, 21 (12.65%) patients were in stage 1, 31 (18.67%) in stage 1.5, 56 (33.73%) in stage 2, 20 (12.05%) in stage 2.5, 28 (16.87%) in stage 3, and 10 (6.02%) in stage 4. Among them, 134 (80.72%) patients were treated with levodopa, 92 (55.42%) with dopamine agonists, 44 (26.51%) with monoamine oxidase B inhibitor, 9 (5.42%) with catechol-oxyl-methyltransferase inhibitor, 26 (15.66%) with anticholinergic drug, and 15 (9.04%) with amantadine.

Comparison of general characteristics between patients with constipation and non-constipation

Of all patients with PD enrolled, 87 (52.41%) were accompanied with constipation. Among constipation patients, 30 (34.48%) had constipation occurring before 6.30 ± 5.06 years at onset of motor symptoms. The age of patients, disease duration, Hoehn-Yahr grade, duration of levodopa treatment, incidence of motor complications, scores of UPDRS total and UPDRS III, NMSS, HAMD, HAMA, and PDQ-39 in the constipation group were significantly higher than those in the non-constipation group ($P < 0.05$), but there was no statistical difference in the scores of MoCA, clinical types, or medications between the two groups ($P > 0.05$). Details are given in Table 2.

Incidence of depression, anxiety, and cognitive impairment between patients with and without constipation

Compared to the non-constipation group, there was a higher incidence of depression in patients with constipation (46.84% *vs* 64.37%, $P < 0.05$). But there was no statistical difference in the incidence of anxiety and cognitive impairment between the two groups ($P > 0.05$). Detailed data are shown in Table 3.

Incidence and severity of constipation in patients of different Hoehn-Yahr stages

According to the modified Hoehn-Yahr stage, there were 52 patients in stage 1-1.5, 76 in stage 2-2.5, 28 in stage 3, and 10 in stage 4. Although the incidence of constipation did not increase while Hoehn-Yahr stage increased ($P > 0.05$), the severity of constipation increased while Hoehn-Yahr stage increased ($P < 0.05$). Detailed results are shown in Table 4.

Risk factors for constipation

Pearson correlation analysis showed that constipation was moderately positively correlated with age, Hoehn-Yahr stage, NMSS scores, UPDRS III and total scores, PDQ-39 scores, MoCA scores, HAMD scores, and HAMA scores ($r = 0.255$, 0.172, 0.361, 0.194, 0.221, 0.237, 0.238, and 0.207, respectively, $P < 0.05$). Results are shown in Table 5. Other variables such as sex, age at onset, MoCA scores, and medication did not have a correlation with constipation ($P > 0.05$).

Using constipation as the dependent variable, and factors such as age, disease duration, Hohen-Yahr stages, UPDRS III scores, duration of medication, depression and anxiety, and NMSS score as independent variables, the logistic regression analysis demonstrated that only NMSS score was an independent risk factor for constipation ($P < 0.001$).

DISCUSSION

Traditionally, cytotoxicity and Lewy body (LB) formation mediated by α-synuclein (α-SYN) was preferential in the pathogenesis of PD. In fact, the pathological changes of PD are extensive. Besides the brainstem, abnormal α-SYN also deposits in many other parts of the body including the intestine, pancreas, heart, salivary glands, and skin. PD is a syndrome of multiple organ dysfunction involving dopaminergic, adrenergic, serotoninergic, and cholinergic pathways[4]. Therefore, the clinical manifestations of PD include varieties of NMS such as olfactory hypothyroidism, cognitive disorders, sleep disorders, depression, constipation, and other motor symptoms[1]. We have realized the negative impact of NMS on quality of life. For some PD patients, disability may be more severe in NMS than dyskinesia[9]. Although PD has been recognized for 200

Table 1 Clinical characteristics of the subjects

Characteristic	Value	Characteristic	Value
Patients *n*	166	Hoehn-Yahr stage *n* (%)	
Male *n* (%)	90 (54.22)	Stage 1	21 (12.7)
Mean age ± SD (yr)	65.92 ± 9.02	Stage 1.5	31 (18.7)
Hypertension *n* (%)	60 (36.14)	Stage 2	56 (33.7)
Diabetes *n* (%)	14 (8.43)	Stage 2.5	20 (12.0)
Coronary heart disease *n* (%)	16 (9.64)	Stage 3	28 (16.9)
Family history of PD *n* (%)	8 (4.82)	Stage 4	10 (6.0)
Mean age at onset ± SD (yr)	61.01 ± 9.97	Mean scores of scale ± SD	
Disease duration (yr)	4.89 ± 3.93	UPDRS total	39.16 ± 18.39
Clinical type *n* (%)		UPDRS III	21.79 ± 11.72
Tremor	91 (54.82)	Wexner	4.29 ± 5.30
Non-tremor	75 (45.18)	HAMD	10.00 ± 8.61
Motor complications *n* (%)		HAMA	11.18 ± 10.27
Symptom fluctuation	51 (30.72)	MoCA	19.56 ± 5.75
Dyskinesia	25 (15.06)	PDQ-39	35.66 ± 24.06
Medication *n* (%)		NMSS	49.89 ± 32.55
Levodopa	134 (80.72)		
Dopamine agonist	92 (55.42)		
MAO-B inhibitor	44 (26.51)		
COMT inhibitor	9 (5.42)		
Anticholinergic	26 (15.66)		
Amantadine	15 (9.04)		

PD: Parkinson's disease; UPDRS: Unified Parkinson's disease Rating Scale; HAMD: Hamilton depression scale; HAMA: Hamilton anxiety scale; MAO: Monoamine oxidase; COMT: Catechol-o-methyltransferase; NMSS: Non-motor symptoms assessment scales; PDQ-39: Parkinson's disease questionnaire-39; MoCA: Montreal cognitive assessment.

years, the mechanisms of its pathogenesis and treatments still need to be explored, especially outside the central nervous system[10]. The present research showed that NMS are common during the whole course of PD. Almost all PD patients complained of at least one NMS, with an average of eight NMS[11]. NMS may involve multiple regions and neurotransmitter disorder in the pathogenesis of PD[1]. A Korean population study showed that gastrointestinal symptoms were widespread even in patients with early PD without treatment, with the incidence of constipation being 46.3%[12]. Some studies have shown that before the midbrain dopaminergic neurons were affected, a variety of NMS could occur, which was associated with a higher risk of developing PD. It was suggested that NMS may be considered an early clinic manifestation in PD patients[13]. Therefore, constipation, one of NMS, in PD patients may be an intrinsic symptom.

Our findings confirm that constipation (52.41%) is a common NMS in PD with a relatively high frequency. Constipation had occurred in about 34.48% of patients for a mean of 6.3 years before the onset of motor symptoms. The incidence of constipation in patients with PD has been reported to be 4%-71%, mostly at 24%-63%, some even up to 80%[2,14]. The reason for the inconsistencies in epidemiological surveys may be related to differences in study population and inclusion criteria. A prospective clinical study found that people who had defecated more than once a day had a 2.7 times risk of developing PD after 10 years of follow-up than those who defecated less than once a day[15]. Pathological studies also demonstrated that patients defecated more than once a day had a four-fold increase in the probability of subsequent Lewy body deposition compared with those who defecated less than once a day[16]. These findings suggested

Table 2 Comparison of general characteristics between the constipation and non-constipation groups

	Constipation	Non-constipation	*t*/χ2 value	*P* value
Male, *n* (%)	52 (59.77)	38 (48.10)	2.271	0.132
Mean age ± SD (yr)	68.10 ± 8.16	63.51 ± 9.42	3.355	0.001
Mean age at onset ± SD (yr)	62.34 ± 9.38	59.56 ± 10.52	1.796	0.074
Mean disease duration ± SD (yr)	5.66 ± 4.41	4.00 ± 3.12	2.732	0.007
Clinical types, *n* (%)				
Tremor	46 (52.87)	45 (56.96)		
Non-tremor	41 (47.13)	34 (43.04)	0.279	0.597
Hoehn-Yahr stage (median, quartile)	2.0 (1.5, 3.0)	2.0 (1.5, 2.5)	-2.451	0.014
Mean UPDRS total scores ± SD	43.02 ± 19.57	34.90 ± 16.05	2.889	0.004
Mean UPDRS III scores ± SD	23.94 ± 12.03	19.41 ± 10.97	2.512	0.013
Mean levodopa equivalent dose ± SD (mg/d)	468.17 ± 357.98	441.92 ± 428.78	0.416	0.678
Mean daily dose of levodopa ± SD (mg/d)	500.41 ± 326.55	430.91 ± 163.93	1.491	0.138
Mean levodopa medication times ± SD (mo)	53.43 ± 49.56	29.25 ± 35.77	3.265	0.001
Medication, *n* (%)				
Levodopa	73 (83.91)	61 (77.22)	1.192	0.275
Dopamine agonist	53 (60.92)	39 (49.37)	2.273	0.135
MAO-B inhibitor	23 (26.44)	21 (26.58)	< 0.001	0.983
COMT inhibitor	7 (8.05)	2 (2.53)	2.455	0.117
Anticholinergic	14 (16.09)	12 (15.19)	0.026	0.873
Amantadine	7 (8.05)	8 (10.13)	0.218	0.641
Motor complications, *n* (%)				
Symptom fluctuation	33 (37.93)	18 (22.78)	4.463	0.035
Dyskinesia	18 (20.69)	7 (8.86)	4.529	0.033
NMSS scores	61.05 ± 32.95	37.59 ± 27.42	4.928	0.000
HAMD scores	11.94 ± 8.59	7.86 ± 8.16	3.113	0.002
HAMA scores	13.20 ± 10.37	8.96 ± 9.75	2.688	0.008
MoCA scores	19.71 ± 5.48	19.36 ± 6.11	0.374	0.709
PDQ-39 scores	41.07 ± 25.58	29.69 ± 20.84	3.104	0.002

UPDRS: Unified Parkinson's disease Rating Scale; MAO: Monoamine oxidase; COMT: Catechol-o-methyltransferase; NMSS: Non-motor symptoms assessment Scales; HAMD: Hamilton depression scale; HAMA: Hamilton anxiety scale; MoCA: Montreal cognitive assessment; PDQ-39: Parkinson's disease questionnaire-39.

that constipation may promote the risk of PD. Although constipation is universal in patients with PD, the clinical manifestations are diverse.

Lifestyles especially food habits are responsible for constipation in PD patients, but not a critical factor. Constipation patients with PD consumed less water fluid and fewer fresh fruits, raw vegetables, fish, meats, *etc*.[17]. The incidence of constipation in PD patients is higher in Asian populations than in Western populations. According to surveys in Asian countries (such as in China, South Korea, and India), the difference may be related to diet habit, exercise, nutritional status, gut flora, education, and drug treatment[18].

Constipation in PD patients is directly related to its pathogenesis. According to the Braak staging scheme, the PD lesions do not start from the dopaminergic neurons in the midbrain. The olfactory bulb, the glossopharyngeal nerve, the vagus nerve dorsal

Table 3 Incidence of depression, anxiety, and cognitive impairment between the constipation and non-constipation groups

	n	Anxiety (%)	Depression (%)	Cognitive impairment (%)
Constipation	87	55 (63.22)	56 (64.37)	71 (81.61)
Non-constipation	79	40 (50.63)	37 (46.84)	63 (79.75)
χ^2		2.695	5.187	0.092
P		0.115	0.029	0.845

Table 4 Comparison of incidence and severity of constipation in different modified Hoehn-Yahr grades (%, ± s)

Grade	1-1.5	2-2.5	3	4	*χ2/F*	*P* value
n	52	76	28	10		
Constipation	22 (42.31)	41 (53.95)	16 (57.14)	8 (80.00)	5.470	0.140
Wexner score	6.73 ± 4.14	6.76 ± 3.58	11.19 ± 5.38	13.50 ± 2.98	10.138	< 0.001

Table 5 Correlations of constipation and different related scale scores

	r	*P* value
Age	0.255	0.001
Modified Hoehn-Yahr stage	0.172	0.027
NMMS scores	0.361	< 0.001
UPDRS III scores	0.194	0.013
UPDRS total scores	0.221	0.004
PDQ-39 scores	0.237	0.002
HAMD scores	0.238	0.002
HAMA scores	0.207	0.008

NMSS: Non-motor symptoms assessment scales; UPDRS: Unified Parkinson's disease Rating Scale; PDQ-39: Parkinson's disease questionnaire-39; HAMD: Hamilton depression scale; HAMA: Hamilton anxiety scale.

nucleus, and the intestinal intermuscular nerve plexus may be involved at the early stage of the disease[19]. Recent studies have shown that the pathological changes of PD may be changed through the intestinal microbial flora to the intestinal nervous system. Intestinal microbial flora changes can result in misfolding of α-SYN. The pathological α-SYN could be absorbed into the intestinal plexus by the intestinal mucosa from the myenteric plexus, and then retrogradely transmitted to the brain stem and brain along the vagus nerve, which may result in dopaminergic property alteration in the substantial nigra. In addition, the intestinal microbial flora may have a direct effect on host neural activity through the production of hormones and neurotransmitters, such as monoamines, GABA, and short-chain fatty acids. These products could lead to central nervous system glial activation and promote changes in inflammatory signaling molecules and oxidative stress, which may be the basic mechanisms of neurodegeneration in PD[3,20]. In the early stage of PD, the Lewy body has been found to be deposited in the submucosal plexus of the intestine[21]. It has been also reported that the incidence of PD in constipation patients was 3.3-4.2 times higher than those without constipation, and the severity of constipation was closely associated with the occurrence of PD[22]. We therefore postulated that constipation may be a precursor sign in the early stage of PD.

It has been found that there is a higher incidence of anxiety and depression in PD patients. The prevalence of depression varies from 2.7% to 90%[23,24], which may be attributed to differences of methodology or diagnostic criteria. A report indicated that the prevalence of depression was 11.17% and anxiety was 25.81% in Chinese PD patients[25]. Our findings show that the prevalence of depression and anxiety in PD patients was higher, and patients with constipation were more prone to depression but

without anxiety and cognitive impairment. Hawkes *et al*[20] have proved that the pathogenesis of PD is not only associated with the substantia nigra, but also related to the raphe nucleus and locus coeruleus before the presence of motor symptoms in PD[20]. It was suggested that serotonin and noradrenaline were involved in the occurrence of depression in PD[9].

Univariate analysis showed that the PD patients with constipation had older age, longer disease duration, more severe motor symptoms, and higher Hoehn-Yahr stages. The causes and mechanisms of constipation with PD are still unclear. The decline of sphincter function and anti-PD drugs such as levodopa and benzhexol are important factors. Other factors such as abdominal muscle weakness, decreased water intake, decreased activity, and bed rest also can increase the risk of constipation occurrence. In recent years, gut-first theory of PD exactly explained the causes of gastrointestinal symptoms. In addition to central nervous system degeneration, PD also undergoes degeneration of the enteric nerves, which is even earlier than that of the central nervous system. During the progression of PD, the changes of intestinal microbial flora could cause changes in the permeability of the intestinal mucosa and intestinal inflammation, which may result in the misfolding of α-SYN, and the misfolded α-SYN is deposited in neurons of intestinal mucosal and parasympathetic neurons of the spinal cord. Subsequently, dysfunction of intestinal neurons could cause delayed colonic transit and outlet obstruction, and finally resulted in constipation[26]. In addition, the degeneration of the dorsal vagus nucleus in PD patients may lead to autonomic nervous dysfunction, exacerbation of gastrointestinal dysfunction, and failure of defecation-related muscle contraction and relaxation. Dysfunction of the pelvic floor and anorectal sphincter is another cause[2]. The incidence of depression in patients with constipation is also increased. Depression may result in decreased ability of physical activity, daily activities, appetite, or gastrointestinal function, and cause constipation to develop and worsen as the disease progresses[27]. Besides, constipation in patients having taken levodopa and dopamine agonists may be related to the stimulation of peripheral dopamine receptors by the drug[28]. The occurrence of motor complications is closely related to the duration of the disease and the treatment effect of levodopa. With the prolongation of the course of disease, the progression of the disease, and the dosage of the drug treatment, the adverse drug reactions may increase further. Constipation is a common adverse reaction of many PD drugs, especially anticholinergics and dopamine agonists[29]. Our study showed that only NMS score is an independent risk factor for constipation by multivariate regression analysis, while medications are not an independent factor. Therefore, constipation is assumed to be an inherent symptom of PD rather than other risk factors.

Constipation in PD patients is widespread throughout the whole course of disease, even before motor symptoms. Thus, it is important to explore the possibility of constipation as a clinical prodromal biomarker for PD. It still needs further investigation on the mechanisms of clinical features and the treatments[30]. The study of gastrointestinal function can deepen the understanding of gut-origin theory of PD.

The current study has some limitations that should be pointed out. First, this is an observational, descriptive, survey study and our sample size is relatively modest. Moreover, the research subjects mainly from outpatients may lead to selective bias of the global PD population. Second, depression, anxiety, and cognition are only suggestibility of state due to the rating scale but not a formal clinical diagnosis. Finally, some variables such as adverse lifestyle and food habits of participants are not taken into account. Follow-up study about constipation in larger PD cohorts would provide accurate specific scales for different variables and a more comprehensive overview.

CONCLUSION

Our findings confirm that constipation has a relatively high frequency in patients with PD. PD patients with constipation have a higher incidence of depression, which leads to worse quality of life.

ARTICLE HIGHLIGHTS

Research background

Parkinson's disease (PD) is a neurodegenerative disorder and causes motor symptoms including resting tremor, akinesia, and rigidity. Recently, the focus of clinical research

on PD is shifting to non-motor symptoms (NMS). Among all NMS, constipation is particularly common, but the reason why PD patients are prone to constipation is still unclear. In addition to physical weakness and other factors, lifestyles and eating habits are important factors as well. The prevalence and influencing factors of constipation may vary among different populations.

Research motivation

At present, the mechanisms and risk factors underlying constipation in patients with PD are still uncertain. Although the prevalence of constipation in Chinese patients with PD has been reported before, it may vary among different populations due to the different lifestyles and eating habits. Therefore, we need to understand the prevalence and influencing factors of constipation in the PD population in northwest China.

Research objectives

To investigate the prevalence and risk factors of constipation in a cohort study of Chinese patients with PD.

Research methods

Based on accepted diagnostic criteria and a series of clinic rating scales, which contained modified Hoehn-Yahr stage, Unified PD Rating Scale (UPDRS) III, non-motor symptoms assessment scale (NMSS), Hamilton depression scale (HAMD), Hamilton anxiety scale (HAMA), Parkinson's disease Questionnaire-39 (PDQ-39), Montreal cognitive assessment, etc. The incidence and related factors of constipation was identified based on a retrospective survey. All subjects were recruited from March to November 2018 at the Department of Neurology of the First Affiliated Hospital of Xi'an Jiaotong University. In the following statistical analyses, *t*-test, spearman correlation, nonparametric test, one-way ANOVA, and unconditional logistic regression analysis were used.

Research results

In this study, 52.41% of patients were accompanied with constipation, and 34.48% had constipation occurring 6.30 ± 5.06 years before the onset of motor symptoms. The age of patients, disease duration, Hoehn-Yahr stage, duration of levodopa treatment, incidence of motor complications, scores of UPDRS total and UPDRS III, NMSS, HAMD, HAMA, and PDQ-39 in the constipation group were significantly higher than those in the non-constipation group ($P < 0.05$). Compared to the non-constipation group, there was a higher incidence of depression in patients with constipation (46.84% *vs* 64.37%, $P < 0.05$). The logistic regression analysis demonstrated that only NMSS score was an independent risk factor for constipation ($P < 0.001$).

Research conclusions

Our findings confirm that constipation has a relatively high frequency in patients with PD. PD patients with constipation have a higher incidence of depression, which leads to worse quality of life.

Research perspectives

Constipation is a common symptom in PD patients and reduces their quality of life. It should attract more attention in the future studies.

ACKNOWLEDGEMENTS

We thank all patients and their caregivers who agreed to take part in this study.

REFERENCES

1 **Zhang TM**, Yu SY, Guo P, Du Y, Hu Y, Piao YS, Zuo LJ, Lian TH, Wang RD, Yu QJ, Jin Z, Zhang W. Nonmotor symptoms in patients with Parkinson disease: A cross-sectional observational study. *Medicine (Baltimore)* 2016; **95**: e5400 [PMID: 27977578 DOI: 10.1097/MD.0000000000005400]

2 **Su A**, Gandhy R, Barlow C, Triadafilopoulos G. A practical review of gastrointestinal manifestations in Parkinson's disease. *Parkinsonism Relat Disord* 2017; **39**: 17-26 [PMID: 28258927 DOI: 10.1016/j.parkreldis.2017.02.029]

3 **Fasano A**, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's

disease. *Lancet Neurol* 2015; **14**: 625-639 [PMID: 25987282 DOI: 10.1016/S1474-4422(15)00007-1]
4 **Mulak A**, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. *World J Gastroenterol* 2015; **21**: 10609-10620 [PMID: 26457021 DOI: 10.3748/wjg.v21.i37.10609]
5 **Ueki A**, Otsuka M. Life style risks of Parkinson's disease: association between decreased water intake and constipation. *J Neurol* 2004; **251** Suppl 7: vII18-vII23 [PMID: 15505750 DOI: 10.1007/s00415-004-1706-3]
6 **Meek PD**, Evang SD, Tadrous M, Roux-Lirange D, Triller DM, Gumustop B. Overactive bladder drugs and constipation: a meta-analysis of randomized, placebo-controlled trials. *Dig Dis Sci* 2011; **56**: 7-18 [PMID: 20596778 DOI: 10.1007/s10620-010-1313-3]
7 **Cersosimo MG**, Benarroch EE. Pathological correlates of gastrointestinal dysfunction in Parkinson's disease. *Neurobiol Dis* 2012; **46**: 559-564 [PMID: 22048068 DOI: 10.1016/j.nbd.2011.10.014]
8 **Postuma RB**, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015; **30**: 1591-1601 [PMID: 26474316 DOI: 10.1002/mds.26424]
9 **Titova N**, Padmakumar C, Lewis SJG, Chaudhuri KR. Parkinson's: a syndrome rather than a disease? *J Neural Transm (Vienna)* 2017; **124**: 907-914 [PMID: 28028643 DOI: 10.1007/s00702-016-1667-6]
10 **Kadastik-Eerme L**, Rosenthal M, Paju T, Muldmaa M, Taba P. Health-related quality of life in Parkinson's disease: a cross-sectional study focusing on non-motor symptoms. *Health Qual Life Outcomes* 2015; **13**: 83 [PMID: 26088201 DOI: 10.1186/s12955-015-0281-x]
11 **Przedborski S**. The two-century journey of Parkinson disease research. *Nat Rev Neurosci* 2017; **18**: 251-259 [PMID: 28303016 DOI: 10.1038/nrn.2017.25]
12 **Kim HS**, Cheon SM, Seo JW, Ryu HJ, Park KW, Kim JW. Nonmotor symptoms more closely related to Parkinson's disease: comparison with normal elderly. *J Neurol Sci* 2013; **324**: 70-73 [PMID: 23102851 DOI: 10.1016/j.jns.2012.10.004]
13 **Sung HY**, Park JW, Kim JS. The frequency and severity of gastrointestinal symptoms in patients with early Parkinson's disease. *J Mov Disord* 2014; **7**: 7-12 [PMID: 24926404 DOI: 10.14802/jmd.14002]
14 **Chen H**, Zhao EJ, Zhang W, Lu Y, Liu R, Huang X, Ciesielski-Jones AJ, Justice MA, Cousins DS, Peddada S. Meta-analyses on prevalence of selected Parkinson's nonmotor symptoms before and after diagnosis. *Transl Neurodegener* 2015; **4**: 1 [PMID: 25671103 DOI: 10.1186/2047-9158-4-1]
15 **Stirpe P**, Hoffman M, Badiali D, Colosimo C. Constipation: an emerging risk factor for Parkinson's disease? *Eur J Neurol* 2016; **23**: 1606-1613 [PMID: 27444575 DOI: 10.1111/ene.13082]
16 **Abbott RD**, Petrovitch H, White LR, Masaki KH, Tanner CM, Curb JD, Grandinetti A, Blanchette PL, Popper JS, Ross GW. Frequency of bowel movements and the future risk of Parkinson's disease. *Neurology* 2001; **57**: 456-462 [PMID: 11502913 DOI: 10.1212/wnl.57.3.456]
17 **Abbott RD**, Ross GW, Petrovitch H, Tanner CM, Davis DG, Masaki KH, Launer LJ, Curb JD, White LR. Bowel movement frequency in late-life and incidental Lewy bodies. *Mov Disord* 2007; **22**: 1581-1586 [PMID: 17523195 DOI: 10.1002/mds.21560]
18 **Cassani E**, Barichella M, Ferri V, Pinelli G, Iorio L, Bolliri C, Caronni S, Faierman SA, Mottolese A, Pusani C, Monajemi F, Pasqua M, Lubisco A, Cereda E, Frazzitta G, Petroni ML, Pezzoli G. Dietary habits in Parkinson's disease: Adherence to Mediterranean diet. *Parkinsonism Relat Disord* 2017; **42**: 40-46 [PMID: 28647435 DOI: 10.1016/j.parkreldis.2017.06.007]
19 **Sauerbier A**, Jitkritsadakul O, Titova N, Klingelhoefer L, Tsuboi Y, Carr H, Kumar H, Banerjee R, Erro R, Bhidayasiri R, Schrag A, Zis P, Lim SY, Al-Hashel JY, Kamel WA, Martinez-Martin P, Ray Chaudhuri K. Non-Motor Symptoms Assessed by Non-Motor Symptoms Questionnaire and Non-Motor Symptoms Scale in Parkinson's Disease in Selected Asian Populations. *Neuroepidemiology* 2017; **49**: 1-17 [PMID: 28803229 DOI: 10.1159/000478702]
20 **Hawkes CH**, Del Tredici K, Braak H. A timeline for Parkinson's disease. *Parkinsonism Relat Disord* 2010; **16**: 79-84 [PMID: 19846332 DOI: 10.1016/j.parkreldis.2009.08.007]
21 **Lin A**, Zheng W, He Y, Tang W, Wei X, He R, Huang W, Su Y, Huang Y, Zhou H, Xie H. Gut microbiota in patients with Parkinson's disease in southern China. *Parkinsonism Relat Disord* 2018; **53**: 82-88 [PMID: 29776865 DOI: 10.1016/j.parkreldis.2018.05.007]
22 **Shannon KM**, Keshavarzian A, Dodiya HB, Jakate S, Kordower JH. Is alpha-synuclein in the colon a biomarker for premotor Parkinson's disease? *Mov Disord* 2012; **27**: 716-719 [PMID: 22550057 DOI: 10.1002/mds.25020]
23 **Reijnders JS**, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord* 2008; **23**: 183-9; quiz 313 [PMID: 17987654 DOI: 10.1002/mds.21803]
24 **Yamanishi T**, Tachibana H, Oguru M, Matsui K, Toda K, Okuda B, Oka N. Anxiety and depression in patients with Parkinson's disease. *Intern Med* 2013; **52**: 539-545 [PMID: 23448761 DOI: 10.2169/internalmedicine.52.8617]
25 **Cui SS**, Du JJ, Fu R, Lin YQ, Huang P, He YC, Gao C, Wang HL, Chen SD. Prevalence and risk factors for depression and anxiety in Chinese patients with Parkinson disease. *BMC Geriatr* 2017; **17**: 270 [PMID: 29166864 DOI: 10.1186/s12877-017-0666-2]
26 **Lin CH**, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. *Parkinsonism Relat Disord* 2014; **20**: 1371-1375 [PMID: 25293395 DOI: 10.1016/j.parkreldis.2014.09.026]
27 **Knudsen K**, Fedorova TD, Bekker AC, Iversen P, Østergaard K, Krogh K, Borghammer P. Objective Colonic Dysfunction is Far more Prevalent than Subjective Constipation in Parkinson's Disease: A

Colon Transit and Volume Study. *J Parkinsons Dis* 2017; **7**: 359-367 [PMID: 28157109 DOI: 10.3233/JPD-161050]

28 **Gökçal E**, Gür VE, Selvitop R, Babacan Yildiz G, Asil T. Motor and Non-Motor Symptoms in Parkinson's Disease: Effects on Quality of Life. *Noro Psikiyatr Ars* 2017; **54**: 143-148 [PMID: 28680312 DOI: 10.5152/npa.2016.12758]

29 **Borovac JA**. Side effects of a dopamine agonist therapy for Parkinson's disease: a mini-review of clinical pharmacology. *Yale J Biol Med* 2016; **89**: 37-47 [PMID: 27505015]

30 **Kulshreshtha D**, Ganguly J, Jog M. Managing autonomic dysfunction in Parkinson's disease: a review of emerging drugs. *Expert Opin Emerg Drugs* 2020; **25**: 37-47 [PMID: 32067502 DOI: 10.1080/14728214.2020.1729120]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com